THE ART AND

FIRST EDITION

Editors: Howard S. Smith **Julie G. Pilitsis**

Assistant Editor: Pya Seidner

FIRST EDITION

LIATIVE MEDICINE





SCIENCE OF PALLIATIVE MEDICINE

Editors: Howard S. Smith, MD Julie G. Pilitsis, MD, PhD Assistant Editor: Pya Seidner, MEd



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The Art and Science of Palliative Medicine (FIRST EDITION)

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Preface

Death. Are you ready?

Simple, but complicated. Pessimistic, but optimistic. Morbid, but cathartic. I have asked myself this question many times over the 20 years since it was posed to me and noted that the answers become surprisingly more complex with experiences and responsibility. For me, however this question is currently hypothetical. For the palliative care patient, this is the daily question as they live with the knowledge that death is imminent. This is the question the patient's caregivers and physicians constantly grapple with as the patient's clinical situations wax and wane on the way to an end that is guaranteed. This is the question that underlies every decision that is jointly made and every decision to treat or not to treat. This is the question that transcends religion, culture, ethnicity, gender, and age.

Becoming at peace with the situation (dying) and the known outcome (death) is the ultimate goal for the palliative patient, the caregiver, and the healthcare team caring for the patient. In order to allow for this ideal mental catharsis, the patient must be comfortable and every aspect of this comfort must be examined. Relieving pain, treating sleep disturbances, and addressing depression and anxiety are some of the cardinal features of effective palliative care. This book goes on to look at each organ system and how to maximize its comfort.

The goal of the book was to provide a resource that is usable in all countries, providing straightforward data as well as food for thought for providers worldwide. Its design by Howard Smith, MD, was brilliant in its simplicity as well as its breadth of coverage. It is useful both for the student and resident physician being first exposed to death and dying as well as the palliative care specialist that may be an expert in one facet of the patient's disease, but not in others. After reading this book, it was Dr. Smith's goal to arm the reader with a new set of tools in their daily responsibility and to be the best provider possible for their patients. It is meant to spawn interest in further reading on topics of interest and to promote future directions of study.

The text starts with an introduction to palliative care as a specialty, situations unique to the palliative care patient, and the mind-body connection. The next section focuses on palliative management related to different organ systems as each of these patient groups faces a novel set of concerns. Next, treatment of specific symptoms is discussed. These chapters provide excellent detail on the differential diagnosis of various signs and symptoms, and standard as well as creative treatment options ranging from the very traditional to the futuristic. Finally the book concludes with discussion of special conditions that may occur in palliative patients.

It was a great honor to be able to take over the task of editing this text from Dr. Smith and to continue working with his long-time associate Pya Seidner, MEd. I am a better provider for having this knowledge and I am confident that using this text will afford readers the same experience.

Julie G. Pilitsis, MD, PhD Albany, NY, USA

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Foreword

"... to cure sometimes, to relieve often, to comfort always."

Attributed to Dr. Edward Livingston Trudeau, founder of a 19th century tuberculosis sanatorium, this could easily be a defining slogan for palliative care because nearly all care models highlight the reigning importance of the individual as the central point of care. From its humble beginnings, the hospice movement and practice of palliative medicine have experienced a paradigm shift in the locus of treatments. Thought leaders and practitioners have transitioned from care when death is imminent to instituting palliative measures upon initial diagnosis of a life-threatening or serious illness.

The profession is riding a rising tide of recognition of the importance of best end-of-life care for the patient and family. Serving over 1 million patients each year and receiving high praise from families touched by impending death, palliative care still remains somewhat on the periphery of mainstream medicine until death approaches and curative therapies have been stopped. Families, however, appreciate and embrace the broad tenets of palliative care that promote and encourage communication, advance care planning, and interventions for the highest possible quality of life by providing continuous, competent, and comprehensive care that addresses each patient's specific complications and distress.

This book, envisioned and initiated by Dr. Howard ("Howie") Smith and finished by his colleagues after his passing, brings an unparalleled exploration of our field. Assembled is an impressive faculty of thought leaders who are active researchers, practitioners, and educators, bringing critical background knowledge that has helped build the field, shape its domains, and inform future direction.

This valuable resource begins with issues that influence the staffing of a palliative care team, continues with the palliative issues associated with specific medical conditions and treatments across the scope of symptoms afflicting those with life-limiting illness, before concluding with unique populations and circumstances. In total, providers will raise their understanding of the role of palliative medicine through practical and investigative experiences of those who have struggled with the distinctive physical, psychosocial, and spiritual challenges that distinguish this population of patients in need of special care. Be confident that the experiences learned and presented here will strengthen the ability of both the newly credentialed physician and the mature practitioner's ability to deliver culturally sensitive and personalized care based on sound practical and theoretical experiences. Only by increased awareness and thought will we continue to advance empathetic practices that continue to define and improve our roles in advocacy, treatment, care, and support for the end of life patient by raising professional standards in the core palliative care competencies that are applied in the hospital, long term care facilities, and at home.

I am confident that this authoritative, comprehensive, diverse, and readable compendiums like The Art and Science of Palliative Medicine will further elevate and influence the potential, growth, development, policy, ethics, and very future of our field through balanced presentations about providing quality care as the dying patient comes to terms with their own mortality, and also for the families and their loved ones as grief, bereavement, and death approaches.

I add my gratitude, alongside the rest of the authors of this book, that Dr. Smith's vision has been realized so that patients, caregivers, and providers in the community will grasp his caring and unselfish dream in this important work that he felt would "set the standard for further development of collaborations between professionals from many disciplines and countries." Ultimately, our successes will shift the caring professions from believing there is 'nothing more we can do' to realizing that 'there is more that we can do' by reaffirming the person and improving their quality of life.

Amy P. Abernethy, M.D., Ph.D.

Current President, American Academy of Hospice & Palliative Medicine; Associate Professor, Division of Medical Oncology, Department of Medicine, Duke University School of Medicine; Director, Center for Learning Health Care, Duke Clinical Research Institute; Director, Duke Cancer Care Research Program, Duke Cancer Institute, Durbam, North Carolina, USA November 2013

Dedication

I would like to dedicate this book in memory of Howard Smith, a great mentor, family man, and friend. Many thanks to my husband Tim, and children Ryan and Lauren.

Julie G. Pilitsis MD, PbD Albany, NY, USA

In memoriam

Howard Steven Smith, MD, known to his friends as "Howie," left the world on Wednesday, May 8, 2013. Howie was a distinguished physician, having completed training and receiving board certification in anesthesiology with a subspecialty in pain medicine, internal medicine, and nuclear medicine.

Born in San Francisco, California, Howard Smith grew up in East Meadow, New York, completing his medical school and residencies in Chicago, Albany, Cincinnati, and New York. He held many positions in various departments as an academician along with multiple positions as a prolific researcher with a wide range of publications. He was editor-in-chief of two pain journals—*Pain Physician and Journal of Pain Research*. Howie was not only a prolific writer, but he was also a scientist. His publications ranged from basic science to clinical aspects of patient management. He was a great teacher and guided many with his knowledge and wisdom.

His involvement in the American Society of Interventional Pain Physicians (ASIPP) since its inception was intense in all aspects including teaching with participation in board reviews and publication of evidence-based guidelines of interventional techniques and opioids.

Above all, he was a loving husband, father, son, and brother. Howie's loss is such that no one can express in words personally and professionally for all of us who have been associated with him.

Laxmaiab Manchikanti, MD Chairman of the Board and Chief Executive Officer, ASIPP and SIPMS, Medical Director, Pain Management Center of Paducah; Clinical Professor, Anesthesiology and Perioperative Medicine, University of Louisville, Kentucky, USA

I don't think I ever met a better listener or someone more interested in his colleagues' points of view than Howard Smith. It is rare that you talk to someone these days who is not fiddling with their cell phone or answering their email while nodding at every fifth word you say as if to say, "I'm listening (to every fifth word you say)." Talking to Howard was so utterly different than that; he always seemed genuinely fascinated by what you were saying. As many of us know, Howard was a prolific editor of books and now that I think of it, I can see the connection between his listening ability and why he so often took on this thankless task - because he wanted to present not just his own views to alleviate the suffering of those with chronic pain, but those of his colleagues. He valued them and he wanted everyone else to have the opportunity to see them as well. Howard and I published together a number of times; one of these instances was a textbook on pain and chemical dependency. When it was done he flipped a coin in Albany (while I was on the phone from NYC) to see whose name was to be listed first. Has there ever lived a more honest, less egotistical person than Howard whom you could trust to do an absentee coin flip? The byline reads Smith and Passik. The world has lost a gentle, wonderful soul and an advocate for the suffering. When I miss him I will look at this book and be content to simply see my name next to his and remember what it felt like to share ideas with him and be truly listened to.

Steven D. Passik, Ph.D. San Diego, California, USA Dr. Howard Smith (Howie as we knew him) was my best friend, neighbor, and partner in pain. He was a dedicated husband to his wife Joan, father to his adored daughter Alyssa and sons Joshua, Benjamin, and Eric (in age and alphabetical order to be fair as Howie always was), and of course his yellow lab canine companion Maggie. He was a jovial man that everyone loved; he'd give you the shirt off his back, and he had the heart of a saint.

Howie was the most unpretentious man I've ever known. He often spoke of world-renowned pain and palliative care scholars and their various interests and accolades without ever considering that he was actually one of them. He also recognized the import of a team approach to patient care and treated each member, from every conceivable discipline, with respect as he listened intently to any perspective and insight anyone had to offer.

Howie was a respected scholar, teacher, medical doctor, and anesthesiologist with a long list of accolades, board certifications and scholarly achievements, not the least of which were perhaps hundreds of publications dedicated to improving outcomes for pain sufferers. But he was a family man too who enjoyed watching his children play sports, vacations at the Narragansett beaches, outings to Disney Parks, and an evening around the camp fire eating marshmallows, smiling and laughing vociferously with family friends.

I worked with him in his Pain Clinic several years ago as a doctoral student. His bedside manner was impeccable. I remember him saying that even if we can't help the patient, we can make them feel better by listening—and listen he did. Howie would sit with his patients and listen intently to their stories. He wouldn't rush anybody; he'd just listen and nod his head, listen some more, nod again and hold their hands and warm their hearts. Everybody loved him. It was true, at least half of the job was listening to the patient and he taught that to all of his pain disciples with compassion and vigor.

In a world of technology, word processing, text messaging, and the like, Howie insisted on doing things the old fashion way. He was a brilliant scholar that refused to succumb to the electronic disconnect that has become the norm. He told his coworkers and friends that he wasn't good with computers, but few know the real reasons he spurned technology. In a weak moment, he once told me that he liked to hold a hard copy in his hands as he read and reviewed various writings because he felt closer to the persons that spent so much time and effort on whatever works he was reviewing.

Howie was peaceful, gentle, kind, and dedicated. His legacy includes loving-kindness, warm smiles, heartfelt handshakes he insisted on at each encounter, skillful clinician, teachings, writings, family, friendship, and his passion to selflessly make life better for everyone else here in the United States and by his many visits to China and around the globe.

Indeed Dr. Howard Smith will be sorely missed, but his zest for life will live on for eternity in the hearts and minds of all those he touched.

Jeffrey Fudin, B.S., Pharm.D., FCCP

Diplomate, American Academy of Pain Management, Owner & Managing Editor, PainDr.com; Adjunct Associate Professor of Pharmacy Practice & Pain Management (Albany College of Pharmacy & Health Sciences), Albany, New York 12208, USA Ever since my friend, Howie passed away, I have been reflecting on his life and how remarkable he was. His life was devoted to advancing the field of pain medicine. This is reflected by the many contributions he made to the field. He wrote several books, served on editorial boards of several journals, and, finally, published numerous high quality articles. Most importantly, he was dedicated to his patients. As such, the pain world is poorer for the loss of a dedicated doctor, Dr. Howard Smith, who worked tirelessly to train, mentor, and inspire and collaborate with many of our current prominent Pain Physicians. It was a pleasure to hear his views on so many areas—medical research, clinical medicine, policy and politics of medical societies, etc. In sum, Howie was a deeply thoughtful and smart man, who will be missed by his patients, friends and trainees.

On a personal note, Howie was my best friend, a trusted friend with whom I could always enjoy being with to share my joy and frustration. We genuinely enjoyed each other's company. We frequently called each other to share our successes and failures, happiness, joy and sadness. We frequently checked on each other that both of us were OK. It was always a joy to have him around, sip a beer or two and have interesting conversations and toast ideas.

My friend was a down to earth gentleman and a type of person whom anyone liked to have around all the time. He truly had a big heart, a bright mind and a clear soul. Anywhere he went, he fitted in very quickly and everyone loved him immediately. He just seemed to have a special magnet. Finally, I was blessed and fortunate to have traveled with him during his last trip to Busan, South Korea where we both had a good time. We talked a lot about everything including about where the pain medicine is heading to. We enjoyed our stay and were planning our next get together at a future meeting. He left Busan alone and came back home while I stayed there a day more. Unfortunately, I was informed that he passed a few days later. I was shocked and did not believe what I heard. It felt like a dream. I am still in disbelief and denial. I cannot believe that he is no longer with us. What a lost!

I miss my friend Howie and his memories live forever-May his soul rest in peace!

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Healthcare ethics and pain management

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I will prescribe regimens for the good of my patients according to my ability and my judgment and never do harm to anyone.

—From the Hippocratic Oath, 4th Century BC [Miles, 2004]

I will consider the welfare of humanity and relief of human suffering my primary concerns.

-From the Oath of a Pharmacist, 1994 [Fink, 2007]

Introduction

One might begin a discussion about the ethical dilemmas which physicians, pharmacists, and others confront in healthcare, pain management, and palliative medicine with a rhetorical question: would any reasonable person challenge the proposition that there is a moral obligation to help patients suffering with pain? The response is certain to be: "No." How might anyone dispute-or even questionthe accepted belief that physicians and pharmacists have an ethical obligation to assist in relieving pain? Moreover, one might observe that in giving this answer, the respondent is simultaneously asserting-as an assumed element of the reply-that it is universally held among physicians and pharmacists generally, and the entire community of patients and society itself, that physicians and pharmacists have an ethical duty, or professional responsibility, to help relieve patients' pain. Thus, without realizing it, or maybe quite fully understanding it, the individual who answers the question states and accepts a professional ethical norm. That is, in giving the response, one recognizes that it is normative ethical conduct or behavior for a physician or pharmacist to act in ways to help patients suffering with pain symptoms. Concurrently then, one acknowledges an ethical standard in

medical and pharmacy practice.

Meeting ethical obligations—or more simply, *ethics* is about "right" conduct; conduct that is accepted to be right—or at least, believed to be the most appropriate action or choice given the circumstances—by an individual actor, and hopefully by the individual's peers and the individual's community [Morris, 1999]. *Ethics* is a field or sub-set of philosophy and encompasses not only the study of right conduct, but also how an ethical person might determine which acts or behaviors are right, and the decision-making processes that ethical persons use to make better rather than worse decisions when confronting a moral dilemma within a specific context [Ingram and Parks, 2002]. *Healthcare ethics* deals with dilemmas and decisions impacting the care of patients.

The phrase professional ethics is used to describe more accurately the study of the right conduct of professionals (such as physicians and pharmacists) and the critical examination of how professional persons might determine which professional acts or behaviors are ethical or right. Professional ethics is a branch of *applied ethics*; the analysis of how one applies ethical theory or learned philosophical concepts or recognized ethics principles to everyday practices [Ingram and Parks, 2002]. Similary, heathcare ethics and *bioethics* are broad terms that encompass much more than professional ethics. Bioethics implies decision making about life, much broader than just healthcare, the life sciences, or even quality of life. However, as healthcare professionals, the decisions made by physicains and pharmacists clearly impact the healthcare of patients, individually and collectively. In fact, there is no better example of how compassion, good decision making, and right conduct are intertwined than in the provision of Part I

adequate pain control to palliative care patients. If anything, palliative medicine is about appropriately managing pain and other symptoms, discussing the need for advance planning, and dealing with psycho-social issues, all toward improving quality of life [Jadad & Bowman, 1995].

Concepts and contexts: obligations and choices

Effective pain management has been an ethical obligation of physicians and pharmacists since the professions were first recognized. Few ancient or modern references are necessary to support this idea and acknowledged professional commitment. Hippocrates (460 BC to 380 BC)-the Father of Western Medicine-prescribed willow bark and leaves to women during childbirth to help relieve pain [Chapman and Gavrin, 1996]. Scribonius, a court physician or pharmacist to the Roman Emperor Claudius in 47 AD, wrote one of the first pharmacopeias or formularies; its pages included prescriptions for pain medicines [Pellegrino, 2002]. (Incidentally, one should note that this same early manuscript is believed to be the first historical record identified thus far to use the word profession in reference to those who practice the healing arts. In this brief work, the author defined profession as "a commitment or compassion or clemency in the relief of suffering." In the few leaves surviving, Scribonius made the argument that the proper use of medicines was consistent with the Hippocratic injunction to help and heal the patient).

Of course, pain control and relief are just as important in the practice of medicine and pharmacy today as in previous centuries. Albert R. Jonsen, Mark Siegler, and William J. Winslade, in their book *Clinical Ethics*, list "relief of symptoms, pain, and suffering" second only to "promotion of health and prevention of disease" when describing broad practice objectives, or the "goals of medicine" [Jonsen *et al.*, 2002]. This essential conviction about professional ethical obligation is easily supported by empirical evidence (AP analysis finds U.S. pain medicine use has skyrocketed 88 percent, 2007):

- "People in the United States are living in a world of pain and they are popping pills at an alarming rate to cope with it";
- "The amount of five major prescription painkillers sold at retail establishments rose 88 percent between 1997 and 2005, according to an Associated Press analysis of statistics from the Drug Enforcement Administration";
- "More than 200,000 pounds (90,720 kilograms) of

codeine, morphine, oxycodone, hydrocodone and meperidine were purchased at retail stores during the most recent year represented in the data. That total is enough to give more than 300 milligrams of [prescription] painkillers to every person in the country";

• "Oxycodone, the chemical used in OXYCONTIN[®] (Purdue Pharma L.P.), is responsible for most of the increase. Oxycodone use jumped nearly six-fold between 1997 and 2005".

Although the word *pain* in not mentioned specifically in either the American Medical Association's (AMA's) [American Medical Associaton, 2001] or the American Pharmacists Association's (APhA's) [Fink, 2007] most recent codes of ethics, one may reasonably infer that pain control and relief are subsumed in the applicable passages which read: "a physician shall be dedicated to providing competent medical care, with compassion and respect for human dignity and rights"; "a pharmacist promotes the good of every patient in a caring, compassionate, and confidential manner"; and "a pharmacist respects the autonomy and dignity of each patient". Moreover, in documents expounding on the scope of the relevant AMA code section, the association's Ethical and Judicial Council states specifically, in reference to patients near the end of life, that "physicians have an obligation to relieve pain and suffering and to promote the dignity and autonomy of dving patients in their care" [American Medical Association Council on Ethical and Judical Affairs, 2002]. Similarly, in recent APhA publications discussing pharmacists' duties and pain management, one will find these statements [Singh and Wyant, 2003; American Pharmacists Association, 2005]:

- "In a curricular review of 28 pharmacy schools, the topic of pain management was included as a part of the coursework of all 28 schools";
- "Participants (in a study of pharmacy faculty who teach pain therapy topics) generally thought that pharmacy students must understand that they are in a unique position to act as patient advocate for appropriate pain management, particularly with regard to chronic pain at the end of life";
- "Pharmacists, regardless of their specialty, are in a pivotal position within the health care team to influence and monitor the success of pain management in patient care";
- "Goals of pharmacist pain management should include both reducing pain levels and preventing pain from recurring";

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• "The imperative to provide appropriate medications to patients with pain must be balanced with the imperative to prevent inappropriate dispensing of opioids".

(One should readily note that the last statement immediately above highlights the difficult ethical "balance" that physicians and pharmacists share in prescribing and dispensing the "right" medicine, in the "right" dose, and at the "right" time in helping patients with acute and chronic pain. Too much pain medicine might lead to overuse and abuse and addiction; too little to continued suffering with the patient's pain untreated or undertreated. Professionals and patients and regulators would alike soundly condemn either extreme of the spectrum as inappropriate—outside the expected professional norm—or *unethical.*) [American Pharmacists Association, 2005]

In addition to the codes and standards established by medicine and pharmacy practitioners themselves, one should remember that the community through its authorized representatives—through statutes, regulations, quasi-regulatory mandates, and the courts—has established parallel behavioral norms in enforceable legal standards, for example:

- model guidelines regarding the use of controlled substances for the treatment of pain—adopted as regulation or policy by several state medical boards have been endorsed by the Federation of State Medical Boards since 1998 [Federation of State Medical Boards of the United States, Inc., 2004];
- standards promulgated by the Joint Commission on Accreditation of Healthcare Organizations (JC) in 2001 recognized pain symptoms as the "fifth vital sign" and required accredited organizations to establish measures to assure quality pain management for symptomatic patients [Landis, 2001]; and
- a number of jury and appellate court cases, such as Bergman v. Chin [Okie, 2001] and U.S. v. Hayes [U.S. v. Hayes, 1979], illustrate that providing too little pain medicine in a terminal situation and knowingly filling controlled substances prescriptions with no "legitimate medical purpose" may led to civil or criminal liability.

One might observe that even with statements of recognized normative ethical conduct, as from the AMA and APhA codes and the other expository materials, it is still difficult at times to determine what a right decision or course of action is because of the particular circumstances of the cases. It may be of value to assert that doing "good" and avoiding "harm" and "caring" and "compassionate" and "autonomy" and "dignity" and "justice"—to use the exact words in the Hippocratic Oath and the AMA and APhA codes of ethics—are important in making choices about what is the right thing to do, but it may be a very different matter at the pharmacy counter or patient's bedside given the complexities of a specific situation. One must be able to move beyond mere words and aspirational platitudes to "doing good" in practice and taking defensible ethical action.

These difficulties in interpreting words and phrases and actually putting the words into action are not new. Philosophical sages throughout the millennia have attempted to offer advice and counsel to those facing ethical dilemmas. An important few include:

- Aristotle (384 to 322 BC, Greece) who suggested that virtuous people or people with "good character" would make virtuous or "right" decisions when confronting moral choices. His is known for describing virtue-based ethics, or showing that making good decisions in life is a tension or struggle to maintain a mean or moderate character between opposites of noble and ignoble traits [Aristotle, 1987]. Applying Aristotle's teachings, one might conclude that virtuous or good physicians and pharmacists will make good decisions;
- St. Thomas Aquinas (1225 to 1274, Italy) who wrote that by understanding the immutable laws of nature and Nature's God, one could reason through to a correct resolution or universal standard of conduct. His ideas were instrumental in developing what theologians and ethicists term natural law theory [Pence, 2004]. Applying St. Thomas' teachings, one might conclude that physicians and pharmacists when faced with a moral dilemma will be able to reason and come to a better conclusion about proper conduct;
- Immanuel Kant (1724 to 1804, Germany) who believed that a person confronting a moral dilemma needs only to determine one's duty in the given circumstances and a resolution will surely present. Kant regarded duties as obligations that must be met; he felt duty was at the core of ethics. (His work promotes what supporters call duty-based or deontological ethics, from the Greek *deon* meaning "obligation" or "duty".) [Kant, 1964]. Applying Kant's teachings, one might conclude that a physician or a pharmacist facing a moral crisis just needs to identify the correct "duty" or "duties" required to meet a particular ethical obligation or set of obligations;
- John Stuart Mill (1806 to 1873, Great Britain) who

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expanded the utilitarian or consequentialist theories of Jeremy Bentham (1748 to 1832, Great Britain) to explain that one should always consider the possible outcomes of making one ethical choice verses any other in order to maximize beneficial results for the greatest number impacted by the decision [Pence, 2004]. (End results or consequences of actions in this context have to do with aims and goals; philosophically this is a teleological view, from the Greek *telos*, or "target.") Applying Bentham and Mill's teachings, one might conclude that a physician or a pharmacist should always consider the possible consequences or outcomes of various decisions when resolving moral problems and act to help as many as practical;

• John Rawls (1921 to 2002, United States) who contributed that individualized decision making may not be enough if society is to be truly just or fair (justice-based ethics). Rawls noted that within a "just" community equal opportunity means minimizing the impact of luck (the accidental privileges of birth and intellect), permitting a more fair distribution of collective benefits based on merit and need [Pence, 2004]. Applying Rawls' teachings, one might conclude that physicians and pharmacists should take into account concepts of fairness and justice to the degree achievable in solving ethical dilemmas.

(It may be observed that philosophical thought through the ages may not add that much more to healthcare professional's ability to resolve real-life moral problems than the words and platitudes found in codes of ethics, but perspective and historical analysis are certainly helpful for more complete reflection and consideration).

Contributing to the codes and theoretical ethical frameworks for determining good conduct and making better rather than worse decisions are more recent ethical decision-making approaches or doctrines, including:

- *Principalism*—the notion that resolving ethical dilemmas results from identifying competing principles and weighing or prioritizing each to give precedence to the one that may be more important or critical [Beauchamp and Childress, 2001]. The four principles identified by Tom Beauchamp and James Childress in their seminal volume *Principles of Biomedical Ethics* are:
 - Beneficence—that one should strive to "do good" (from the Latin *bene*, "well" or "to do good"; embodied in the Hippocratic Oath);
 - Nonmaleficence-that one should try to "avoid

harm" (from the Latin *non*, "do no"; and *maleficencia*, "evil doing"; "do no harm"; recall the similar Latin injunction to doctors *primum non nocere*, "first, do no harm"; again embodied in the Hippocratic Oath);

- Autonomy—that one should respect the selfdetermination of each individual (transliterated from the Greek *auto*, "self," and *nomos*, "law"; or "self law"; embodied in the AMA and APhA codes of ethics); and
- *Justice*—that one should resolve dilemmas in a way that is just or fair for the individual and community (again found in the AMA and APhA codes of ethics and strengthened by Rawls' teachings).

One of the difficulties with balancing competing principles is that physicians and pharmacists cannot always make the *best* choice between two: to "do good" without risking some harm as a by-product (for example, almost every drug has unfortunate and deleterious side effects that are unavoidable).

- *Casuistry* (case-based ethics)—the belief that each ethics dilemma is unique (in the same way that each patient is unique, each patient's anatomy and physiology and drug absorption and metabolism are different, each person's psychosocial milieu is dissimilar from those of every other individual) and that one problem should not necessarily be resolved relying on previous similar cases or application of principles [Jonsen *et al.*, 2002]. However, using a case-by-case analysis to resolve ethical dilemmas leaves many bewildered or confused because it opens decision makers to the charge of being relativistic, ungrounded in changeless truths;
- *Narrative ethics*—a system of reflection that offers those confronting an ethical dilemma opportunity to work through a problem in much the same way as a narrator tells a story, filling in as many important details as necessary for the plot or resolution to unfold [Nelson, 1997]. Regardless of how issues or facts are identified or cataloged or considered, one must still make a decision; narrative ethics may perhaps offer a better way to teach about ethics than resolve dilemmas;
- "An ethic of care" (as suggested from feminist ethics) a view that ethics should focus more on community and wider connectedness or relationships in providing care rather than on individuals (and autonomy) [Sherwin, 1997]. One would hope that rejection of

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absolutist, coldly objective, or callously impartial approaches to ethics might be an element of most good decisions which emphasize the higher moral good of inclusiveness and caring for (and about) others without being critical of best intentions to resolve problems in better rather than worse ways;

• *Pragmatism*—a bottom line acceptance or realization that after appropriate analysis and reflection, one must make a decision just to get it over with and move on, recognizing that there may be untoward fallout to deal with afterwards [McGee, 2003]. Regrettably, in haste and without due regard for values, codes, community standards, philosophical contemplation, or contemporary opinion, one may not make as good a decision as possible if too pragmatic about issues or processes.

Apart from using various techniques or schemas to think about ethics, one must also have a method or process to come finally to a resolution or decision. David Bruce Ingram and Jennifer A. Parks have written: "An ethical dilemma forces us to choose in a way that involves breaking some ethical norm or contradicting some ethics value" [Ingram and Parks, 2002]. One might characterize an ethical dilemma then as one in which a decision which involves conflict between two or more "right" actions must be made with results possibly compromising treasured values, principles, or deeply-held beliefs [White, 2007].

Robert A. Buerki and Louis D. Vottero, in their pharmacy ethics textbook, *Ethical Responsibility in Pharmacy Practice*, offer a systematic decision-making outline for those facing an ethical dilemma [Buerki and Vottero, 2002]. Their modified question sequence is offered below from the way it is presented in the casebook, *Drugs, Ethics, and Quality of Life* [White, 2007]:

- "(I) Identify the problem(s).
 - (i) Identify technical facts;
 - (ii) Identify moral parameters;
 - (iii) Identify moral constraints;
 - (iv) Identify legal constraints;
 - (v) Identify relevant human values.
- (II) Develop alternative courses of action.
 - (i) Identify relevant ethical principles for each alternative;
 - (ii) Recognize ethical assumptions for each alternative;
 - (iii) Assess additional emerging ethical problems.
- (III) Select the one best course of action that permits the decision maker to have the greatest peace of mind or that which satisfies the demands of conscience.
 - (i) Justify the selection;

- (IV) Anticipate logical, rational objections to the selected course of action.
 - (i) Be prepared to defend the selection against objections arising from factual errors;
 - (ii) Be prepared to defend the selection against objections arising from faulty reasoning;
 - (iii) Be prepared to defend the selection against objections arising from conflicting values."

Commentary and clarification: difficult cases and hard decisions

Unfortunately or fortunately, a physician or pharmacist in any particular instance—may not find codes or policy statements, or sagacious ethical opinion, or modern biomedical ethics thought as helpful or as determinative as one would like or hope in resolving dilemmas involving effective pain management and good patient care; but still one is left with identifying ethical concerns and then attempting to make better rather than worse decisions given the options. Four hypothetical cases dealing with pain management may offer opportunity for practice ethics issue identification and analysis.

Hypothetical case 1

Ms. Jones is a 17-year-old African-American teenager who has suffered with sickle cell disease all of her life. She lives with her mother and one-year-old child; she is a senior in high school. She was diagnosed with clinical depression about six months ago and is taking an antidepressant daily. About every six- to nine-months for the last several years, she has been hospitalized for severe sickle cell vaso-occlusive or pain crises. Quite often, each crisis has been triggered by a viral illness or a streptococcal throat infection that Ms. Jones contracts from a sick contact at school. Each crisis has had a relatively predictable course that resolves over three to five days with intravenous hydration, oxygen, narcotics and non-steroidal-anti-inflammatory drugs (NSAIDs), and bed rest. Typically, when the patient leaves the hospital, she receives prescriptions for oral medicines, including VICODIN[®] (hydrocodone and paracetamol, Abbott Laboratories) and TYLENOL® No. 3 (acetaminophen and codeine, Ortho McNeil Pharmaceuticals) tablets. Regrettably, since the last crisis about three months ago, the doses of narcotics required for adequate pain control have been escalating remarkably, more that might be expected

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given her control for the last several years. The amount of narcotics now required are so unusually high that both her long-standing hematologist and pharmacist worry that she may be physiologically and psychologically habituated and may require intervention now for a narcotic addiction.

In the case, involved physicians and pharmacists are probably worried about adequately controlling any trueethically, "real"; legally, "legitimate"-pain symptoms, but not making the situation worse by providing too much pain medicine that the patient may misuse or abuse. From the facts of the case, there may be reasonable suspicion that the patient is diverting legally prescribed and dispensed narcotics from a legitimate medical purpose (to control sickle cell disease pain) to a non-legitimate purpose (to support an addiction). It may be this concern or this tension between the beneficence principle (doing good, controlling the pain) and the nonmaleficence principle (avoiding harm, contributing to habituation and diversion of controlled substances, violating the law) that receives the most attention when pharmacists and physicians think about ethical considerations in pain management cases [White, 2007]. Noted commentators-such as pharmacist-attorneyteacher David B. Brushwood-have spoken and written much on this topic [Smith & Brushwood, 2012].

Involved physicians and pharmacists in this case should act on their reasonable suspicions in the best interests of the patient. It is not permissible for physicians and pharmacists to violate recognized legal and ethical norms; improper action would not be fair or just (the justice principle) to other patients or the rest of society. There may be a number of appropriate actions that the physician or pharmacist might take here: observe the patient when presently experiencing pain symptoms and when comfortable without pain (monitoring for appearance or physical state or changes in heart rate, respirations, blood pressure, inability to focus or concentrate) to understand the extent of the problem better; have appropriate conversations with caregivers and peers and compare observations and views; ask the patient about the escalating use of narcotics; reflect about the change in the amount of medicine now required to relieve the pain; learn more about the risks of addiction for patients with chronic acute pain; reassess the need for narcotics and the level of the patient's pain; investigate mitigating circumstances (for example, the patient's depression or perhaps stressful family situation or medication tolerance or possible drug interactions); institute a "contract" with the patient about the proper use of medicines; set boundaries for the amount of medicines to be prescribed or dispensed;

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advise the patient about risks and the established legal standards; report any illegal diversion to the authorities; and document any actions properly. If it is determined that the patient is habituated to a controlled substance and diverting use from a "legitimate medical purpose," then the primary physician's and pharmacist's relationship with the patient shifts to one now controlled by legal norms rather than ethical norms because of the legal standards that now apply. Drug Enforcement Administration (DEA) regulations have sections that deal directly on point with these changed conditions [White, 2007]. (One might say that the recognized legal norm dictates the commonly accepted ethical course of action in such cases; or that the ethical norm is merged in the legal norm).

One may query why a physician or pharmacist might take other action(s) as well, such as ignoring the dilemma, telling the patient that they cannot prescribe or dispense the narcotic any more, simply not being available for continued care, or not stocking the narcotic in the pharmacy. One of these options (not being available or abandoning the patient) may bear civil or malpractice risk [White, 2007]; more particularly, a physician should terminate a physicianpatient relationship ethically and legally by advising the patient of the unilateral decision and assisting the patient to the degree possible in finding alternative sources of care (for example, providing a written 30 day notice of future nonavailability and a list of other competent practitioners in the area that treat sickle cell patients). Also, perhaps one should note that with these alternative option(s), the physician and pharmacist might be resolving the key ethical issues in their own best interests (for example, simply avoiding the patient altogether or acting to minimize or avoid legal hassles), rather than in the patient's best interests. (This may be a very good and practical example of a conflict of interests in ethical decision-making).

Edmund D. Pellegrino has written that should physicians or pharmacists do this, then they do not strictly meet the historical definition of a *professional* as he understands it: professionals are those who suppress self-interest when the welfare of those they serve—or profess to serve—requires it [Pellegrino, 2007].

Additionally, there is at least one other ethical issue in this case that needs to be addressed: the patient's status as a minor and the recognition that *consent* and *assent* are different [O'Rourke, 2000]. Recall that the patient is 17-year-old, legally a minor and thus technically incompetent (legally incapacitated) to give informed consent for medical treatment [White, 2007]. (Note: that just because the patient has given birth to a child typically does not automatically emancipate her from her legal status as a minor and her inability to consent or refuse medical treatment). However, a number of states have relaxed the purely technical legal definition of competency; in favor of a more ethically sound view of obtaining informed consent for those who have clinical decision making capacity (some legal scholars and judges refer to this as the "mature minor doctrine") [Moore, 2006]. This rule is an extension of the autonomy principle in ethics that promotes allowing individuals with decision-making capacity to make their own decision because they have power for self-determination. The idea of the informed consent process may be described as follows:

"In order to obtain informed consent, the practitioner should be assured that the patient fully comprehends and understands the nature of the proposed encounter; the diagnosis (diagnoses); the prognosis (prognoses); and the available, reasonable evaluation and treatment options and the benefits and risks of each (including the possibility of forgoing any treatment at all) [White, 2007]."

The 17-year-old patient as described in the case certainly appears to have autonomous capacity. However, even if the patient is incompetent legally to give consent because of age, it may be ethically appropriate and beneficial to obtain the patient's *assent* (or agreement) to treatment before proceeding.

Hypothetical case 2

Ms. Smith is 28 years old; she is pregnant with her first child. The mother and father have planned for a "natural childbirth"; they have attended Lamaze classes and have arranged to be followed and delivered by a nurse midwife. The nine-month pregnancy went well; she received excellent prenatal care. Ms. Smith went to the hospital when her "water broke" (the membranes ruptured and leaked amniotic fluid); however, Ms. Smith experienced very few and relatively weak contractions. In the hospital's birthing suite, with stronger contractions, Ms. Smith began complaining of severe discomfort (more severe than might be usually anticipated by the delivery team). After an hour of increasing dis-ease, Ms. Smith demanded medicines to relieve the pain. Mr. Smith and the nurse midwife were quite surprised and somewhat frustrated by her repeated requests given what they both knew (or believed they knew) about her wishes from prior conversations and actions. After she refused to be swayed from her increasingly hostile Part I

demands for pain medicines, the nurse midwife ordered VISTARIL[®] (hydroxyzine, Pfizer Inc.) 50 mg IV for anxiety and mild analgesia. However, there was only minor relief for Ms. Smith and after a few minutes, the patient demanded more drugs (again, a somewhat unusual response for a patient to have so little relief as compared to other similar deliveries). Moreover, the cervix was only dilated to about 4 cm and the delivery appeared to be progressing was quite slowly. The nurse midwife elected to wait a little longer before administering more medicines, but after 30 minutes Ms. Smith was concentrating less and less on the impending delivery and more and more on the unrelieved pain. At this point, the nurse midwife ordered morphine sulfate and promethazine (PHENERGAN[®], Wyeth Pharmaceuticals) for additional pain relief and comfort. Again, the usual doses of medicines for such cases provided relatively little relief. After another hour of ever increasing and more excruciating pain and little progress, the nurse midwife called her obstetrician colleague and an anesthesiologist for assistance and the placement of an epidural (regional nerve block) for better pain control. After placement of the regional anesthetic, it appeared to the team that some of the discomfort the patient was experiencing was in part resulting from the tissue tension and stretching. The patient required another small dose of morphine and promethazine and then delivered a term baby with some mild depression believed secondary to the narcotic and antihistamine.

This hypothetical case should remind health care providers that pain (I) occurs during "normal" (for example, delivery) as well as "abnormal" (for example, diseases or traumatic injuries) body function processes; (II) that it can be anticipated or unanticipated, expected or unexpected; (III) that it is completely subjective to the individual patient; and (IV) that autonomous patients are at liberty to change their minds about available treatments and interventions as time goes on. It would seem quite awkward-some might say ludicrous-for a physician or a pharmacist in the delivery room (or operating room, recovery room, intensive care unit, or emergency department, or an outpatient setting for that matter) to engage in some sort of disagreement or argument with a patient or the patient's legally authorized representative about the nature, character, degree, or duration of pain symptoms. At least initially, one would think it might be best to give the patient the benefit of any doubt and treat pain symptoms for resolution until more information is available.

This case allows opportunity to discuss the ethical nature of the mother-fetus treatment unit and the doctrine

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of proportionality. Some may be reluctant to offer the pregnant patient treatments that might be considered injurious to the fetus. Undoubtedly there are some medicines that may be administered during the childbirth process or pregnancy that might "harm" the unborn child (for example, magnesium sulfate administered to slow the delivery will cause neonatal hypotonia and may negatively impact neonatal respiratory efforts). But usually, the care team defers to the mother for informed consent with little other question except to more fully understand that any consent or refusal truly is *informed* (that is, that the mother understands the risks to the fetus and the possible ill effects on the child after birth). Perhaps a more extreme example might be considered: the pregnant woman who has been diagnosed with cancer and the contemplated or proffered chemotherapy will unquestionably harm the fetus or endanger the pregnancy itself. Even more conservative ethical reflection-as expressed in the Ethical and Religious Directives for Catholic Health Care Services adopted by the United States Conference for Catholic Bishopsunderstands the implications on the mother-fetus unit and the mother's unique position to give informed consent:

"Operations, treatments, and medications that have as their direct purpose the cure of a proportionately serious pathological condition of a pregnant woman are permissible when they cannot be safely postponed until the unborn child is viable, even if they will result in the death of the unborn child [United States Conference of Catholic Bishops, 2001]."

Hypothetical case 3

Josiah Quincy is three years old; he was diagnosed with neuroblastoma at eight months of age when he presented to his doctor for a well-child examination and an abdominal mass was identified. At the time of diagnosis, cancer cells were seen in his bone marrow. He received treatment at a world-class children's research and teaching hospital with a new "up-front" chemotherapy regimen which included irinotecan and gefitinib with sixteen months of maintenance chemotherapy after stem cell transplant with alternating oral 13-cis-retinoic acid and topotecan (the drugs were an experimental protocol offered to fewer than 25 children). Unhappily, the cancer has progressed. The caregivers believe the child remains in continuous discomfort and pain and is irritable and fretful almost all the time. He gets very little restful sleep. His irritability and pain are relieved temporarily or short-term with increasing doses of morphine by intravenous drip. He is taking less and less food and liquids by mouth. His parents have allowed artificial feedings with a naso-gastric tube in the past, but now refuse because they believe the tube causes more discomfort and the patient has abdominal distention and loose stools. He has just been admitted to the hospital for a fever of 39 °C and better pain control. He is somnolent with the narcotics and near coma, but still appears fretful and uneasy even when asleep. His parents are asking his attending physician and hospital's clinical pharmacist now about "terminal sedation" as a pain relief option.

This hypothetical case with such sad and unfortunate facts offers opportunity to think about: (I) the "goals of medicine" more completely; (II) medical futility; (III) surrogate decision making and the role of surrogate decision makers in assessing pain and discomfort; (IV) the doctrine of double effect; and (V) "terminal sedation".

Hippocrates was reported to have said that it is the "master physician" who learns the signs and "refuses to treat those patients over-mastered by their illness" [Hippocrates, 1950]. It is not an accepted goal of medicine to continue to treat in order to achieve a cure when a "cure" is no longer possible. Similar in thought to Hippocrates "master physician" characterization is an aphorism attributed to the French tuberculosis sanatorium physician Edward Trudeau in the 1800s: "To cure sometimes, to relieve often, to comfort always" [Cayley, 2006]. The word *comfort* is derived by joining the two Latin words *cum* (meaning "with") and *fortis* (meaning "strength"); to comfort is to "come along side with strength." At the end of life, maybe all caregivers can do is to come along side of the patient and give some meager strength, support, and comfort.

To treat for a cure when a "cure" is no longer possible may be one definition of medical futility. Philosopher Mark Wicclair has suggested that a medical futility intervention situation occurs in three instances, when treatment: (I) is physiologically impossible; (II) "will not achieve the goals of the patient"; and (III) is one in which "there is no reasonable chance [the proposed treatment] will achieve any goals that are consistent with the rules of professional integrity" [Wicclair, 1996]. In the hypothetical case, it seems that the most appropriate medical intervention is comfort care (with as many pain medicines as are necessary to relieve symptoms), particularly when the artificial feedings previously tried now might cause more discomfort or burdens than give benefit (that is, the burdens outweigh the benefits, more harm results from the attempts to do good).

In this case, the caregivers and parents believe that the

patient is clearly dying and appears septic. The parents request as much pain medicine as needed to keep the child comfortable. Few would doubt the parents' moral authority to better judge their child's condition and symptom level, but if there is concern it should be addressed calmly, compassionately, and deferentially. Some pharmacists and physicians might hesitate in providing higher and higher doses of morphine in this instance because of the fear of respiratory depression and death. The doctrine of double effect in the ethics literature—as described in Jonsen-Siegler-Winslade's *Clinical Ethics*—might offer those at the bedside some consolation:

"The principal of double effect recognizes that, occasionally, persons are faced with a decision that cannot be avoided and, in the circumstances, the decision will cause both desirable and undesirable effects. These effects are inextricably linked. One of these effects is intended by the agent and is ethically permissible [for example, treating severe pain], the other is not intended by the agent and is ethically undesirable [for example, respiratory depression and death]. Roman Catholic medical ethics employs this argument to justify clinically appropriate pain medication for relief of pain, even if the unintended foreseen effect is the shortening of the patient's life [Jonsen *et al.*, 2002]."

"Terminal sedation" is used to provide comfort and pain control to patients at the end of life when other treatment modalities have failed [Orentlicher, 1997]. Terminal sedation in this context is described in the reference *Pain Management in Children with Cancer* published by Texas Children's Hospital and Baylor College of Medicine:

"In very rare circumstances, children may experience such unrelenting pain or other symptoms, that the need for sedation may be considered. Sedation is generally indicated when pain and distress cannot be controlled by any other means either due to limited timeframe or risk of excessive morbidity. The health care professional must determine what are truly uncontrollable pain or symptoms versus under-treated pain and/or symptoms. It is important that prior to considering sedation, all efforts have been made to achieve pain and symptom control.

Sedation must not be confused with euthanasia. Euthanasia refers to the active intent by another person to end a terminally ill person's life for the sake of compassion or mercy [Hockenberry-Eaton *et al.*, 1999]."

Hypothetical case 4

Mr. Williams, a ninety-six year old retired policeman and

Part I

part-time Methodist minister who lives in Portland, Oregon, has colon cancer that has metastasized to his lumbar vertebrae. The severe back pain he experiences is controlled with liquid morphine, liquid DOLOPHINE® (methadone, Roxane Laboratories Inc.), and a DURAGESIC® (fentanyl, Janssen Pharmaceutica) transdermal patch. The patient is enrolled in a hospice program. Because, terminallyill Oregon residents may avail themselves of physicianassisted suicide under the authority of the Oregon Death with Dignity Act, Mr. Williams received a prescription for 100 SECONAL[®] (secobarbital, Ranbaxy Pharmaceuticals Inc.) from his oncologist. When filled, the directions on the prescription label were to read: "Take as directed. Prescribed per Oregon Assisted Suicide Law." When the prescription was presented at the pharmacy counter, Mr. Williams' pharmacist and life-long friend, John Able, took Mr. Williams aside to the private counseling station and quietly informed the patient that he-"in all good conscience"-could not fill the prescription because he believed that he would be a party to a "murder." Mr. Williams said, "John, you're a good friend-I understand." The patient left the pharmacy with the prescription. Within minutes though, three of Mr. Williams' granddaughters demanded to see Mr. Able, loudly calling him a "heartless bastard" in front of other patrons and pharmacy staff before he even had opportunity to say hello.

Oregon has permitted physician-assisted suicide since 1998 [Egan, 1998]. Between 1994 (when Oregonians first voted to approve Ballot Measure 16—the Death with Dignity Act or DWDA—by public referendum) and 1997 (when Oregon voters re-approved the law as Ballot Measure 51), there were several federal and state attempts to overturn the law and prevent its going into effect [White, 2007]. (Some might say that it was the 2006 US Supreme Court decision—Gonzales vs. Oregon—that finally settled the matter conclusively) [Greenhouse, 2006].

According to the 2007 official report [Oregon Department of Health Services, 2007], 341 persons have received drugs to have available to take their own lives since the practice began:

"During 2007, 85 prescriptions for lethal medications were written under the provisions of the DWDA compared to 65 during 2006. Of these, 46 patients took the medications, 26 died of their underlying disease, and 13 were alive at the end of 2007. In addition, three patients with earlier prescriptions died from taking the medications, resulting in a total of 49 DWDA deaths during 2007. This corresponds to an estimated 15.6 DWDA deaths per 10,000 Part I

total deaths."

Thus, the law appears to be settled public policy in Oregon regardless of what those who oppose assisted suicide personally think about the ethics or "rightness" of the issue. It would not seem proper for anyone to characterize a death from a self-administered lethal dose prescribed under the law as a murder or otherwise unlawful death. The law sanctions the autonomous decision of a terminally ill patient to die pain-free and in control [Schmidt, 2007]. The law similarly respects the right of Oregon health care providers-of course, including pharmacists-not to participate in the process if they do not wish to do so [Schnabel and Schnabel, 2007]. It remains to be seen how far this policy might extend into other states; but to date Washington, Montana, and Vermont have adopted DWDA-like physician-assisted suicide schemas for terminally-ill patients.

This case shows how a pharmacist may as a *conscientious objection* opt not to fill a lethal—and legally prescribed—order for a terminally ill patient under the law:

"Conscientious objection arises from the concept that people are not obligated to perform acts that violate their conscience, even if the acts are legally or professionally sanctioned. Conscientious objection by health care professionals is a principle that is upheld by professional codes of ethics, for example, the refusal of a nurse to participate in an abortion done in a hospital. The Oregon Death with Dignity Act endorses conscientious practice and respect by stating unequivocally: "No health care provider shall be under any duty, whether by contract, by statute or by any other legal requirement to participate in the provision to a qualified patient of medication to end his/her life in a humane and dignified manner" [Dunn *et al.*, 2007]."

Pharmacists are under no legal or ethical obligation to fill every prescription that is presented at the counter. In fact, it is in their financial best interests to fill as many prescriptions as possible since pharmacy income is generated typically on a per prescription-filled basis. However, pharmacists may not illegally or unethically discriminate between prescriptions to be filled or not. Refusals to fill prescriptions should be just, fair, impartial. One dictionary definition of *justice* is "upholding... what is just, especially fair treatment and due reward in accordance with honor, standards, or law" [Soukhanov, 1992]. Examples of decisions not to fill prescriptions then may turn on: *law* (for example, the pharmacist may believe that the prescription was written by a practitioner outside the "course of professional practice" or for a reason other than a "legitimate medical purpose") [Drug Enforcement Administration, 2004]; *standards* [for example, the pharmacist may believe the dose of the ordered medicine is too high and might risk injury (malpractice standards) or because the pharmacy does not participate in the patient's insurance or prescription reimbursement plan (business standards)]; or *bonor* (for example, a conscientious objection).

This hypothetical case includes another ethical issue for pharmacist Able: communication of confidential information or invasion of privacy associated with meeting professional obligations. It is unfortunate that the patient's granddaughters had the conversation they did with the pharmacist. However, Able perhaps should just say: "I'm unable to talk with you about this." Further conversation risks violating confidence or invading Mr. Williams' privacy. Any medicines that Able fills or does not fill for a patient is a private professional matter and should not be discussed with others outside the pharmacist-patient relationship unless authorized by the patient or law, standards, or honor.

Summary

Any chapter written as a survey of the field of ethics to be included in a book about a healthcare professional's role in quality pain management is sure to omit material that may be important to address if used to attempt resolution of specific dilemma. In this vein, the chapter would have much in common with professional codes of ethics, works by noted bioethicists, and casebooks more generally. There are some questions not easily answered or dilemmas not comfortably or effortlessly resolved. Ethical dilemmas are by their very nature not settled without difficulty, sometimes many difficulties. Ethics too is a personal field of study and resolutions may depend on the unique qualities of the decision maker(s) as well as a particular set of facts.

In this regard, ethics differs in many respects from the law. Law is intended to have universal application and set minimum standards of behavior. Resolution of ethics dilemmas is done case-by-case; ethics attempts to set an ideal or aspirational standard of conduct. However standards in law may at times be more rigorous and demanding because they are enforceable by the community and thus carry penalties for noncompliance. For example health care law professor Barry R. Furrow has written: "Failure to properly manage pain—to assess, treat, and manage it—is professional negligence" [Furrow, 2001].

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Healthcare ethics and pain management

The number of ethics dilemmas about pain management that physicians and pharmacists will face in the future is certain to increase: newer agents with greater benefits and undeterminable burdens will be synthesized or identified; different professional and legal standards of conduct will evolve; and the delivery of health care will continue to transform as it becomes more interdisciplinary and costly. However, ethical principles and philosophical values like beneficence, nonmaleficence, autonomy, and justice if for no other reason than the fact that good persons have had to deal with moral problems since civilization began will continue to vex compassionate, caring professionals in theory and practice.

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Advance care planning

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Introduction

Death is the final chapter of life. Death is not medical failure, as it has become viewed over the last century. What would happen if you experienced a sudden illness that prevented you from making your own medical decisions? Would your family or loved ones know enough about what you value and believe to feel comfortable making decisions about your care?

Advance care planning is a process of planning for both death and any potential loss of capacity to make medical decisions, such as in the face of acute illness or injury with potential recovery. Planning for incapacity to make medical decisions is a gift to self, family, loved ones and health care professionals who provide care in the future. Advance care planning discussions should begin prior to a crisis, with a commitment to review and update plans as values, beliefs and personal goals for care change with time, after major life events, and with new life-threatening or chronic illnesses. When done well, advance care planning represents preventive ethics.

When advanced chronic illness is accompanied by frailty near the end of life, shared, informed medical decisionmaking is the essence of the advance care planning process. The Physician Orders for Life-Sustaining Treatment (POLST) Paradigm is a clinical process designed to facilitate communication between health care professionals and patients with advanced illness (or their authorized legal representatives) that facilitates shared, informed medical decision-making. The result is a set of portable medical orders, documented on a single form, that is applicable in all settings and across care transitions, are reviewable, and respects the patient's goals for care regarding the use of cardiopulmonary resuscitation, intubation and mechanical ventilation, hospitalizations and other life-sustaining treatment interventions.

important. t Advance care planning: key element of future care planning

Advance care planning is a key pillar of palliative care. Palliative care is interdisciplinary care that is offered simultaneously with all other appropriate medical treatment from the time of diagnosis. Palliative care combines the art and science of medicine, focuses on quality of life and provides an extra layer of support for patients with advanced illness and their families. High quality medical care is more than supplying appropriate, timely medical interventions without error. Quality medical care is compassionate, person-centered care that respects an individual's wishes, values, and beliefs. This is more difficult when the person requiring care is unable to communicate his or her own wishes, which is often the case in end-of-life care.

Ensuring accessibility and reviewing advance care plans in the form of advance directives and/or medical orders

for life-sustaining treatment when appropriate, is critically

Simply put, advance care planning is a process of planning for future medical care in the event the individual loses the ability to make medical decisions. It is most often associated with planning for death and the end of life. However, it is also about planning for potential loss of medical decision-making capacity as a result of acute injury or illness where there is the possibility of death or recovery. In this larger context, individuals can be engaged to initiate advance care planning discussions earlier, at a time when it may be otherwise difficult to face the possibility of death, but easier to consider the possibility of an accident or other acute event where prior advance care planning would also be essential. Framed as a wellness initiative, attention is focused on the importance of choosing a trusted individual to make decisions in the event of incapacity and assessing personal values, beliefs and goals for care, as recovery may present itself in many ways. The choice of interventions may vary, based on what may be expected in the face of recovery. Individual values, beliefs and personal goals for care should guide the choice of interventions and should be made by the individual's trusted spokesperson.

Advance care planning is a key element of future care planning. Other domains are equally important such as legal, financial, practical issues, and importantly, healing and closing relationships. Recognizing the value and interrelationships of the key elements of future care planning provides support to other professionals (attorneys, financial planners, etc.) to encourage individuals to complete advance care planning as part of a natural future care planning process.

A patient's perspective on future care planning: setting affairs in order

Because of my diagnosis of terminal cancer, I have been given an opportunity to reflect on end-of-life issues. In one sense, I have been given a gift. I have had the chance to set my affairs in order, down to the last detail, including requests and instructions to be made of loved ones my death. I have had the chance to write out loving, caring notes to my family and friends, and I have been able to plan for circumstances I may not have otherwise planned for, such as what will happen to my beloved cat. Bank accounts have beneficiaries, and a real estate agent has already been notified, and is prepared to offer care and support to my family as my home is prepared to be sold. I have thought about what will happen to my care, who will call my valued clients, and how everyone will be notified.

Regarding the specifics of advance care planning, I have spoken to my parents and beloved friends about end-of-life wishes and care, including my wishes not to be a burden, to work with hospice and palliative care nurses, and to accept that we will not take extreme measures to prolong my life if we see that the time has come. My family and friends understand and support my belief that death is not the end, and we are looking at this event not as a tragedy but as a closing of one chapter and beginning of another. It has been important to me to document my wishes in writing so my loved ones will be reassured when the time comes. I continue to hope to have deeper conversations with my treating doctors about what to expect physically and what wisdom they have, medically and beyond, that will help this process. Some would find this level of planning almost macabre, or perhaps, jinxing my good fortune, which is that I have already lived longer than expected. From my point of view, making detailed arrangements "for when" has given me peace of mind. I do not have to worry about these particulars anymore, and I have a sense of peace in knowing that I have made things easier for my loved ones, who have provided such unconditional support and compassion, and whose positive energy has carried me through.

I know it can be a challenge for caregivers to approach the issue of end-of-life care. In my experience, these conversations hold the potential to deepen the patientcaregiver relationship. A gifted doctor said to me, at the end of one appointment, "You should be able to ask me anything." That is truly a beautiful thing for a caregiver to say. If a patient comes in saying, "I'm worried about what's going to happen to my dog after I die," that is an opportunity to talk about end-of-life concerns in a way that is meaningful and healing for the immune system of a patient.

The Palliative Care Study, which appeared in the New England Journal of Medicine [Temel *et al.*, 2010], confirms that patients receiving early palliative care report better quality of life. Palliative care is defined as bringing pain relief and comfort to a patient on a physical, emotional, and spiritual level. Talking about sensitive end-of-life issues can in itself be deeply palliative. A patient can feel relieved in unburdening himself and in knowing there is plan in place. Caregivers can help with this by gently walking a patient through the specific medical issues that may arise.

Recently, in presenting my ideas to the medical community, I said that when my time comes, I want my doctors to go radically positive and say, "We are glad to have worked with you, and we will help you have a good and peaceful death." Isn't that one of the deepest gifts of palliative care? Knowing that our doctors will help us in our greatest moment of need can give us a sense of solace that is, in itself medical [Webster, 2013].

Current state

Compassionate care for dying patients is a social obligation that is not adequately met. Over the past century, death has transformed from a natural experience in the home surrounded by family and loved ones to a medical event in a hospital, where death is often considered a medical failure, rather than the inevitable final chapter of the individual's life [Institute of Medicine, 2013]. Many people approaching death fear isolation, abandonment and suffering. Gaps exist between patient and family wishes and current practices. Further discrepancies exist between an individual's desire to discuss their preferences for end-of-life care and the initiation of such discussions by physicians and other clinicians. Too often, discussions do not occur until a crisis when the individual is unable to voice their goals and preferences for care. For example, one study found that approximately 42.5% of people age 60 and older who were near the end of life required medical decisions to be made before death. Of those individuals, 70.3% lacked medical decision-making capacity [Silveira *et al.*, 2010]. These figures demonstrate the frequency with which people lose capacity, particularly when they are seriously ill or near the end of life. Early advance care planning is essential for everyone.

In order to combat entrenched problems with endof-life care, the Institute of Medicine (IOM) launched a project on Transforming End-of-Life Care [Institute of Medicine, 2013]. An ad hoc consensus committee of the IOM will review progress since the landmark IOM 1997 report Approaching Death: Improving Care at the End of Life, stated that end-of-life care must improve on all levels [Institute of Medicine, 1998]. The IOM plans to examine the current state of end-of-life care with respect to delivery of medical care and social support; patient-family-provider communication of values and preferences; advance care planning; health care quality and financing; and education of health professionals, patients and their loved ones [Institute of Medicine, 2013]. The overall objectives of the project are to advance policies that will improve the care patients and their families receive at the end of life by better aligning that care with individual values and preferences and to stimulate a national conversation involving individuals, families, and communities on improving the way we approach death.

Variation exists in the current approach to advance care planning across the United States and internationally. However, several key elements are consistently highlighted, including:

- identification of a designated trusted spokesperson, if the person loses the ability to make medical decisions;
- recognition that the person's values, beliefs and goals for care may change with time;
- the value of early discussions among persons, their families, their loved ones and their health care providers; and
- an ethical framework for medical decision-making that is founded in the principles of professionalism.

With respect to end-of-life care, years of research in the

United States have demonstrated that there are variations in the type of care delivered to patients as they near death including the utilization of hospital vs. home-based care, and the choices people make about life-sustaining treatments. These variations do not typically translate into better quality of care or lower mortality rates. In fact, there are some data to suggest that people who live in regions where less-intensive treatments are the norm in the last six months of life do not die any earlier than those living in areas where high-intensity treatments are common [The Dartmouth Atlas of Health Care, 2013]. Given this apparent unwarranted variation in end-of-life care, clinicians need a systematic approach to advance care planning respecting the psychosocial and spiritual needs of a diverse society, characterized by disparate medical and social circumstances, varied cultural values and beliefs, and differing preferences for end-of-life care.

Basic process element for general population

In 1990, Terri Schiavo, age 26, entered a vegetative state for undetermined reasons and remained in this persistent vegetative state for the last fifteen years of her life. Her personal physicians and court-appointed physicians expressed the opinion that there was no hope for recovery or rehabilitation. Schiavo's parents, Bob and Mary Schindler, refused to accept the medical opinions, feeling that their daughter would somehow recover. Her husband, Michael Schiavo, contended that it was his wife's wish that she not be kept alive through unnatural, mechanical means. The conflict could not be resolved informally through conflict resolution process or the hospital ethics process. As a result, the Schiavo case was heard in Florida courts more than twenty times. Schiavo's parents repeatedly refused to accept the verdicts. On all occasions the court ruled that Terri's fate was under her husband's control. Schiavo's feeding tube was finally removed on March 18, 2005, and she passed away 13 days later [Wikipedia, 2013; The Boston Globe, 2005].

The widely publicized case of Terry Schiavo supports the recommendation that everyone 18 years and older should be encouraged to complete a health care proxy and engage in advance care planning discussions with family, loved ones and health care providers.

Globally, advance care planning is recognized as a process, not merely a form. Similar basic elements of advance care planning are addressed including: appointing the right medical decision-maker (also known as a health

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Formally designating a person to speak for you about your medical care should you become unable to speak for yourself is called designating a health care proxy. The best way to designate the person to speak for you is to conplete a Health Care Proxy form. Which answer best describes your level of readiness to fill out a Health Care Proxy form?

I see no need to fill out a Health Care Proxy form.
(Stage I—Precontemplation)
I see the need to fill out my Health Care Proxy form, but I have barriers or reasons why I have not done it.
(Stage II—Contemplation)
I am ready to fill out a Health Care Proxy form or I have already started.
(Stage II—Preparation)
I already filled out my Health Care Proxy form and it reflects my wishes.
(Stage IV—Action)
I already filled out my Health Care Proxy form but it needs to be changed.
(Stage V—Maintenance)

Figure 1 Behavioral readiness to complete a health care proxy [Bomba and Vermilyea, 2006].

care agent, health care proxy, durable power of attorney for health care, or surrogate); discussing person-centered values, beliefs, and goals for care; recognizing the value of beginning discussion before a crisis occurs; acknowledging the problems with a living will; accessibility to documented discussions and formal legal advance directive documents; and finally, reviewing and updating the basic elements periodically.

The process of advance care planning should begin early with proactive discussions of personal values, beliefs and goals of care and deciding who is best suited to serve as the medical decision-maker, in the event that medical decisionmaking capacity is lost. Conversations among families, loved ones, close friends, as well as with physicians and other health care providers, should focus on open, honest discussions, employing active listening communication skills and compassion. Discussions may be difficult for many people; conversation of this type may conflict with personal values, beliefs, and cultural traditions. Starting the process early establishes trusting relationships among family, close friends, health care professionals and others who will care for or be with the individual in the face of incapacity due to acute illness, injury or impending death. Advance care planning reduces the potential for conflict. Peace of mind is achieved for the individual and family by reducing uncertainty and helping to avoid confusion and conflict over care and treatment preferences. Completion of legal documents codifies the process and the individual's preferences at a specific period of time.

Advance care planning should be framed as a wellness

initiative, as anyone may face a sudden and unexpected acute illness or injury with the potential risk of losing the capacity to make medical decisions. Behavioral change theory has been used to effect change with other wellness issues, such as smoking cessation. Assessing an individual's readiness to participate in advance care planning discussions can help focus discussion and interventions on the stage of change to help individuals engage in the process.

Assessing behavioral readiness for advance care planning

The Stages of Change theory recognizes behavior is too complex to systematically and consistently respond to one type of intervention [Prochaska and DiClemente, 1984; Prochaska and DiClemente, 1985; Prochaska and Goldstein, 1991]. The transtheoretical model of change provides a framework for behavior change that can be applied to encouraging advance care planning. Individuals who are successful in adopting change follow an unwavering sequence of activities and attitudes prior to finally changing an undesirable lifestyle. To improve effectiveness, interventions on encouraging advance care planning discussions can be focused and linked with the stages of change. To be effective, counseling should include key elements of the advance care planning process and be individualized according to the patient's current condition and behavioral readiness to complete an advance directive, as exemplified in Figure 1 [Bomba and Vermilyea, 2006].

Using behavioral change and the stages of change, the Health Care Proxy Readiness Survey was developed in
2002 to assess the success of Community Conversations on Compassionate Care (CCCC) a community educational workshop on advance care planning [Bomba *et al.*, 2013]. In Stage 1 (precontemplation), the person sees no need to complete an advance directive; interventions focus on providing educational information about advance directives. In Stage 2 (contemplation), the person sees the need to complete an advance directive but has barriers or reasons why the advance directive is not done; interventions identify patient barriers and assist in removing them. Barriers may include:

- I do not know enough about it; I do not know what it is;
- It is not important;
- I do not want to think about it; I do not want to discuss it;
- I do not have enough time;
- I do not know how to bring up the subject with my family;
- It is too difficult.

In Stage 3 (preparation), the person is ready to complete an advance directive or has already started; interventions focus on motivating the patient. In Stage 4 (action), the person has completed an advance directive that reflects personal values and wishes. In that case, discuss patient values and preferences, encourage family discussion, assess the appropriateness of the designated medical decisionmaker and obtain a copy of the advance directive. Stage 5 (maintenance) reflects the need to review and update advance directives. With measurable success, as demonstrated in a 2008 survey, additional educational resources developed for the CCCC program focus on behavioral change [Excellus BlueCross BlueShield, 2008].

Designating the right medical decisionmaker

Medical decision-making can be problematic for health care providers if a patient loses the capacity to make medical decisions and there is no documentation that the patient has designated a surrogate to make decisions on his or her behalf. Decisions regarding medical treatments may be made that are not consistent with the patient's values, beliefs or preferences.

Traditional advance directives like the health care proxy focus on designating the right medical decision-maker who will make decisions in accordance with the person's current values and beliefs.

The medical decision-maker should know the person

well, understand what the person values, be willing to talk about sensitive issues and be willing to listen. In addition, the designated medical decision-maker must be willing to speak and act on behalf of the individual, separating their personal values from the individual's values as part of any future medical decision-making process. The medical decision-maker should be available in the future; thus, the medical decision-maker should live close by or be willing to come. Most importantly, the medical decision-maker must be able to handle the responsibility of working with health care providers during periods of crisis and be able to handle potential conflicts between family, loved ones and the health care team.

Discussing values, beliefs and goals for care with family, loved ones and physicians

The strongest predictor of satisfaction with care is the presence of advance care planning discussions [Tierney et al., 2001]. Elderly patients with chronic illnesses who discussed advance directives with their primary care physicians show significantly greater satisfaction with their care than those who did not have advance care planning discussions [Tierney et al., 2001.] There is an association between completion of an advance directive and greater hospice use, as well as fewer problems with physician communication, as shown in a retrospective study of over 1,500 decedents and their bereaved family members [Teno et al., 2007]. Unfortunately, physicians are often unaware of patient preferences for end-of-life care; when preferences are known, they may not have been communicated to the family. As a result, the care provided is often inconsistent with patient preferences and associated with factors other than preferences or prognosis [Covinsky et al., 2000]. Several tools are available to help patients explore feelings about end-of-life care, such as the questionnaire shown in Figure 2 [Bomba and Vermilyea, 2006].

While variation may exist in the approach to advance care planning, discussions about death, dying and end-oflife care among different cultural, religious, spiritual and sociodemographic groups, individual variation exists within such groups and the unique preferences of the individual must be ascertained. Thus, it is important to ask the person about their personal values, beliefs and goals for care and avoid making invalid assumptions.

In summary, advance care planning discussions with the patient and family unit designated by the patient should include person-centered goals for care, treatment options Instructions: for each row, check one answer to express how important these issues would be to you if you were dying.

	Not import	Moderately	Very impor	Extremely
	ant	/ important	tant	mportant
Avoid pain/suffering, even if means that I might not live as long				
Being alert, even if it means I might be in pain				
Being around my family and close friends				
Being able to feel someone touching me				
Having religious or spiritual advisors at my side when I die				
Being able to tell my life story and leave good memoriea for others				
Reconciling differences and saying "goodbye" to my family and friends				
Being at home when I die				
Being in a hospital when I die				
Being kept alive long enough for my family to get to my bedside to see				
me before I die, even if I'm unconscious				

What are some of the things that you would hope for that could make your last weeks, days or hours the most peaceful?

What are your biggest hopes about the end of your life?

What are your biggest fears about the end of life?

Figure 2 Exploratory questions to elicit patient feelings about end-of-life care. The information contained within this page is from © EPEC Project, The Robert Wood Johnson Foundation, 1999.

and the preferred setting to receive care.

Problems with the living will

While completion of traditional advance directives is recommended, communicating end-of-life care wishes solely using the living will has proven insufficient. The living will applies to future circumstances, require further interpretation by the designated medical decision-maker and medical providers and do not result in actionable medical orders. The situation is further complicated by the difficulty in defining "terminal" or "irreversible" conditions and accounting for the different perspective that the physician, the medical decision-maker and loved ones may have of the clinical situation. For example, a patient with dementia nearing the end of life eats less, has difficulty managing secretions, aspirates and often develops pneumonia. While end-stage dementia is "terminal," pneumonia may be potentially "reversible." Decisions regarding care depend on interpretations of prior conversations, physician's estimates of prognosis, and, possibly, the personal convictions of the physician, medical decision-maker and loved ones. The presence of the living will does not help clarify the patient's wishes in the absence of antecedent conversation with the family, close friends and the patient's personal physician. Increasingly, individuals are being counseled that appointing a medical decision-maker is a best practice due to the clear limitations of the living will as an advance care planning tool.

In addition, legal documents cannot account for every circumstance. Therefore, the designated medical decisionmaker, family and loved ones need to know the patient's values, beliefs and goals for care and general wishes for the end of life. Such knowledge is best attained through open conversations. Completed advance directives should

Advance care planning

be reviewed by the physician to ensure they are completed accurately, comply with applicable public health law and are consistent with patient wishes.

Practical issues

Accessibility

Accessibility of completed advance directives is an important measurable outcome of the process, but should not be viewed as a substitute for conversations. Easy access to completed legal documents ensures prompt decisionmaking and helps to prevent undesirable outcomes.

Periodic review and update

Advance directives need ongoing reassessment and periodic updates. After major life events like marriage, divorce, birth of a child, death of a spouse, the patient may wish or need to choose a new medical decision-maker. Person-centered goals for care and preferences may change as chronic illness progresses and after patients receive complicated lifesustaining treatments.

While traditional advance directives provide a vehicle for conveying patient preferences for treatment when a patient is incapacitated, all possible clinical scenarios and potential treatment options cannot be included in an advance directive. Therefore, patient values, beliefs and goals for care, treatment options and setting of care should be reviewed and documented at first assessment and at frequent intervals as conditions change [Fischer *et al.*, 2000].

Essential process elements for persons with advanced illness

An 85-year-old gentleman is admitted to a nursing home after a hospitalization for a massive stroke with resulting hemiplegia and aphasia. He is bed-bound, requires total care, has reduced oral intake and is noncommunicative. His palliative performance scale is estimated at 30 and his life expectancy is estimated to be less than six months. The attending physician determined the patient lacks medical decision-making capacity and that the incapacity is expected to be permanent.

He has no prior advance directives and lacks capacity to choose a medical decision-maker. His daughter is appointed in accordance with state law as his surrogate. His daughter indicates if her father were able to speak, he would wish to focus on aggressive comfort measures. After a thoughtful discussion ensuring shared, informed medical decisionPart I

making and focusing on comfort as the patient-centered goal for care, the daughter indicates her father would prefer to allow a natural death and requests a Do Not Resuscitate (DNR) order. Guidelines for life-sustaining treatment and other treatment options are reviewed. In keeping with the goal of achieving maximal comfort, the patient's daughter expresses a wish to forego intubation and mechanical ventilation, refuses a feeding tube and intravenous fluidsrequesting that food and fluids be offered using careful hand feeding, and asks that her father not return to the hospital unless pain and symptoms cannot be otherwise controlled at the nursing home. The physician completes and signs the POLST form. The care plan is designed to support the patient's goals for care and the medical orders, as outlined on the POLST form. Staff are made aware of the patient's goals for care, POLST orders and care plan.

POLST paradigm®

POLST: a new approach to end-of-life care

Since passage of the Patient Self-Determination Act in 1990 in the United States, the current system of communicating end-of-life wishes solely using traditional advance directives, such as the living will, has proven insufficient [Patient Self-Determination Act of 1990]. A growing body of literature supports the efficacy of the POLST approach in honoring and communicating patients' wishes [Dunn *et al.*, 1996; Tolle *et al.*, 1998; Lee *et al.*, 2000; Hickman *et al.*, 2004; Hickman S, 2010].

The POLST Paradigm Program, known by a variety of names in different states, is a clinical process designed to facilitate communication between health care professionals and patients with advanced illness (or their designated medical decision-maker) that facilitates shared, informed medical decision-making. The result is a set of portable medical orders documented on a brightly colored form (*Figure 3* POLST form) that is applicable in all settings and across care transitions, is reviewable, and respects the patient's goals for care regarding the use of cardiopulmonary resuscitation, intubation and mechanical ventilation, hospitalization and other life-sustaining interventions.

POLST vs. traditional advance directives

POLST is different from traditional advance directives (like the health care proxy or living will) because while traditional advance directives are for everyone, POLST is only appropriate for people who meet one of the following criteria:

HIDA				ECISTRY A	SNECESSA		ATMENT
THE AV	Bhygigign Orders for I	ifo Suctoi	ning T	rootm	ont (D		
Follow th	riysician orders for L	Patient Last Name	ning i		atient First Na	ame	Middle Int.
medical of complete treatmen condition	ed does not invalidate the form and implies full to does not invalidate the form and implies full to for that section. With significant change of n new orders may need to be written.	Date of Birth: (mm/	dd/yyyy)	Gender:	F	Last 4 SS	
For more	e information on Oregon POLST visit:	Address: (street / c	ity / state / zi	p)			
<u>www.orp</u>	CARDIOPUL MONARY RESUSCITA	TION (CPR):	Patient	has no n	ulse and i	s not brea	əthina
A	CARDIOPOLIMONARY RESUSCITATION (CPR). Patient has no pulse and is not breathing. Check One Do Not Attempt Resuscitation/DNR						iunig.
Спеск One							
	When not in cardiopulmonary arrest, follow	w orders in B and	C.				
B	MEDICAL INTERVENTIONS: If patient has pulse and/or is breathing.						
Check One	Comfort Measures Only (<u>Allow Natural Death</u>). Relieve pain and suffering through the use of any medication by any route, positioning, wound care and other measures. Use oxygen, suction and manual treatment of airway obstruction as needed for comfort. <i>Patient prefers no transfer to hospital for life-sustaining treatments</i> . <i>Transfer if comfort needs cannot be met in current location</i> . Treatment Plan: Maximize comfort through symptom management.						
	Limited Additional Interventions medical treatment, antibiotics, IV fl airway interventions, or mechanica CPAP, BiPAP). <i>Transfer to hospit</i> Treatment Plan: Provide basic methods.	In addition to ca uids and cardiac al ventilation. Ma al if indicated. Ge nedical treatme	re describe monitor as consider enerally av	ed in Con s indicate less inva oid the in	nfort Meas d. No intub sive airway tensive cal	ures Only pation, adv y support of re unit.	, use /anced (e.g.
	Full Treatment In addition to care Interventions, use intubation, adva indicated. Transfer to hospital ar Treatment Plan: Full treatment i Additional Orders:	e described in Co inced airway inte ind/or intensive ca including life su	mfort Mea rventions, re <i>unit if in</i> pport mea	sures On and mecl dicated. sures in	lly and Lim hanical ver the intens	ited Addit ntilation as sive care	onal s unit.
			Offer for	d by ma	with if food	sible	
C	ARTIFICIALLY ADMINISTERED NUTRITION: Offer food by mouth if feasible.						
Check One	 Defined trial period of artificial nutrition Long torm artificial nutrition by tube. 	n by tube.					
D	DOCUMENTATION OF DISCUSSIO	N: Care Representat	ve or legally	recogniz	ed surrogat	0	
	□ Parent of minor condition □ Court-Appointed □ Other_ □ Guardian	ate for patient with on (Note: Special I	developme equirement	ntal disab s for comp	ilities or sign pletion. See	nificant me e reverse si —	ntal health de.)
	Signature of Patient or Surrogate						
	Signature: recommended	Name (print):			Relationshi	p (write "self	" if patient):
	This form will be sent to the POLST Regi	stry unless the pa	tient wishes	to opt ou	it, if so cheo	ck opt out	box 🗌
F	SIGNATURE OF PHYSICIAN / NP/	PA					
	My signature below indicates to the best of my knowledge Print Signing Physician / NP / PA Name: requi	that these orders are co i <u>red</u> Signer	nsistent with the Phone Numl	patient's cur per:	Signer Lic	ndition and pre cense Numb	ferences. er: (optional)
	Physician / NP / PA Signature: required	Date: <u>i</u>	equired	Office L	Jse Only		
S © CENTER	END FORM WITH PATIENT WHENEVER T FOR ETHICS IN HEALTH CARE. Oregon Health & Scier	RANSFERRED OF	DISCHAR	GED, SUB Rd. UHN-86.	MIT COPY Portland, OR 9	TO REGIS	TRY (3) 494-3965

HIPAA PERMITS DISCLOSURE TO HEALTH CARE PROFESSIONALS & ELECTRONIC REGISTRY AS NECESSARY FOR TREATMENT Information for patient named on this form **PATIENT'S NAME**: The POLST form is always voluntary and is usually for persons with advanced illness or frailty. POLST records your wishes for medical treatment in your current state of health. Once initial medical treatment is begun and the risks and benefits of further therapy are clear, your treatment wishes may change. Your medical care and this form can be changed to reflect your new wishes at any time. However, no form can address all the medical treatment decisions that may need to be made. The Oregon Advance Directive is recommended for all capable adults, regardless of their health status. An Advance Directive allows you to document in detail your future health care instructions and/or name a Health Care Representative to speak for you if you are unable to speak for yourself. **Contact Information** Surrogate (optional): Relationship: Phone Number: Address: Health Care Professional Information Preparer Name: Preparer Title: Phone Number: Date Prepared: PA's Supervising Physician: Phone Number: Primary Care Professional: **Directions for Health Care Professionals** Completing POLST · Completing a POLST is always voluntary and cannot be mandated for a patient. Should reflect current preferences of persons with advanced illness or frailty. Also, encourage completion of an Advance Directive. · Verbal / phone orders are acceptable with follow-up signature by physician/NP/PA in accordance with facility/community policy. · Use of original form is encouraged. Photocopies, faxes, and electronic registry forms are also legal and valid. A person with developmental disabilities or significant mental health condition requires additional consideration before completing the POLST form; refer to Guidance for Health Care Professionals at http://www.ohsu.edu/polst/programs/documents/Guidebook.pdf. Sending to Oregon POLST Registry (Required unless "Opt Out" box is checked) For the Oregon POLST Registry the Send a copy of both sides of this POLST form to the Oregon POLST Registry. following must be completed: Date Submitted _ FAX or eFAX: _ /_ _/_ Patient's full name 503-418-2161 Date of birth MAY PUT REGISTRY ID STICKER HERE: or Section A Mail: MD / DO / NP / PA signature Oregon POLST Registry CDW-EM Date signed 3181 SW Sam Jackson Park Rd. Portland, OR 97239 Registry Phone: 503-418-4083 *Please allow up to 10 days from receipt for processing into the Registry. Mailed confirmation packets may take four weeks for delivery. Reviewing POLST This POLST should be reviewed periodically and if: · The patient is transferred from one care setting or care level to another, or · There is a substantial change in the patient's health status, or The patient's treatment preferences change, or The patient's primary care professional changes. Voiding POLST · A person with capacity, or the valid surrogate of a person without capacity, can void the form and request alternative treatment. Draw line through sections A through E and write "VOID" in large letters if POLST is replaced or becomes invalid. Send a copy of the voided form to the POLST Registry as above (required). If included in an electronic medical record, follow voiding procedures of facility/community. For permission to use the copyrighted form contact the OHSU Center for Ethics in Health Care. Information on the POLST program is available online at www.orpolst.org or at polst@ohsu.edu. SEND FORM WITH PATIENT WHENEVER TRANSFERRED OR DISCHARGED, SUBMIT COPY TO REGISTRY

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June 2011

Figure 3 Physician orders for life-sustaining treatment (POLST).

Table 1 Differences between POLST and advance directives							
Characteristics	POLST	Advance directives					
Population	For the seriously ill	All adults					
Timeframe	Current care	Future care					
Who completes the form	Health care professionals	Patients					
Resulting form	Medical orders (POLST)	Advance directive					
Health care agent or surrogate role	Can engage in discussion if patient lacks capacity	Cannot complete					
Portability	Provider responsibility	Patient/family responsibility					
Periodic review	Provider responsibility	Patient/family responsibility					

Abbreviation: POLST, physician orders for life-sustaining treatment.

- Might die within the next year;
- Resides in a long-term care facility or requires long-term care services;
- Wants to avoid or receive any or all life-sustaining treatment.

These criteria considerably narrow the population to patients who would be appropriate for POLST and intensive end-of-life discussions. A common question used by clinicians to help identify POLST-appropriate patients is: "would you be surprised if this patient died in the next year?" If the clinician would not be surprised if the patient died then they are appropriate for POLST. Other key differences between POLST and traditional advance directives can be seen in *Table 1* [Bomba *et al.*, 2012].

Completing the POLST process

Health care professionals working as an interdisciplinary team play a key role in educating patients and their families about advance care planning, in ensuring shared, informed medical decision-making, as well as in resolving conflict. Health care professionals engaging in these conversations can use the eight-step POLST protocol (*Table 2*) that provides an ethical framework to elicit patient preferences at the end of life [Bomba *et al.*, 2012].

POLST in action

Emergency medical technicians in Oregon report that the POLST form provides clear instructions about patient preferences, and is useful when deciding which treatments to provide [Schmidt *et al.*, 2004]. In contrast to the single intervention focus of out-of-hospital DNR orders, the POLST form provides patients with the opportunity to document treatment goals and preferences for interventions across a range of treatment options, thus permitting greater individualization [Hickman *et al.*, 2004]. The multi-state

study of POLST published in 2010 consisted of a stratified random sample of 90 Medicaid-eligible nursing facilities that included a comprehensive review of nursing facility residents' medical records. POLST was compared with traditional advance care planning in terms of the effect on the presence of medical orders reflecting treatment preferences, symptom management, and on use of lifesustaining treatments. The study found residents with POLST forms had significantly more medical orders about life-sustaining treatments than residents with traditional advance directives. There were no differences between residents with or without POLST forms on symptom assessment or management measures. POLST was more effective than traditional advance care planning at limiting unwanted life-sustaining treatment. The study suggests that use of POLST offers significant advantages over traditional advance directives in the nursing facility setting [Hickman et al., 2010]. Research on the POLST program confirms that it improves documentation of a range of treatment preferences and is associated with low rates of unwanted hospitalizations [Hickman et al., 2010].

POLST is spreading

POLST is now in use or in development in most areas of the United States (*Figure 4* POLST map). While the model originated in Oregon there are many examples of the program using differing names across the U.S., including New York's Medical Orders for Life-Sustaining Treatment or "MOLST" or West Virginia's Physician Orders for Scope of Treatment or "POST." The Veterans Health Administration refers to POLST documents as SAPO (State-Authorized Portable Orders) [Department of Veterans Affairs, 2012]. More information about the POLST programs and the states that are using it can be found at POLST.org. *Table 3* lists tools and resources Table 2 POLST 8-step protocol POLST 8-step protocol Prepare for discussion Review what is known about patient and family goals and values Understand the medical facts about the patient's medical condition and prognosis Review what is known about the patient's capacity to consent Retrieve and review completed Advance Directives and prior DNR documents Determine who key family members are, and (if the patient does not have the capacity), see if there is an identified health care agent, guardian or health care representative Find uninterrupted time for the discussion Begin with what the patient and family knows Determine what the patient and family know regarding condition and prognosis Determine what is known about the patient's views and values in light of the medical condition Provide any new information about the patient's medical condition and values form the medical team's perspective Provide information in small amounts, giving time for response Seek a common understanding; understand areas of agreement and disagreement Make recommendations based on clinical experience in light of patient's condition Try to reconcile differences in terms of prognosis, goals, hopes and expectations Negotiate and try to reconcile differences; seek common ground; be creative Use conflict resolution when necessary Respond empathetically Acknowledge Legitimize Explore (rather than prematurely reassuring) Empathize Reinforce commitment and nonabandonment Use POLST to guide choices and finalize patient/family wishes Review the key elements with the patient and/or family Apply shared medical decision making Manage conflict resolution Complete and sign POLST Get verbal or written consent from the patient or health care agent, guardian, health care representative Get written order from the treating physician, and witnesses Document conversation Review and revise periodically *POLST is a medical order form designed to provide a single, community-wide document that would be easily recognizable and enable patient wishes for life-sustaining treatment to be honored. This 8-step Protocol was originally developed by Dr. Patricia Bomba for the MOLST Program of New York State. Program information is found at www.CompassionAndSupport.org. Abbreviations: POLST, physician orders for life-sustaining treatment; MOLST, medical orders for life-sustaining treatment.

to enhance the understanding of the role of POLST in advance care planning [Bomba *et al.*, 2012].

While primarily found in the United States, POLST has been spreading to other countries [Pope and Hexum, 2012]. POLST has been implemented somewhat in Germany and has become popular in Canada and Australia. The National POLST Paradigm Taskforce (NPPTF) and Respecting Choices have been consulting with policy makers in Brazil Part I



Figure 4 Status of POLST programs, by state, as of June 2013.

Table 3 Tools and resources to enhance the understanding of advance care planning and POLST
Tools and resources to enhance the understanding of advance care planning and POLST
AARP Public Policy Institute. Improving Advanced Illness Care: The Evolution of State POLST Programs.
http://assets.aarp.org/rgcenter/ppi/cons-prot/POLST-Report-04-11.pdf
Center for Ethics in Health Care and National POLST Paradigm Program. www.polst.org
Community-wide End-of-life/Palliative Care Initiative and New York State's MOLST www.CompassionAndSupport.org
Aging Institute of UPMC Senior Services and the University of Pittsburgh website www.aging.pitt.edu/professionals/resources.htm
West Virginia Center for End-of-Life Care POST www.wvendoflife.org
End-of-Life and Palliative Care Education Resource Center www.eperc.mcw.edu
Abbreviations: POLST, physician orders for life-sustaining treatment; MOLST, medical orders for life-sustaining treatment; POST,

physician orders for scope of treatment.

and Singapore [Pope and Hexum, 2012]. The Respecting Choices program is addressed later in this chapter.

Ethical framework for medical decision-making

Capacity determination

Advances in health care and changing demographics have led to an aging population facing increasingly complex endof-life care. Since the incidence of cognitive impairment increases with age, it is critically important to understand how to assess the patient and determine medical decisionmaking capacity.

Capacity is the ability to take in information, understand its meaning and make an informed decision based on the information. Capacity allows us to function independently. Capacity assessment includes a cluster of mental skills people

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use in everyday life and includes memory, language, the ability to use logic and do calculations, the flexibility to turn attention from one task to another and executive function. Executive functions are the cognitive processes that orchestrate relatively simple ideas, movements or actions into goal-directed behaviors. Without executive functions, behaviors important for independent living can be expected to break down into their component parts. Executive functions include: problem solving, sequencing, abstraction, insight, planning (including the ability to appreciate the consequences of an action), initiation, direction and execution of actions, and the capacity to both monitor one's own behavior and inhibit inappropriate behaviors.

Determination of capacity is often difficult as no standard assessment tool is available. Capacity is a complex process that cannot be determined simply by using the Mini-Mental Status Exam (MMSE). Capacity assessment should involve a detailed history from the patient, collateral history from family, focused physical examination that includes cognitive, function and mood screens and appropriate testing to exclude reversible conditions.

Capacity is task specific. The overarching principle in capacity determination is the assessment of the patient's ability to understand the consequences of a decision. An individual patient may retain the ability to choose a trusted individual as an appropriate medical decision-maker, but may not have the capacity to agree to a simple medical procedure, palliative treatment, or to make complex medical decisions related to life-sustaining treatment. In that case, the patient may choose the person they trust to make medical decisions about:

- life-sustaining treatment, for example cardiopulmonary resuscitation, intubation and mechanical ventilation, dialysis, and feeding tubes;
- ordinary treatment, such as antibiotics for infection;
- palliative treatment, for pain and symptoms.

Competence and Incompetence are legal terms. These terms imply that a court has taken a specific action. From a legal perspective, capacity depends on ability to understand the act or transaction, understand the consequences of taking or not taking action, understand the consequences of making or not making the transaction, understand and weigh choices, and make and commit to a decision.

Standards for the medical decision-maker

The medical decision-maker is obligated to act in accordance with the patient's previously-expressed

When there is no prior oral or written advance directive and the patient's values and preferences are unknown or unclear, decisions should be based on the patient's best interests whenever possible, as interpreted by a guardian or a person with loving knowledge of the patient, if available. When making the decision to withhold or withdraw lifesustaining treatment, often people consider reversibility of disease, dependence on life-sustaining treatment, loss of capacity for social interaction, personhood, or nearness to death. It is important that family members and clinicians avoid projecting their own values or views about quality of life onto the incapacitated patient. Quality of life should be assessed according to the patient's perspective [Karlawish *et al.*, 1999; American College of Physicians-American Society of Internal Medicine, 2001].

2010]. Patients can specify what authority and discretion in

decision making they are giving.

Establishing plans of care for patients who lack decisionmaking capacity

Advance care planning for patients lacking decision-making capacity requires special consideration to ensure maximal patient participation with appropriate involvement of the medical decision-maker [Miller and Bolla, 1998]. The most common pitfalls in establishing plans of care for patients who lack decision-making capacity include failure to:

- use effective communication skills;
- recognize patient values and goals of care;
- acknowledge goals guide care and the choice of interventions;
- reach a mutual appreciation of the patient's condition and prognosis by physician and family;
- offer the choice between life prolongation and quality of life and instead offer the choice between treatment and no treatment;
- address the full range of end-of-life decisions from do-not-resuscitate orders to exclusive palliative care;
- engage in conversation that provides evidence of previous repeated oral expression of wishes and instead apply a literal interpretation of an isolated, out-of-context, patient statement made earlier in life;
- apply the principle of substituted judgment, in

Part |

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which the surrogate attempts to establish with as much accuracy as possible what decision the patient would have made if that patient were competent to do so. This standard seeks to preserve the patient's right to self-determination by placing the patient's own preferences at the center of deliberation, while recognizing that it is the exception rather than the rule that the patient will have articulated his or her specific preferences in advance [Bomba and Vermilyea, 2006; Lang and Quill, 2004].

Surrogate decision-making for patients who lack medical decision-making capacity must be consistent with ethical professional standards; for example, as outlined in the Ethics Manual of the American College of Physicians [Snyder, 2012]. Adequate safeguards must be provided to assure decisions for seriously ill patients lacking medical decision-making capacity by surrogates are fair, consistent and based on the patient's and not the surrogate's or physician's personal values and beliefs. Less aggressive treatment should not be chosen for homeless, socially marginalized, or other vulnerable patients if that is not what the patients themselves would choose.

Shared, informed medical decision-making

Patients, family members, and surrogates are often reluctant to ask these questions and afraid to discuss the dying process. Physicians cannot predict the full implications of complex medical decisions. A physician rarely knows all the consequences of an intervention or the precise natural history of a disease. Thus, it is extremely helpful to explore a patient's goals for care so that treatment options offered are based on these goals for care. In order to be effective, shared medical decision-making must be well-informed. The medical decision-maker should weigh the following questions:

- Will treatment make a difference?
- Do burdens of treatment outweigh benefits?
- Is there hope of recovery? If so, what will life be like afterward?
- What does the patient value? What is the patient's goal of care?

Functional health literacy and life-sustaining treatment

Functional health illiteracy results in a decreased comprehension of medical information and a lack of understanding and use of appropriate services ranging from basic preventive care to end-of-life care services, like palliative care and hospice. Patients with reduced health literacy have "reduced ability to interpret labels and health messages, limited ability to take medications appropriately, lower likelihood of receiving preventive care, more hospitalizations, greater use of emergency care, andamong elderly people-worse overall health status and higher mortality rates" [Koh et al., 2012; Berkman et al., 2011]. Many of these problems, particularly the increase in hospitalizations and greater use of emergency care, can drive up health care costs, particularly among the elderly and those with serious illness [Koh et al., 2012]. The U.S. Department of Health and Human Services (DHHS) estimated that only 12% of the population has "proficient" health literacy, 53% of individuals have "intermediate" health literacy, 21% have "basic" health literacy, and 14% have "below basic" health literacy [Koh et al., 2012; DHHS, 2008]. When it comes to complex issues, such as decisions about life-sustaining treatments, clinicians must recognize that the vast majority of patients and surrogate decisionmakers do not have adequate health literacy.

Ensuring functional health literacy is a critical element in improving the advance care planning process and the quality of end-of-life care. Functional health literacy is based simply on a "need to know" and a "need to do," with respect to being informed about medical information required to make specific medical decisions, especially complex decisions related to life-sustaining treatment. Thus, the medical decision-maker must have a basic understanding about medical care, medical conditions, health status and prognosis. Functional health literacy is an essential element of a shared, informed medical decision-making process and thoughtful advance care planning discussions leading to completion of POLST.

Information should be shared in terms that the patient can understand and never delivered in a careless manner. Providers should be sensitive to the patient's responses in setting the pace of communication, especially in discussing options for end-of-life care. Breaking bad news should be presented to the patient in a way that minimizes distress. If the patient cannot comprehend his or her condition, it should be fully disclosed to the appropriate medical decision-maker.

Conflict resolution

Losing a loved one is a difficult, emotion-laden experience. When conflict arises, trained and qualified health care professionals can assist in resolving conflict by identifying and managing misunderstanding that may occur if the diagnosis is unknown or uncertain, too much jargon is used, contradictory information is provided, or an overoptimistic prognosis was previously rendered. Further, the provider can provide support to the decision-maker who is often emotionally distressed, sleep-deprived, and psychologically unprepared when decisions are made in the midst of a crisis. The provider may identify and deal with distrust in the health care professionals or the system, guilt, grief, interfamily issues, and explore potential secondary gain. A team of professionals can assist with resolving conflicts in values that result in disagreement about the goals of care and relative benefit of treatment. If unresolved, referral to the ethics committee can assist with resolution of the conflict.

There is no ethical or legal difference between withdrawing and withholding life-sustaining treatment; however, the standards for and cultural and religious beliefs about withdrawing or withholding such treatment may vary. Treatments should not be withheld because of the mistaken fear that if they are started, they cannot be withdrawn. This would deny patients potentially beneficial therapies. Instead, a time-limited trial of therapy could be used to clarify the patient's prognosis. At the end of the trial, reassessment and revision of the treatment plan should occur. Conflict may arise if some family members are reluctant to withdraw treatments even when they believe that the patient would not have wanted them continued. Health care professionals can resolve conflict by addressing feelings of guilt, fear, and concern that the patient may suffer as life support is withdrawn; professionals can also ensure that all appropriate measures to relieve distress are used, and explain the ethical and legal obligations to follow the patient's wishes.

Vital considerations in special populations

Minor patients

If the minor patient lacks the capacity to make medical decisions, the parent or legal guardian makes medical decisions. As the decision-makers, they must be fully informed about the minor patient's medical condition, as well as the risks, benefits, burdens, and alternatives to possible life-sustaining treatment. The parent's or legal guardian's decision must be made in accordance with the minor patient's wishes, if known, including the patient's religious and moral beliefs; or if the patient's wishes are not reasonably known and cannot with reasonable diligence be ascertained, in accordance with the patient's best interests. Part |

The parent's or legal guardian's assessment is based on the patient's wishes and best interests, not the parent's or guardian's wishes, and includes consideration of the dignity and uniqueness of every person; the possibility and extent of preserving the patient's life; the preservation, improvement or restoration of the patient's health or functioning; the relief of the patient's suffering; and any medical condition and such other concerns and values as a reasonable person in the patient's circumstances would wish to consider.

If the minor patient has the capacity to make medical decisions, the minor patient should also participate in the decision-making process, in tandem with the parent or legal guardian.

Special considerations and requirements may apply to decisions about life-sustaining treatment made by "emancipated" minor patients, defined as those who are living independently, have a child of their own, or as otherwise delineated.

When the minor patient turns 18, he/she should be counseled about advance care planning and encouraged to choose a medical decision-maker and discuss his/her values, beliefs and goals for care.

Persons with developmental disabilities

Persons with developmental disabilities who possess the capacity to make medical decisions, including medical decisions related to withholding and/or withdrawing life-sustaining treatment, have the right to make such decisions.

Persons with developmental disabilities who lack the capacity to make decisions regarding life-sustaining treatment may still have the capacity to choose a medical decision-maker and should be encouraged to do so. Others may have an appointed guardian to make medical decisions. Similar to decision-making for minor patients, when making decisions for persons with developmental disabilities considerations for the patient's wishes, beliefs, dignity, functional status, and best interests should be taken into account.

Persons with mental illness

Persons with mental illness, such as chronic schizophrenia and bipolar disorder, may pose challenges in determining capacity, selecting a medical decision-maker and understanding person-centered preferences regarding end-of-life care. The presence of mental illness itself is not evidence of lack of medical decision-making capacity.

Models embracing a community approach

Effective advance care planning models promote culture change through professional training, community education, system implementation and continuous performance improvement focused on quality. Community engagement is necessary to promote awareness and readiness for advance care planning discussions through education and empowerment. Health care and community collaborative partnerships can be formed by engaging individuals and faith-based, patient advocacy, community and professional organizations to help achieve the goal. Respecting Choices and Community Conversations on Compassionate Care (CCCC) are two examples of health care and community collaborations cited by the National Quality Forum [National Quality Forum, 2006].

Respecting Choices[®]

Respecting Choices is an evidence-based advance care planning program based in La Crosse, Wisconsin, that combines facilitator training in tandem with developing systems and processes to integrate trained facilitators into clinical practice in a way that enhances quality care. Respecting Choices promotes culture change by forming community partnerships with community institutions and engagement of individuals and groups. The goal of this community work helps promote readiness for advance care planning [BJ Hammes, personal communication, February 2, 2013]. Respecting Choices emphasizes four necessary, coordinated elements: (I) system design; (II) competent advance care planning facilitators; (III) community engagement and (IV) continuous performance improvement [BJ Hammes, personal communication, February 2, 2013].

Numerous peer reviewed publications document positive results that involve the Respecting Choices facilitated intervention [Hammes and Rooney, 1998; Briggs, 2004; Hammes *et al.*, 2010; Hammes *et al.*, 2012; Romer and Hammes, 2004; Schellinger *et al.*, 2011; Schwartz *et al.*, 2002; Song *et al.*, 2005]. Facilitators are trained for three stages of planning including basic, disease-specific, and endstage illness. It is only in the last stage of planning where the POLST form is used as the typical documentation tool. Trained facilitators, who may not have extensive health care experience, are only trained to do basic advance care planning that typically results in the completion of a health care proxy or durable power of attorney for health care. These facilitators are commonly clergy or lay ministers who have a basic role in advance care planning and do not need extensive health care knowledge or experience. Facilitators who would be doing discussions resulting in POLST form completion are typically very experienced nurses and medical social workers who know the patients well and understand the course of illness of these patients. They work in the context of a health organization that monitors quality and work as part of team that includes the patient's physician.

A two-step approach to advance care planning: CCCC and MOLST

In 2001, an innovative two-step approach to advance care planning was developed in Rochester, New York [CompassionAndSupport.org. Advance Care Planning, 2013] by the Community-wide End-of-life/Palliative Care Initiative (the Initiative), a health care and community collaborative that aims to improve quality of care at the end of life [CompassionAndSupport.org About Us, 2013]. This twostep approach has been successful in increasing completion rates for health care proxies across upstate New York, and in development and implementation of the MOLST, New York State's approved POLST Paradigm Program.

The two-step approach is a targeted approach to both traditional advance care planning and MOLST, recognizing that different population segments have different needs. Advance care planning is appropriate for all adults 18 years of age and older, not only the subset of individuals living with life-limiting illness. People who are healthy and independent can face sudden, unexpected life-limiting illness or injury.

All individuals should complete traditional advance directives. Individuals with advancing disease benefit from more intensive discussion while they have capacity and should complete actionable medical orders, like MOLST. Thus, advance care planning should be incorporated along the entire continuum of care.

The CCCC program encourages all persons eighteen years of age and older to complete a health care proxy when healthy, as well as review and update the advance directive routinely along the health-illness continuum (*Figure 5*) from wellness until end of life [Bomba and Vermilyea, 2006]. Seriously ill individuals with advanced chronic



Compassion, Support and Education

Figure 5 The health-illness continuum. Advance care planning is appropriate for all adults 18 years of age and older, not only the subset of individuals living with life-limiting illness. People who are healthy and independent can face sudden, unexpected life-limiting illness or injury. These individuals should complete traditional advance directives. Individuals with advancing disease benefit from more intensive discussion while they have capacity and should complete actionable medical orders like the POLST form. Thus, advance care planning should be incorporated along the entire continuum of care [Bomba and Vermilyea, 2006]. *Reprinted with permission from JNCCN-Journal of the National Comprehensive Cancer Network*.

illness who may die in the next year and those interested in further defining their wishes are encouraged to have more intensive conversations focused on goals for care and consider completing a MOLST [CompassionAndSupport. org Advance Care Planning, 2013].

The CCCC workshop focuses on storytelling and "Five Easy Steps," based on behavioral readiness, and aligns with the CCCC Advance Care Planning Booklet (English), 2011; CCCC Advance Care Planning Booklet (Spanish), 2011; CCCC Advance Care Planning Booklet (Spanish), 2011]. The Pilot Study Results from 2002-2004, shows that the CCCC workshop motivates individuals to complete an advance directive [CCCC Workshop Attendee Responses, 2004]. For those who attended a CCCC Workshop, on average, 48% had done an advance directive before the workshop; a follow-up survey was done six to eight weeks later and, on average, 55% of respondents had an advance directive at that time. The difference is statistically significant (P-value =0.01). Based on this success, the CCCC program produced the CCCC videos, the "Five Easy Steps" web

page, and other web pages on CompassionAndSupport.org, the community website designed by the Initiative [CCCC Videos, 2013; CompassionAndSupport.org, 2013].

The CCCC Program was shared across upstate New York. The End-of-Life-Care Survey of Upstate New Yorkers: Advance Care Planning Values and Actions, Summary Report describes results of the most comprehensive survey ever done in upstate New York to assess consumer attitudes and actions regarding two advance directives (health care proxy and living will) and assess the impact of the CCCC Program. Evidence suggests that advance care planning completion is driven, in part, by community education and physician communications with patients. The highest rate of discussion with doctors occurred in the Rochester area (47%) compared with the Utica area (27%); similarly, health care proxy completion was highest in Rochester (47%) and lowest in Utica (35%). Survey responses from locations where doctors were more likely to have discussed advance care planning with their patients had higher completion rates of advance directives. [Excellus BlueCross BlueShield, 2008]

Summary

A more comprehensive, systematic approach to advance care planning is needed. For effective advance care planning and end-of-life decision-making to become the routine throughout a health care organization or a community, a comprehensive system of provider training, consumer education, practices, and policies must be developed, embraced and implemented. Trained and qualified health care professionals can provide advance care planning education to patients, families and loved ones in all health care settings.

Alignment with the National Quality Forum (NQF) seven preferred practices on advance care planning is recommended [National Quality Forum, 2006]. These seven preferred practices are explained below.

Surrogate/decision maker designation

Document the designated surrogate/decision maker in accordance with state law for every patient in primary, acute, and long-term care and in palliative and hospice care.

Patient/surrogate preferences

Document the patient/surrogate preferences for goals of care, treatment options, and setting of care at first assessment and at frequent intervals as conditions change. Part I

Medical orders

Convert the patient treatment goals into medical orders, and ensure that the information is transferable and applicable across care settings, including long-term care, emergency medical services, and hospital care, through a program such as the POLST program.

Advance directives

Make advance directives and surrogacy designations available across care settings, while protecting patient privacy and adherence to the 1996 Health Insurance Portability and Accountability Act (HIPAA) regulations, for example, by using Internet-based registries or electronic personal health records.

Advance care planning promotion

Develop healthcare and community collaborations to promote advance care planning and the completion of advance directives for all individuals through established programs such as Respecting Choices and CCCC.

Ethics consultation

Establish or have access to ethics committees or ethics consultation across care settings to address ethical conflicts at the end of life.

Decisionmaking of minors

For minors with decision making capacity, document the child's views and preferences for medical care, including assent for treatment, and give them appropriate weight in decision making. Make appropriate professional staff members available to both the child and the adult decision maker for consultation and intervention when the child's wishes differ from those of the adult decision maker [National Quality Forum, 2006].

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Nutrition and hydration

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Introduction

Pursuing constant nutrition and hydration is often the most important daily function of a human being. Various cultures and sub-cultures view the activity of eating and drinking quite differently. When the human body becomes ill, one of the first signs of illness can be a change in oral intake. As illness progresses and patients become weaker, or are undergoing treatments which prevent oral intake, artificial nutrition and hydration (ANH) is often used temporarily until the illness or condition improves. If an illness progresses to the point that treatment options for the disease cease to exist, and ANH are ongoing, this can be a source of distress for patients and families if preparations have not been made to address these issues. Likewise, if a patient's terminal condition causes an inability to continue oral intake safely, the dilemma of how to provide nutrition and hydration becomes central to patients, families and health care providers. It is often helpful for patients and families to have the most support possible from all disciplines to discuss options, patient's wishes and concerns, family's wishes and concerns in order to establish the proper care goals. This approach will alleviate patient and family distress, foster trust among patients, families and health care providers and ultimately a better experience of life and death.

Definition and purpose of nutrition and hydration

The act of eating and drinking is a requirement the human body cannot live without. There have been reports of human beings living for several weeks to months with very little food and hydration at sea or on land but eventually without the correct balance of nutrition and hydration the human body will enter an irreversible state and succumb to death. There are many metabolic imbalances which occur with inadequate nutrition and hydration but primarily anorexia, negative nitrogen imbalances, increased skeletal muscle catabolism with decreased muscle mass are usually late signs of long term poor nutrition. Other signs are increased glucose turnover and production, increased insulin resistance, decreased fat synthesis, body lipid mass and lipoprotein lipase activity. Metabolism of nutrients and protein synthesis is affected by our abilities to hydrate ourselves. Our body's intake and output of fluids is controlled by neuroendocrine activity which regulates our intake via thirst and our ability to excrete fluids via the kidneys.

Meaning of food consumption

Food consumption means something different to each person, family, culture and subculture. Anthropologists have long considered and used ethnographic evidence to show how food consumption authenticates social order, moral, aesthetic beliefs and values. Mealtimes are both vehicles for and endpoints of culture. Mealtimes are universal occasions for family members to engage in the activities of feeding and eating but also to forge relationships that reinforce or modify the family relationships. Mealtimes are a social practice that requires certain sensibilities of the participants [Ochs and Shohet, 1996]. A comparative study of U.S. and Italian dinnertime socialization found that U.S. parents urged children to eat their meals, emphasizing that it is for nutrition and part of a social contract which sometimes vields a reward, namely, dessert. Italian parents' emphasized food as a pleasure over the above three attributes [Ochs and Shohet, 1996]. Children's compliance with eating meals for other reasons than pleasure increases tensions and dominates mealtime interaction. The emphasis of dessert as reward competes with the purported value of food as

nutrition. In other words, some U.S. parents articulate mixed messages about the goodness of food. Italian parents do not include dessert in the meals, don't expect children to eat everything on their plate, and assume children develop tastes and preferences, like adults, for certain foods. Italian parents sought to affirm their children's preferences. Both adults and children use a rich grammar of positive affect to praise both the food and the person who prepared or purchased it [Ochs and Shohet, 1996].

The dominant message that meals should be eaten because food is good for your health and is nutritional versus food should be eaten for the pleasure of it has potential to have great impact on decision making regarding nutrition and hydration in palliative medicine in the United States. It is this stance on consumption of food that may be driving many patients and families into believing that providing food whether artificially or not is something that has to be provided on all patients.

ANH

One of the several widely held misconceptions about tube feeding is that it is "ordinary care like spoon feeding". Except for a means to provide calories and fluids, tube feeding is not like natural eating or drinking. In the U.S., tube feeding rates vary widely by state, suggesting that variables other than patient needs are the primary determinants. Nursing home patients with dementia are more likely to receive intravenous antibiotics, rehydration therapy and feeding tubes than Dutch patients [Mehr et al., 2003; van der Steen et al., 2004]. The placement of feeding tubes has been known to cause loss of gustatory pleasure, loss of the social aspect of eating, loss of dignity and altered cosmesis. Sometimes placement of feeding tubes is considered an administrative convenience to help facilitate discharge from an acute care setting. Feeding tubes are also considered by nursing home facilities an easier and substitute means to provide nutrition/hydration than good hand feeding. In other Western countries, the rate of foregoing ANH near death is high but varies between countries. Physicians may have different ideas about the appropriateness of making these decisions which may be related to societal or organizational context with regard to end-of -life decision making.

In a study of 32 terminally ill patients who were dying, 20 of these patients never experienced hunger/thirst and only 11 experienced hunger/thirst initially. Some patients have experienced the sensation of "starving" with continuous

artificial feedings. This may be due to the loss of the expansion and contraction of the stomach which happens when we eat food by mouth and which gives us satisfaction from eating.

Decreased hydration has been found to be beneficial during the dying process because dehydration decreases the sensation of pain and prevents edema, excessive respiratory and GI secretions. Dehydration also decreases the incidence of vomiting and diarrhea. It may be said that dying a little bit on the dry side may be more comfortable.

The use of ANH is widely accepted as medical treatment, which means physicians are not obliged to medically administer ANH in dying patients but to only relieve the patients thirst and or hunger as part of palliative treatment regimen, e.g., basic care. However, some argue for ANH at all times because it is regarded as a form of basic care that should not be denied to anyone, and not as a medical intervention.

ANH may be used as a means to clarify a patient's situation. MD's may have their own opinions on whether ANH is of likely benefit, but they want everyone involved, patient, family, other physicians and nursing staff to be comfortable with the decision.

Terminal illness and ANH

The incidence of dementia is expected to double every 20 years to 81 million by 2040 [Buiting *et al.*, 2011]. Dementia is a terminal illness, progressive and deteriorating, without a cure, before and at the time of diagnosis. The course dementia takes depends on the type of dementia at diagnosis and the long-term support systems surrounding the patient. Patients with advanced dementia commonly develop eating difficulties, and decreased feelings of hunger and thirst are often part of the dementia process [Pasman *et al.*, 2005]. With dementia as in other diseases where patients become incompetent to make decisions, complex situations may arise in which physicians and families decide whether ANH is likely to be beneficial for the patient [Sheldon, 1997; The AM *et al.*, 2002].

Clinical evidence of beneficial effects of ANH for patients with advanced dementia is not available [Sampson *et al.*, 2009; Finucane *et al.*, 1999]. Its use has been shown to cause fluid overload and aspiration pneumonia [Finucane *et al.*, 1999; Winter, 2000; Murphy and Lipman, 2003]. Though existing literature focuses on artificial nutrition which is sometimes used in combination with hydration, one study showed the benefits of artificial hydration in the

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last 48 hours before death is doubtful and there is no clear evidence that forgoing ANH in patients with advanced dementia causes discomfort [Pasman *et al.*, 2005; Di Giulio *et al.*, 2008; McCann *et al.*, 1994].

Despite the lack of evidence, purported goals of ANH in patients with advanced dementia may still be discussed as to prevent aspiration pneumonia, to prolong survival, to prevent malnutrition, to help with wound healing, to improve function and to provide palliation.

Issues in palliative medicine and ANH

Rejecting food or fluids, spitting it out, or pulling out tubes have been considered as expressions of the patient being uncomfortable [Buiting et al., 2011]. Sometimes it may be interpreted as an expression of a wish not to have these interventions-especially by Dutch physicians [Buiting et al., 2011]. If the patients' prospects of recovery are small and if the family agrees, it may be decided not to give ANH, in which case it is not regarded as "withholding ANH" but as avoiding "inappropriate care". In the U.S. it is not uncommon to hear the words by health care providers that the patient and family want "everything". The word "everything" inevitably may include "inappropriate care" for many patients in a given situation. Withdrawing and/ or withholding ANH is widely considered as "changing the direction of treatment" in Palliative Medicine. Withdrawing life sustaining treatments or withholding interventions does not mean that all treatments stop.

Most Dutch and some Australian physicians indicated withdrawing treatments was felt to be emotionally more burdensome than withholding. Some MD's considered withholding easier because they can be clear with the family about the patient's prospects. Others indicated that withholding is easier because the association with the patient's death is less concrete than in cases of withdrawing treatment [Buiting *et al.*, 2001].

Advance directives and informed consent

Advanced directives are found by some physicians to be not specific enough, outdated and no replacement for the ongoing discussion and documentation of care goals. Illnesses, circumstances and patient's wishes change over time. Advanced directives have been found too broad when in discussions about the details of a patient's illness. The approach Dutch physicians have taken in dementia care has been a more comprehensive, holistic approach that Part I

puts emphasis on the patient's actual situation and life story [Buiting et al., 2011]. This approach has been found helpful as a guide to decision-making. The Australia approach is predominantly analytical, with objective and scientific evidence playing important roles in the decision process. It is felt that the differences between Dutch and Australian approaches to decision-making may be due to a difference in health care systems. In Australia, care for dementia patients is more fragmented than in the Netherlands, especially in large cities. GP's, geriatricians and neurologists can be involved in the initial diagnosis and work-up of patients with dementia. Once the disease is advanced, dementia is managed in the nursing homes by the GP. In the Australian health care system and very similar to the U.S., dementia patients who require acute care are admitted to a hospital where they are followed by a hospital specialist and the GP is often left out of the decision making process. In the Netherlands advanced dementia patients are seldom hospitalized and if so for a short period of time. Physician approaches to decision making across health care settings in patients with advanced dementia regarding ANH in the Netherlands and Australia is medically as well as culturally determined and cultural differences seem to be primarily related to a different health care context [Buiting et al., 2011].

An informed consent discussion must precede, and be the basis of, any decision regarding ANH. Adequate informed consent requires three essential elements: (I) that the patient or a surrogate is provided sufficient medical information; (II) that the patient or a surrogate possesses decisional capacity; and (III) that the patient or a surrogate is able to exercise voluntarism (the capacity to make a decision free of coercion). Adequate information includes but is not limited to diagnosis, prognosis, the nature of the proposed intervention (risks and benefits of ANH), and alternative treatments, including doing nothing. The patient or surrogate receiving this information must be able to act on it freely without undue pressure or coercion [Applelbaum and Grisso, 1988]. Research suggests, that the informed consent process for placement of feeding tubes in patients with chronic illnesses and dementia often does not meet this ideal standard [Buiting et al., 2011]. In 2001, a retrospective study of 154 patients who received feeding tubes for symptoms resulting from progressive illnesses, only one patient had discussions of benefits, burdens and alternatives to feeding tubes [Brett and Rosenberg, 2001]. In this same study, only 12 of 33 patients with decisional capacity signed the consent form.

In Palliative Medicine, full, unpressured, and timely discussions regarding advance directives, informed consent and ANH are daily routines with patients, families and many times with other health care providers.

Dysphagia

Normal aging effects are known to affect oropharyngeal swallow function [Logeman, 1993]. The inevitable process of aging comes with the eventual problems of swallowing. Impaired swallow function may be of more significance when combined with the general deterioration associated with advanced disease and reduced reserve [Roe et al., 2007]. Dysphagia, difficulties with swallowing, is a prevalent symptom in the last week of life in up to 46% of patients suffering from cancer and the presence of dysphagia is a significant factor associated with decreased survival [Conill et al., 1997; Vigano et al., 2000]. Dysphagia is one of the most distressing symptoms for patients and families and common in Palliative Medicine. Patients and families suddenly realize the duality of impaired nutritional intake to the possibility of a shorter life span. As many as 63% of all patients with malignant disease experienced swallowing difficulties in the last year of life [Addington-Hall et al., 1998]. Of these, 37% suffered with dysphagic symptoms for over six months [Addington-Hall et al., 1998]. Research suggests that health care providers are generally poor at recognizing signs and symptoms of dysphagia and patients can see the condition as an inevitable part of the aging process [Ekberg et al., 2002]. When patients suddenly stop swallowing, are dependent on artificial hydration/nutrition, families can have significant distress and differences of opinions over what to do next. Distress and conflict can be prevented or reduced when anticipatory dialogue is initiated at earlier stages during treatment of life threatening or life limiting illness.

Quality of life (QoL) and palliative medicine at the end of life

Often the goal of Palliative Medicine is to improve the patient's QoL, by early and periodic assessment of early and periodic assessment of symptoms, nutritional status and performance status which allows patients to live a more active life for as long as possible. A lot of what we believe about QoL is intuitive or based on clinical impressions or on research results from other areas. QoL is what the patient says it is, which constantly changes and needs to be updated in the chart to be shared with other health care providers. Little has been subjected to scientific scrutiny or validation, particularly in the field of palliative medicine [Prevost, 2012]. Malnutrition and cachexia are frequently accompanied by a much higher incidence of depression, which consumes the patient, causing a marked alteration of QoL and a drastic reduction of performance status [Ottery, 1995]. Some studies suggest that weight loss alone is a powerful end point in studying cachexia and that weightlosing patients have a reduced global QoL [Dahele and Fearson, 2004].

In palliative medicine global function monitoring may be based on Karnofsky performance status or the more comprehensive Edmonton Symptom Assessment System (ESAS) by grading nine common symptoms—(pain, fatigue, nausea, depression, anxiety, drowsiness, shortness of breath, appetite, and overall sensation of well-being).

The aims of nutritional care in patients with cancer may change as the disease progresses. In the early stages of the disease the main goal is to restore or maintain nutritional and functional status, while toward the end of life the emphasis shifts to optimizing the QoL and sense of wellbeing, and alleviating unpleasant symptoms [Acreman, 2000]. Nutritional support is focused on maintaining adequate hydration, alleviating or controlling symptoms (nausea/vomiting) and preserving body weight and composition as far as possible [Marin Caro et al., 2007a; 2007b]. When selecting the type of nutritional intervention the wishes of the patient and their family must be taken into account [Acreman, 2009]. Nutritional problems have to be identified in order to plan a strategy that needs to be discussed with the patients and their families and reviewed regularly as conditions change. It is also important to educate the family that aggressive feeding and over-feeding, a very common problem that causes conflict between the patient and family, is inappropriate and that when food becomes more of a discomfort than pleasure, the family members and friends can show affection by means other than feeding. In terminally ill patients, it is important to avoid over-treating malnutrition as it could worsen the patient's QoL [Ho 2003]. The relationship between nutritional status and QoL is a critical issue in these patients. Therefore, providing suitable nutritional care and support to palliative care patients should be one of the goals for improving QoL [Acreman, 2009].

There is very little evidence with control trials of whether or not hydration is beneficial or not towards the end of life in terms of alleviating symptoms. The

emphasis in clinical practice has been on obtaining a better understanding of individual patients' and caregivers' perceptions through improved communication between health professionals, patients and families. This is vital to decision making about providing hydration at end of life and individualize treatment decisions to best meet specific patient needs [Cohen et al., 2012]. Nutrition and hydration needs critical daily assessment in patients with serious, life threatening illnesses or those with multiple chronic and complex medical problems who are not responding to therapies. When making patients NPO while waiting for tests or those who may be developing dysphagia and diets are being altered may be a crucial time to begin patient/ family discussions regarding QoL. These discussions need to take place early on when aggressive treatments are being given. This allows patients and their families a chance to discuss these issues with one another so that they are aware of issues that may arise regarding oral intake, nutritional deficiencies and hydration problems ahead of time.

Having these unwelcome discussions about potential problems in the future may help reduce the impact to the patient and family later on in the course of the disease as well as reduce the anxiety around withholding or withdrawing such treatments. Many times feeding tubes are not generally accepted treatment options and patients and families may want to consider the option of having the choice not to put in a feeding tube. Some families may want the patient to have it as they may feel the patient is "starving" and may "stay alive" longer despite not being able to communicate or have minimal awareness of what is happening to their bodies. Some families may come to terms with the patients' irreversible condition and wishes and opt to forgo artificial feedings.

The reality of sickness, aging and death is often not part of the discussions surrounding nutrition and hydration and some families may want these discussions.

When treatment therapies for a terminal illness have been exhausted, many patients may be receiving IV hydration and artificial feedings. Often the patients treating Oncologist, Neurologist or Surgeon may say to the patient and family there are no available treatment options for their disease and they advocate for Palliative Medicine and/ or Hospice. Patients, if they are aware and families often become focused and distressed about what to do with the treatments of ANH they are still receiving. Many patients and families may not have had the time to come to terms with the reality of the current situation of the patients' terminal condition, no further treatment options for the disease and imminent death. Distress and conflict can be prevented or reduced when anticipatory dialogue is initiated at earlier stages during treatment of life threatening or life limiting illness. There is no evidence that patients who are receiving feedings via nasogastric or gastrostomy tubes with advanced cancer that these treatments prolong life or improve metabolic abnormalities [Brennan, 1981]. There is evidence that cancer growth may be accelerated with nutrition, thereby increasing local symptoms from the cancer [Rice and van Rij, 1987]. Nutritional support is helpful for patients who have local disease, have swallowing problems and not yet widely disseminated end stage cancer, such as patients with head and neck cancer.

The signs of acute dehydration in a healthy person can be a sequelae of thirst, dry mouth, headache, fatigue, cognitive impairment, circulatory collapse, renal failure, anuria and death. The first clue suggesting that the dehydration in the cancer patient is not the same as acute dehydration in a healthy person came from clinical observations from dying patients who were not taking medications and who did not have correctable causes for their deterioration. In patients with advanced cancer, fatigue and drowsiness usually precedes the cessation of fluid intake by days or weeks. Even after cessation of fluid intake, dying patients are arousable and respond to family questions.

A prospective study of dying cancer patients with a 6-week prognosis showed that there was no evidence of association between biochemical markers for dehydration, such as serum osmolality, urea and sodium and the symptom of thirst [Burge, 1993]. Giving additional hydration to a dying patient in order to alleviate dry mouth and thirst may not meet its goal. Hunger is often not a feature in an anorexic-cachexic patient as thirst is often not associated with decreasing fluid intake in dying patients. In a study on terminal patients receiving oral fluids versus intravenous hydration, there was no difference between biochemical parameters and state of consciousness between the two groups [Waller *et al.*, 1991].

It may be seen as reasonable to not offer nutritional or fluid supplementation in patients where it cannot be medically justified as in actively dying patients. Fluid therapy may also be seen as harmful as in patients with low albumin levels who tend to have low colloid osmotic pressure, the pressure responsible for moving fluid out of the blood vessels. This may cause pulmonary edema, acsites and peripheral edema interfering with comfort of the dying patient. Often when families are distressed or have disagreements about discontinuing hydration it is continued for the sake of the family unless there has been a contrary opinion expressed by the patient. It is sometimes decided to give fluid hydration intermittently at night only rather than 24 hours administration as it is often easier for the family to make the decision to discontinue therapy when therapies are given intermittently. This can be the case with artificial nutrition as well.

Summary

Detailed discussion about nutrition and hydration is often discussed too late in the course of a patient's illness. It is a stressful topic to discuss as most of the time oral intake stops suddenly, discussions are initiated, and "temporary" ANH is started almost routinely. It would benefit the patients and families to initiate discussions ahead of time when either patient's have known terminal conditions such as dementia before they become advanced to discuss some of the benefits/burdens and alternatives to having no ANH. Doing less at the right time may actually add to a patients quality of life.

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Part I

Spirituality

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Introduction

Spirituality has been traditionally synonymous with religiosity but is more recently viewed as life-enhancing, subjective, and personal [Elkins, 1995; Emblen, 1992]. Often what is heard in clinical practice when asking patients about religion, faith tradition or spirituality is "I'm spiritual but not religious". Religiosity is often a belief in a religious doctrine which may include numerous religious activities and dedications. Spirituality has also been defined as a way an individual may seek meaning or purpose in life or with self. It may be a way of experiencing inner connectedness to self, to others, to nature or to something significant or sacred [Puchalski et al., 2009]. Religion can be viewed as a construct of human making which helps humans to conceptualize and express spirituality, especially in those religions with rituals. Spirituality is the key function of religion and has been defined as "the search for the sacred" [Pargament, 1999]. The "sacred" has been characterized as the concept of God, of the divine, and of transcendent reality although anything outside of this can also be considered sacred [Pargament and Mahoney, 2009]. These concepts are difficult to prove as "real" or "true".

Within spirituality, it is difficult to stray from the philosophical thoughts surrounding the nature of being, existence and reality. Principal philosophical questions are "What is the meaning of existence or being? What levels of existence are there, and what constitutes a "level"? In Palliative Medicine, these questions are discussed quite frequently between patients and clinicians.

Many conflicts around spirituality and the meaning of life, one's purpose in life, often centers on what constitutes existence, and what we perceive as real or not real. Spirituality may require one to be inspired or influenced by objects which are believed to have divine significance, making them sacred. Examples of objects are the timing of the Sabbath, the crucifix, music, wine, prayer beads, and statues. Spirituality can thought to be a perception of the sacred to some or as a mystical experience to others.

The diversity of definitions of religiousness and spirituality are broad with many tendencies to differentiate and polarize the two [Zinnbauer *et al.*, 1999]. The definition of religiousness by Batson *et al.* [1993] seems to be a functional approach whether we experience religiousness, spirituality or mysticism. Religiousness is "whatever we as individuals do to come to grips personally with the questions that confront us because we are aware that we and others like us are alive and that we will die". In Palliative Medicine, it is often about searching tediously with individuals and their families for their thoughts of this very important statement.

Spiritual exploration

In exploring the sacred, it may refer to conceptions of the divine or God and/or a spirituality which may or may not become more prominent when human limitations are exposed through illness (*Figure 1*). Spirituality is often shaped by external factors such as familial, institutional, cultural, and internal factors such as ones' own thoughts. The divine or God, may be described by various cultures as wrathful, strict, and controlling or loving, kind, and forgiving. Parents may sanctify their children as blessings which are ways of expressing the sacred. Palliative Medicine consults require spiritual assessments and exploration of what the patient values as sacred, spiritual conflicts regarding treatment options, spiritual or mystical experiences, and whether or not they have been helpful to the patient.

Spiritual protection

Spiritual protection is an individual's relationship with the

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Figure 1 Search for meaning.

sacred. It may occur through organized religion, spiritual movements, newer individualized worldviews, or mystical experiences. It is an effort of spiritual coping which may help a person during a life threatening or life limiting illness [Pargament and Ano, 2005]. In Palliative Medicine, a spiritual assessment of the patients relationship between their self and what they value as sacred or spiritual is important in order to understand what the person has available for support or protection. Some patients may not find what they have been practicing or believing spiritually in the past helpful to them in the present when health is failing. It is clinically supportive to be sensitive and open to the many different ways patients experience and express their spirituality.

Spiritual shift

Spiritual struggles can be described as a questioning of our belief system, religious communities or whatever we hold as sacred. Poorer mental and physical health has been linked to spiritual struggles [Pargament *et al.*, 2005]. Religious

rituals are ways people can spiritually shift their thoughts in preparation for death, coming to terms with potential loss of a family member, and allowing for redirection of sacred value for ones' life. The patient or family may be able to find a different definition of the world around them and sense of purpose in life [Paloutzian, 2005]. The process of transforming the sacred is felt to happen over an entire life span and is the essence of spirituality [Pargamant and Mahoney, 2009].

Spiritual assimilation and dissolution

The search for the sacred, religious meaning or spirituality is not always successful or helpful and can sometimes be destructive. It may lead patients to collide with their social system or have misguided approaches to spirituality and distress especially during illness. It can also help patients assimilate, in the sense that it provides a person with a different perspective about themselves and the world around them in view of the situation they are facing especially in terminal illness. These changes in a patients' perspective of themselves and the world around them have been found to occur through the use of entheogens.

Entheogens

The use of entheogens or psychoactive substances, with a history of bad publicity resulting from clandestine use in the 1950s, 1960s, and 1970s eventually caused all psychedelic research in North America to cease by the late 1970s. An entheogen, thought to "generate the divine within", have been used in rituals for centuries for their religious or spiritual effects such as psilocybin and ayahuasca. The term entheogen is often used to contrast recreational use of the same substances. States of consciousness believed to be sacred along with drugs which induce these conscious changes have existed for centuries [Walsh, 2003]. Whether drugs produce effects similar to religious or mystical experiences is still under investigation, particularly regarding long term effects. There are five arguments by Huston Smith [Smith 1964; 2000] that drug experiences can never be mystical. His thoughts were that drugs are clearly not mystical or beneficial, experiences induced by drugs are different than those induced by mystics, a mystical experience is a gift of God which can never be controlled or experienced by humans, drug-induced experiences are too quick and easy and could not be identical to years of hard practice in the contemplative disciplines, and the after-effect of drug induced experiences are different, less beneficial and less long lasting than contemplative mystical experiences. In evaluation of Huston Smith's suggestion that drug experiences can never be truly mystical, it can be said that not all drugs produce mystical experiences, but it cannot prove that no drug experiences are mystical [Walsh, 2003]. Philosophically, drug and mystical experiences can have phenomenological differences. It is difficult to differentiate drug experiences from religious experiences. Spiritual teachers with contemplative experience have concluded from their experience that drug induced and contemplative induced experiences are identical. Hence, it appears that the argument that mystical experience is a gift of God which can never be under human control can only be valid for those with certain theological beliefs. The argument that drug experiences are too quick and easy to be genuine as, for example, contemplative experiences take years to develop whereas drug experiences could happen in a few hours is a moot point if the experiences are the same. Subjectively identical experiences can be produced by multiple causes. However, the effects of drug induced experiences may not be as long lasting or beneficial in terms of transformations of personality and behavior [Walsh, 2003].

The debate is whether entheogens produce "really genuine" mystical experiences. There is no current theory to account for the identical states of mystical experience by entheogens or meditation and their possible different after-effects [Walsh, 2003]. With more understanding of psychological and neural processes, the causes of altered states of consciousness may now be possible. There are arguments that mystical experiences are different and can overlap [Katz, 1983; Foreman, 1990; Walsh and Vaughn, 1993; Wilbur, 2000]. Most can agree that a specific altered state can be reached via different methods whether that may be through visualization, focusing on the breath, or taking a psychedelic medication. What happens in the brain with chemical and neuronal processes may be different, but the resulting state of consciousness may be similar. Charles Tart felt that "chemical mysticism" may be experientially similar to natural mysticism [Tart, 1983]. Despite the arguments, the use of psychedelic medications producing mystical experiences have produced some long lasting valuable effects which have enhanced ones spirituality [Doblin, 1991].

The contemplative practitioner with a prepared mind after years of work to retrain habits along spiritual lines, with a strong belief and support system rather than the single profound user of a psychedelic medication, may be more prepared to make sense of the drug-induced mystical experience rather than someone without these hard-earned skills.

In the 1950s, Valentina Pavlovna Wasson, a pediatrician, first suggested the use of psychedelic drugs as a useful therapy in patients dying of incurable diseases. During this same decade, the writer and philosopher, Aldous Huxley, was interested in the phenomenon of dying and in the religious and mystical experiences induced by psychedelic drugs. He felt that the living could do a lot more to help the dying, by increasing the awareness and consciousness of not only the physiological act of human existence but possibly of spirituality too. Mystical insights were felt to be helpful in reducing the fear of death and by making death less of a mere physiological process [Grof and Halifax, 1977].

In the 1960s, Eric Kast of the Chicago Medical School, described in his studies; patients' improved abilities to tolerate their illnesses, improved communication with their families, enhanced self-respect and morale, and increased abilities to enjoy the subtleties of everyday life. He also noted a change in philosophical and religious attitudes in

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dying among patients [Grof and Halifax, 1977]. Dr. Sidney Cohen, a psychiatrist, saw the importance of Kast's previous research and felt "death must become a more human experience. To preserve the dignity of death and prevent the living from abandoning or distancing themselves from the dying is one of the great dilemmas of modern medicine" [Grof and Halifax, 1977].

Palliative Medicine is often confronted with intractable spiritual conflicts with reactions of panic, fear, and physical dependency which occur when a patient's health changes in an unexpected direction. These medications, although not without significant risk, may be shown to be helpful in certain patients to alleviate or reduce the thought of physical dependency or death as the ultimate biological disaster.

Problems with spiritual expeditions

Negative perceptions of the divine have led to psychological stress [Exline and Rose, 2005]. A person's concept of God can be harsh and punitive interfering with the capacity to enjoy life. In contrast, exclusive thoughts of a kind and loving God can be difficult to reconcile when experiencing pain, suffering, or evil in the world. William James [1902] states "healthy-minded" religious thoughts of a loving God are incomplete and inadequate as a philosophical doctrine. The evil or pain that a person experiences may be what brings reality to a present situation and the only key to life's significance and possibly the only eye openers to their deepest levels of truth. Idolizing a God may breakdown because the object of worship is unable to bear the full weight of the divine qualities that have been projected onto it [James, 1902]. Some studies report an investment in religious capital can compensate for declines in human stock [Wink and Dillon, 2001]. Deeply internalized spirituality is tied to mental health benefits, unlike spiritualities motivated by guilt or external pressures [Ryan et al., 1993]. People with a stronger attachment to God are reported to have less psychological distress than those who have a weaker attachment [Kirkpatrick, 2005]. However there are studies among gay men, lesbians, and transgender despite strong attachments to God, may find themselves in conflict with their faith, congregations, or clergy causing them to experience considerable pain, rejection, guilt and shame [Schuck and Liddle, 2001].

Growth or decline of a spiritual trajectory is determined by many factors in a person's life. As we strive to adapt our world views, relationships with the self and those closest to us, spiritual growth either occurs or it does not. As medical providers, it is important to try to find practical ways to enhance the well-being of patients through evaluation of spiritual expeditions when they are confronted with illness.

American psychology tries to help people develop better control over their lives. However, most of what happens to us, birth, illness, loss of a job, accidents, and death is out of our control. If we think deeply about what truly is in our control, it is only our thoughts and how we think about ourselves and the world around us. Spiritual expeditions may or may not help us to understand our human deficiencies, allow us to manage our lives with an understanding of its limits of control and help us come to terms with our limitations as human beings.

Spiritual judgment

Searching for a higher power, ultimate truth, reality or meaning in life to achieve some sort of beneficial spirituality can be a daunting task, especially when faced with serious life threatening illness. It is believed that finding a religious or spiritual belief will help with coping and provide a way to grieve impending death. Finding a higher power may give some a way to find meaning and purpose in life or help mend past relationships. Others may not find it helpful to believe in a higher power. They may be indifferent to present drawbacks of life and prefer to practice patience, resignation and trust. Belief in a higher power for some is the excitement of a higher kind of emotion, and nonbelievers may be satisfied by their own effort or volition. Our attitudes inevitably breakdown when we have illness or morbid fears of losing our life. "To suggest personal will and effort to a sick person with a sense of irremediable impotence is to suggest the most impossible of things. What he craves is to be consoled in his very powerlessness, to feel that the spirit of the universe recognizes and secures him, all decaying and failing as he is" [James, 1902]. In Palliative Medicine, it is not infrequent to see family members and even medical providers try to implore the dying patient to believe, pray, and hope for an outcome that may never happen. Our individual beliefs give definite meaning to our individual lives. It is important in the practice of Palliative Medicine, for this reason, to find out if a patient's religion, faith, tradition, or spirituality makes a genuine difference in their life.

The sure knowledge and close presence of a higher power does not have to be interpreted as a revelation of a deity's existence. Many people have expressed different

versions of a presence of a strong existence, physical atmosphere, or presence that has been "real" to that individual. However it comes about, it is human ontological imagination and brings with it a reality to that individual. They are convincing experiences stronger than mere logic. For this reason, it is imperative that as medical providers we are open and search for spiritual meanings within individuals and their families without judgment.

Mystical experiences

Personality changes have been found to occur with dramatic change in a person's life such as the diagnosis of a life threatening or life limiting diagnosis, divorce, and remarriage [Roberts and Mroczek, 2008]. The use of entheogens, such as naturally occurring psilocybin, used sacramentally in some cultures, has been found to have mystical experiences, long-term spiritual significance and personal meaning through its use [Griffiths, 2008]. Drug induced mystical experiences have produced long lasting changes in the personality domain of Openness [MacLean et al., 2011]. The five personality domains Neuroticism, Extroversion, Openness, Agreeableness and Conscientiousness have been found to be similar across cultures [Digman, 1990; McCrae, 2009]. Openness includes appreciation, sensitivity, imagination and broad-minded tolerance of others' viewpoints and values [MacLean et al., 2011]. The only other experimental intervention to change healthy adults' personality involved hundreds of hours of solitary meditation over several months [Sahdra et al., 2011]. Psilocybin was shown to have lasting changes in core personality traits but will need to be replicated with a larger group of individuals with more diverse baseline personality traits [MacLean et al., 2011]. Studies have shown positive changes in attitudes, values and behaviors following mystical or spiritual experiences [Miller, 2004; Paloutzian et al., 1999].

Summary

Helping patients in Palliative Medicine cope with life threatening illnesses is primary to the specialty. If mystical, religious or spiritual experiences, whether they are pharmacological or non-pharmacological, can offer patients beneficial coping mechanisms, further research into these areas seems to be warranted. The profound encounter humans face with their own impermanence and mortality during illness, brings complex dimensions of emotion, psychological, philosophical and physiological changes to one's life and family. The use of entheogens carries significant risks, though if given in supportive environments with prepared minds may become a helpful treatment option for some patients.

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Family issues

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Introduction

Family issues in Palliative Medicine are usually multifactorial. The family is often difficult to separate from patients and vice versa. When patients are diagnosed with life-threatening or life-limiting illnesses, family dynamics and functional roles of each family member are affected. Despite this, medical therapies and treatment options are usually entirely focused on the patient. This has the potential to cause family members to be on the outskirts of what is really happening to the patient. When a health care system is primarily geared toward the patient this has potential to create conflicts between patients, families and medical providers when treatments fail, treatments become too burdensome for the patient or the family, or patients suddenly approach death quickly with symptom management or comfort measures becoming a patients only remaining option for extending life. The trajectory from the moment a patient is diagnosed with a life-threatening or life-limiting illness, through the various treatment options and patient's and family's endless internet searches, through physician follow ups, second and third opinions, through side effects of treatments and success or failure of treatments is often a long and winding road. The patient is often alone with him or herself despite all the support which may be offered but is inevitably lacking in our health care system. The patient is the one who happens to have the illness and only the patient has the experience of the illness.

Patients, families and the medical community

Family's are most often the patient's intimate caregivers and historian, their only link to those not fighting disease, treatment side effects and the often slow decline of their bodily functions. When patients are not going in the direction intended by the medical staff, those in Palliative Medicine are usually the ones who enter and stay in the room while others retreat. As modern medicine advanced and death became more controlled, the dying person was no longer the center of attention. The focus of attention has been shifted to the grief of family members left behind. By reassigning death to the medical providers and institutions, we have taken it from the family structure and made it into an emotional aversion. In Palliative Medicine, we often facilitate the transition between life and death, bringing back the focus of care and thoughts to the dying patient.

The need to take family relationships into account in today's world of medicine is becoming more and more important. Assessing family functioning often involves discovering whether family members are focused on the patient's well-being, their own individual needs, or whether they are concerned about the effects of the patients situation on each other or not. Diligent collection of information from different family members, usually over time, helps determine whether the family functions more cohesively or loosely as individuals. Families were found to have improved coping skills when they found the flexibility to shift functions and transfer power during the course of a patients' illness [Minuchin and Nichols, 1993]. The medical community has an obligation to assist families make these transitions as the family structure is being changed by illness or death. Some family members need time to build trust with medical providers before sharing viewpoints. Others may not feel comfortable discussing their differing viewpoints in front of one another. Certain family members may take on the role of spokesperson and it is important to assess whether other family members share in the viewpoint

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of the spokesperson. Family stories are often helpful in allowing medical providers to understand family functioning but not necessarily to change family functioning.

There may be a time when family members take over and the patient will let go. Families eventually come to terms with what is happening before them and this can be a moment of crisis. This awareness often requires all family members to recognize that the process of aging and dying is irreversible. The patients' life as they once knew it is gone and the person who was once so strong is no longer strong.

It has been found that many patients and families mourn at the moment of diagnosis [Minuchin and Nichols, 1993]. In the U.S. our health care system is geared toward advertising our latest medical technologies. There is rarely advertisement about Palliative Medicine services in our institutions. Families and patients often become enthralled in discussions about the latest medical interventions and how illness and death can be defied. Many patients and families who mourn at the moment of diagnosis may also have more denial of death and determined avoidance of illness. At this point it is often most important to make clear that the patient maybe changed but is still alive, with a precious future [Minuchin and Nichols, 1993]. An ill and debilitated patient can still be a productive member of their family or society.

As a family member dies, the strength and function of each family member will change. Some family members are better at certain tasks while others are not and this quite often is a source of anger between family members. It is often felt that if certain family members are not at the bedside performing tasks of a nurse's aide then their contributions are nullified and invalid. Family members have to relearn how to be a family with their abilities to collaborate and accommodate each others needs while taking care of a sick family member. After death, they must also relearn to be a family without their family member.

Most family members have the capacity to collaborate, to seek out what is best for each other and to adjust to differences and new circumstances in order to adapt to the world around them. These collaborative and accommodating processes need to be recognized and emphasized in the medical community and in our various subcultures. Unfortunately what we usually focus our attention on as medical providers are disagreements, tension and strife among family members. We tend to dwell on the causes of discord, inventing or contriving an explanation for difficulties, and do not attend to the harmonies that may exist within families [Minuchin and Nichols, 1993]. Many families possess qualities of kindness, loyalty, responsibility and tolerance of each other which tends to enrich the lives of each individual within the family.

Negotiating family issues

Negotiating family issues during a crisis, which is usually what it is called, when someone is given a life-threatening, life-limiting diagnosis can be difficult. Often during these times family issues are intensified when families challenge the physician's authority, are plagued by their own disagreements, may raise the specter of litigation, or are culturally diverse from the physician and treating medical team. With today's aging population, patients who are themselves facing their own poor prognosis may be caregivers for more seriously ill family members. The needs of family members for timely and clear information are significant but frequently underappreciated.

Over the past decade, the concept of Palliative Medicine, and the attention of the scientific and medical community has dedicated to it, has significantly improved as well as the availability of palliative medicine to patients who need it. Although the subspecialty is poorly understood by many patients, families and medical providers, for example the use Palliative Medicine for end of life issues only, there has been a slow increase in earlier integration of Palliative Medicine consults within the practices of other specialties. Palliative Medicine aims to improve the quality of life of patients and their families when they are faced with life threatening diseases, or they are undergoing potentially toxic medical treatments, as well as when they are diagnosed with an advanced chronic illness.

The World Health Organization (WHO) embraces the approach of Palliative Medicine. It supports the care needed not only by the person who is fighting the disease, but recognizes the struggle that the family experiences too. This includes prevention and relief of suffering by early recognition, assessment and treatment of emotional and physical pain which may not derive solely from the disease itself. Palliative Medicine often requires a psychosocial and spiritual assessment to properly address patient and family concerns during the entire course of illness [WHO, 2013].

In Palliative Medicine, the involvement of families in the everyday care of patients is fundamental. Sometimes it is a spouse, a partner and other times it is the extended family. The degree of involvement differs among families and cultures, but it may also depend on how close family members are, or on how their relationships have developed

over the years, and therefore what connections have been established or severed.

Making decisions about end of life or transition of care is among the hardest decisions a family can face. It can be sudden, or it can occur over a period of weeks, months or years. No matter what, a family is asked to be involved in decision making and to take on responsibilities they sometimes do not ask for. Families are usually the foundation of one's life, the main support, the first resource, and those who should be there during the happiest and the most challenging or saddest time. A family may be composed of one person or many members and may be a friend, a partner, a son, a daughter, a mother. The patient dictates the family structure and who should be involved in decision making [Hudson and Payne, 2009]. When Palliative Medicine becomes part of a patient's treatment, whether it is an end of life issue or not, the role that the family plays is essential as well as the interdisciplinary hospital team that assists patients and families.

One of the most fascinating things about families is that they can be very dissimilar from one another. They have different cultures, values, religion, habits, thought processes, and, most importantly, ideas and wishes about end of life. These factors are always to be taken into consideration by the members of the multidisciplinary team, because the patient and family wishes and goals will ultimately determine the course of treatment. This is more pronounced when the patient cannot make decisions for him or herself and health care proxies are involved in decision making. Palliative Medicine frequently explains the role of health care proxies to families as not making decisions for the patient but rather giving health care providers information about what the patient would want or not want in terms of treatment options. The responsibility of the health care proxy is not to give medical providers blanket authorizations with statements such as, "I want everything" for my family member but rather a more difficult position of trying to be the spokesperson on what is in the best interest of the patient.

Culture and end-of-life

Making decisions about life and death is a tremendous burden for families and they need to know that they are not alone in the decision making process. Cultural issues at the end-of-life may not always be addressed in the depth that they need to be in order to facilitate ongoing decision making. It is important to find out the identity of the patient and then the patient and family must be willing to open up and discuss this with the medical provider. Finding out about cultural beliefs can be done through discussion about patient and family decision making processes, attitudes and beliefs about how they approached life and death and dying, environments in which they lived and worked, and spiritual and non-spiritual support in their community. It may be found that patients and families actually prefer a natural death despite all the seeming demands for the use of advanced technologies to keep them alive because they have not had frank discussions that the patients condition is terminal. Also important is the historical and political context of a persons' life, their place of birth, immigration and refugee status, experiences with discrimination or lack of access to care, degree of integration into their ethnic community and languages spoken [Kagawa-Singer and Blackhall, 2001]. Taking a complete social history from the patient and family gives us reflection into the way culture shapes the lives of patients and also promotes self-reflection into our own biases, beliefs and practices.

A recent study reported that caregivers ranked faith in God second only to physicians recommendations; this gives us a clear idea of how strong religious beliefs can be and what role they play in the lives of many [Brownwynne and Ebere, 2012]. African Americans are much less likely than Caucasian to use Hospice and Palliative Medicine. A study reported that only 8% utilized those services because of less exposure to them, and of that percentage many are likely to withdraw once enrolled and therefore less likely to return [Brownwynne and Ebere, 2012; Haley et al., 2004]. African Americans may view suffering as a part of God's plan and part of generations of struggle which is rooted in a long history of health disparities and discrimination. As a result, African Americans tend to accept more easily comfort care in a hospital environment where they know the family members will receive good care rather than transfer them to another facility where there is uncertainty about the quality of care provided [Johnson et al., 2008; Brownwynne and Ebere, 2012].

Hispanic families frequently choose to directly take care of the patient in the home, they stay together and support one another; they pray, they suffer, and they spend as much quality time as they can with the loved one until the moment of death. The family as a whole is close to the person who is dying. Seeking assistance is an acknowledgment of burden which is culturally unacceptable. A recent study reported that Hispanic decisions about end of life are highly affected by acculturation. More acculturated families do not

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prefer feeding tubes, but do prefer Hospice and Palliative Medicine, and less acculturated chose more aggressive approaches [DeSanto-Medaya *et al.*, 2009]. This is not only a trend that affects Hispanics, but Caucasian individuals too. Hospice services are often unavailable in Hispanic cultures, decreasing the treatment options available for many families.

Communication and families

Communication can be challenging among family members in the US due to geographic distances between many patients and family members. The US is large geographically compared to many European countries and smaller compared to Russia or China. Traditionally teenagers may move far away when going to college and may often start a new job in the same place. According to one study, people generally know that life does not last forever, that it may end unexpectedly and it is a concept understood and internalized at a young age [Schaefer and Lyons, 2010]. Families in the US are spread around the country and this phenomenon seems to be more common than in other parts of the world. Many patients have health care proxies or next of kin living far from where the patient is hospitalized. When communication is required, patients often but not always want families involved in discussions. It is quite burdensome to the patient, to communicate bad news or news of an uncertain future to their family while trying to come to terms with their illness and treatment options. The decision making process especially for end-oflife treatments is a delicate one and family members often do not have a thorough understanding of the patients illness and treatment options.

Family meetings for the purpose of communicating information is often best after family members have had time to speak with physicians, consultants, and nurses. There are many approaches to communicating information but there is no one way which can be considered the right way. The general formula may be something like finding out the patient and family's interpretation of what has been explained to them. Then asking how the patient and family would prefer information to be handled. Information may then be shared; providers may wait for a response to the information which may include responding to the emotions of the family. Then goals of treatment are usually established [von Gunten *et al.*, 2000]. However, it is often more important to have insight into the thoughts of the patient and family prior to these meetings. This can best Part I

be accomplished by frequent interactions with multiple providers if family is available, a thorough social and spiritual assessment and the ability of providers to document actual patient and family thoughts as verbally or nonverbally expressed. If family is not available, then frequent contact via telephone may help establish trust and insight into family dynamics and decision making processes. Family members may attend meetings with intense anger or focused on their individual investigations into the care of a patient or the topic of a feeding tube which may have the tendency to dominate conversations away from what is actually happening with the patient. In these cases, it is sometimes important to quickly re-establish lost trust but emphasizing the medical teams' strong commitment to providing the best care possible. This may require clinicians to dominate discussions by letting the patient and family know that individual efforts at finding fault with the clinicians or hospital is counterproductive to providing the best care possible to the patient. At the same time, it is important to establish emotional closeness with the patient and family in an empathetic way so that they do not develop illusions of unrealistic goals which may prevent them from coming to terms with the reality of the present condition of the patient. By persisting in illusionary thoughts and hoping for an outcome which may never occur can cause patients and families much distress and avoidance of emotional growth, reconciliation and closure. Preparation for a changed functional level, new diagnosis with a long treatment course or death and achieving a sense of completion are important factors to many patients and families [Steinhauser et al., 2000]. Patients suffering during illness and end of life can be profound and often medical providers are unaware or ill prepared to help patients through these difficult times. Studies show that strong relationships between patients and health care providers should be emphasized more than the patient's disease [Steinhauser et al., 2000]. Finding out the priorities of patients and families, aside from disease management or placement, can be beneficial to the patient and medical providers. Some patients have been shown to favor mental awareness, being at peace with God, not being a burden to family and being able to help others as a priority toward the end of life whereas medical providers did not feel these were as important [Steinhauser et al., 2000]. Being prepared for the end of life is what the patient dictates it is and knowing that one's family is prepared can often help patients and families to begin to change their roles within the family before debilitation or death occurs. Discussing patient and family member personal fears

suggests death is more imminent and is often considered unwelcome discussions. It evokes fundamental questions of our existence as human beings [Steinhauser *et al.*, 2000].

Some evidence suggests that longer participation in palliative care decreases anxiety among family members prior to bereavement [Higginson, 1996]. It was anticipated two decades ago that end-of-life care in the next half century would be in much need in helping patients and their families prepare for physical changes and prepare both psychosocially and spiritually as aging and life comes to closure.

Dying: a family issue

There have been various theories of grief, death and dying studied over time. Some authors have raised criticism over the years about grief theory and instead may take the view that grief is a personal reaction that may or may not involve specific stages. The affirmation that these stages are universally valid, would neglect the existence of cultural differences to deal with end of life matters. In fact, some ethnic groups do not see the end of life as a painful event that involves mourning and suffering. They perceive it as a natural consequence of the life cycle, and they celebrate it as one.

Healthcare providers, such as physicians, nurses, and social workers in a hospital setting are the first to encounter and deal with patients and families who are experiencing the stages of grief, anger, fear and many other emotions when a family members' illness requires hospitalization. Although the patient is only one, the family who supports the patient represents a system that the hospital staff must learn about and work with. Families are a set of functional and dysfunctional relationships composed of different dynamics and reciprocal bonds. The moment they have to deal with end of life issues, they may become unpredictable, and those dynamics that have been stable for years suddenly may radically change.

Dying may take minutes, hours, days, weeks or months. Death is life altering for every family member in a different way. Experiencing transitions from life to death can be so profound.

Eastern and western family structure

The focus in Western culture is the individual. The individual human being is differentiated from other human beings. In Western culture there is dependence on the nuclear family, usually with two committed parents, oriented to developing self-esteem, confidence and independence. Within the nuclear family structure there is internalizing of whatever is absent in the relationships between family members. In the U.S., the nuclear family and desire for autonomy of the individual is felt to put much strain on the parent-child relationship [Epstein, 2004]. When a child's behavior is counter to their parents or when the parent's ambitions for the child takes precedent over who the child really is, the nuclear family structure becomes a damaging and claustrophobic environment. The child may try to avoid those they are most dependent upon.

In contrast, Easterners are enmeshed in family hierarchies and group expectations for which privacy is often rare. An Easterner's capacity for empathic awareness, emotional harmony and acclimatization to relationships within the family structure, helps to relax ego boundaries and provide family members a sense of belonging and acceptance [Epstein, 2004]. In Eastern cultures, the positive feelings about oneself is taught early and supported through the many interdependent relationships within the family structure.

The emphasis of the Western nuclear family is on the individual and autonomy which often causes a drive for achievement versus affection creating isolation and alienation from relationships.

In the U.S. it is sometimes difficult to involve families and even larger extended families into the churning health care environment. Western families are often far removed from the bedside with very little involvement in the cleaning, turning and feeding of the patient. In Eastern cultures, families are often expected by their culture and the hospital staff to do much of the care at the bedside. This allows a more intimate connection between family members and the patients' body and improvement or deterioration over time.

Understanding more about family relationships within different cultures may help medical providers to establish goals of care more tailored to the patient and family. This is an area in Palliative Medicine that would benefit from further study.

Decision making

In the U.S. health care system, laws give individuals the power of self-determination. This power is given to the appointed health care proxy or power of attorney if a person cannot make decisions for him or herself. Although the laws of patient rights give patients and health care proxies decision making capacity, in practice, they are not actually

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in the position to demand a certain treatment although it seems at times that they do. If patients are able to make their decisions, they are given choices of treatment options. If they are unable to make their decisions, then the health care proxy's role is to give medical providers what the patient would accept or not accept if they were standing in the room and could decide for themselves. The patient and health proxies are given reasonable treatment options that are focused on improving the patients' condition. If the patient wants to pursue treatments that a physician does not recommend, the physician is not obligated to provide it and the patient can seek a different opinion. Just as health care proxies are not actually making decisions but rather giving the health care provider an idea of what the patient would have wanted. If the health care proxy does not keep the patients best interests as paramount, then the health care proxy can be deemed incompetent. In Palliative Medicine, discussions about reasonable treatment options and the role of health care proxies is common. Family members have responsibilities to each other, and the most important responsibility can be to understand when it is the right time to let go and to recognize and acknowledge that they are acting in the patients best interest.

In some developed countries such as Italy, the legal context of end of life decisions are still made on the basis of the Civil and Penal code laws over 60 years old. Only recently, in 2004, the figure of the "Support Administrator" was approved by the Parliament as the equivalent of a health care proxy in the U.S. [Zamperotti and Proietti, 2006].

One of the hardest topics to discuss with patients and families are treatment preferences and options because they inevitably lead to decisions. When patients and families state "I want everything" invariably many medical providers also state "the patient says they want everything." Underlying this request may be fears of becoming sicker, concerns that medical providers will be less vigilant or abandon them if they choose less aggressive therapies. "Everything" is felt to include various treatment philosophies and it is necessary at the mention of this word to gather more information about patient's treatment philosophies [Quill et al., 2009]. They may include the maximum or minimum amount of suffering a patient is willing to endure with a reasonable chance of prolonging their life and to what degree of debilitation. The degree of debilitation which patients happen to have is quite extensive but the inquiry about the patients level of the cognitive debilitation and awareness of what is happening to their bodies and treatments provided is often most important.

A patients' relationship with their religion and medical treatments may lead them to say that God is the only one to make decisions on life and death and it is separate from

to make decisions on life and death and it is separate from medical treatments. Some patients may request to be kept alive for God to perform a miracle. A discussion to connect medical providers with patients and families may be to discuss that we are all agents of God and we are all trying to do what's best for the patient. Discussing faith in God's will allows a question about when God or the guidance of the patients' religion will let us know it is the patients' time.

Empathizing with the family by communicating a thought similar to their own such as wishing treatments could turn things around and allow the patient to wake up. Statements such as this can often help families realize medical providers are giving all treatments possible and they understand the family's hopes and loss [Quill *et al.*, 2001].

Decision making requires a deeper understanding of the patient and family's thoughts, concerns, emotions and values about extending life, avoidance of suffering, philosophies about the quality of life and death within the context of the family. This can and should be regular and daily routine for all medical providers.

Summary

The family plays an important role in Palliative Medicine. The issues families encounter when facing the deteriorating condition of a family member and the burdens and benefits of treatment options are many. More attention to family context and structure, their concerns, and their experiences with life and death may help to ease tensions between patients, families and medical providers. Normalizing discussions about patients declining condition, limited treatment options and end of life cannot be made without as much information as possible about relationships between family members. How families overcome difficulties related to patients receiving treatments for life-limiting or lifethreatening illnesses and end of life is the work of everyone within the health care environment.

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Palliative medicine and bereavement

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Introduction

The integration of Palliative Medicine should begin upon hospital admission through screening for Palliative Medicine needs in patients with life-limiting or life-threatening illnesses and should be maintained as the patient transitions through different levels of care. Palliative Medicine also encompasses the support of families involved in the care of dying patients and is an additional supportive consultation service to address family grief and bereavement. The definition of bereavement is the objective circumstance of having lost someone significant who has filled many interpersonal functions. Bereavement by itself is a social phenomenon. Grief is the emotional response to the loss of someone significant. Mourning is the action or expression of grief often reflected through cultural or religious practices. Bereavement care is often part of the services received with Hospice enrollment. Integrating bereavement care into Palliative Medicine while patients and families are undergoing aggressive treatments can give health care providers a better understanding of how patients and families grieve and the associated complex emotions which occur with life-threatening or life-limiting illness and loss. With a better understanding of grief and mourning, clinicians may be better prepared to assist patients and families prior to experiencing significant functional decline or death of the patient.

Bereavement research

Bereavement, as it relates to an increase in mortality risk, has been studied as early as 1858, by W. Farr in his book Influence of Marriage on the Mortality of French people. Historically, bereavement research was primarily focused on health impact and social/economic consequences [Stroebe *et al.*, 1988]. The impact of widowhood in terms of the changes in social roles after the death of a spouse, changes in economic status and new self identities within the community were the primary focus. It was found that mortality rates for married persons were lower than they were for widows. Widowers also had a higher mortality risk than widows. Persons widowed at younger ages had a higher risk of mortality than older widows. Short durations of bereavement were also associated with higher risks for health consequences. Freud's early focus on mental health and bereavement [1917] had significant impact on the need to further study grief and bereavement but primarily focused on complicated grief. Some of the first studies on uncomplicated grief were done by Eliot [1930, 1932] with recognition of emotional states such as shock, denial, abandonment, yearning and the gradual successive phases one experiences. In 1944, Lindemann, a psychiatrist, outlined normal grief responses versus pathological grief responses [Lindeman, 1944]. The symptomatology of grief has since been studied in great depth and there is significant evidence that bereavement and the effects of loss can have significant emotional, psychological and physical consequences [Parkes and Weiss, 1983]. By the late 1980s, there was still felt to be a lack of research about the incidence and prevalence of mental health impact between bereaved and non-bereaved individuals. The effects of bereavement on physical health were difficult to detect due to the fact that those people with physically or mentally ill health were less likely to participate in studies. High risk groups for poor outcome of bereavement have become the most recent focus of bereavement research. The nature of a human being's vulnerability to poor and debilitating outcomes after a loss due to risk factors such as sudden death, lack of social support and death at a young age are considered contributory. Identifying risk factors was considered important to prevention of poor bereavement outcomes. There began a shift away from the causes of pathological grief to preventative therapy for the bereaved to reduce the incidence of poor health outcomes. Evidence began to strongly suggest that social interventions can reduce poor bereavement outcomes.

Bowlby's attachment theory [Bowlby, 1983] moved the intrapersonal approach to grief to the interpersonal perspective of a substitute attachment to others as ameliorative to help individuals through grief. Research then focused on how bereaved individuals must utilize social support systems to build a new life and self-concept [Lopata, 1979]. The deficit model of bereavement by Lazarus and Folkman [1984] used both intrapersonal and interpersonal relationships to help analyze and predict those individuals who are likely to cope well and overcome grief following bereavement.

Since bereavement is a social phenomenon and related to deterioration of health, its potential helpers are often health care professionals. It is most important to understand the social context in which the bereavement has occurred in order to understand how individual patients and family members grieve. It is the obligation of all health care professionals to be cognizant and more directly involved as agents of change to help the bereaved, the newly diagnosed patient with life-limiting or life-threatening illnesses to help them through often irreversible conditions.

Grief and loss assessment

Assessment and evaluation of how patients grieve and how they have managed other losses in their lives is something all clinicians can participate in. Loss does not have to be loss of human life but it can also be loss of a job, a pet, a limb or a house. How we manage to cope with loss of something we cherish or take for granted can shed light on how we may grieve with the reality of our own impending death or that of a family member. A regular Palliative Medicine assessment is finding out how patients and family members make decisions. Grief and loss assessments should be as regular as finding out how decisions are made. Each patient and each family member of a patient will grieve and cope differently to loss depending on their relationships with each other. Normalizing discussions around anticipatory grief and discussing with patients and families that it is as normal to not accept certain treatment options as it is to accept them. The dual process model of coping with bereavement [Stroebe and Schut, 2010] describes what may often occur in individuals. This process is an oscillation

between loss-orientation and focus of grief to a gradual transition to restoration-oriented tasks, such as forming new relationships, until total attention is shifted away from these tasks.

Existential suffering

The use and definition of existentialism is difficult to pinpoint. It is believed to have been used by Kierkegaard who borrowed the term from the poet and literary critic Wellhaven, but it was more prominently used by the selfdescribed existential philosopher Sarte. Existentialism was applied by the late 19th and 20th century philosophers with the primary belief that philosophical thinking begins with the individual human beings actions and feelings. The "existential attitude" was described as an individual's sense of disorientation and confusion in a meaningless and absurd world [Solomon, 1974]. Kierkegaard proposed that each individual, not society or religion, is responsible for giving meaning to life and living life with sincere passion and authenticity.

Suffering has many definitions from philosophical, religion, biological, physiological, psychological and emotional. It is usually associated with pain or distress in an individual's life or family. From a Stoic philosophical point of view, the greatest good lies in reason and virtue bringing a sense of indifference to pleasure, pain and suffering. It is a sort of stern self-control of suffering and a way of looking at oneself in regards to painful experiences.

The obligation of health care providers is to relieve human suffering however it may be expressed by the patient and/or family. Advanced illness and the success in the management of chronic and acute illnesses brings with it the inevitable unreliable suppression of our awareness of death and when it will occur [Kissane, 2012]. Suffering is usually when there is threat to or injury of the self resulting in distress, helplessness or the discovery of the likelihood that suffering is without end. Uncertainty in life is suddenly prominent. The recognition of the different modes of suffering within patients and their families is an important assessment, evaluation and diagnosis in Palliative Medicine. It is often unrecognized by the treating physicians and/or communicated to the Palliative Medicine providers rather than to the "treating" or attending physician. Unaddressed existential angst and unrecognized family distress are common aspects of human suffering [Kissane et al., 2001]. Simone de Beauvoir wrote, "There is no such thing as a natural death... for every man his death is an accident,

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and, even if he knows it and consents to it, it remains an unjustifiable violation" [de Beauvoir, 1966].

Our defenses emerge when the possibility of death or a life-limiting/life-threatening diagnosis is made. These defenses are fueled by our powerful sense of individual specialness, our convictions to religion, active denial or unreliable suppression of reality and heroism in ourselves. Palliative Medicine tries to relieve the intensity of suffering by providing additional assistance with symptom management and at the same time finding ways to give patients and families courageous acceptance of impending death or decline in health. Helping patients and their families to find the right balance between fear and excessive self-concern and the opposite, excessive confidence or boldness is how we can also help prepare patients and families with bereavement.

Uncertainty

The uncertainty in medicine remains greater than what most patients and their families want to believe, despite significant medical advances. Often this uncertainty must be mentioned in Palliative Medicine as a way to help patients and families to start to think about, and become more aware of, outcomes that are less than expected. Uncertainty of our humanity is often masked in medicine by being careful to make sure the patient is clean, clothed and free of smell. Patients and families are alienated from the sweat and smell of the ill by our institutions constant control of these offensive reminders of our mortality. Uncertainty is an exceptional opportunity which allows families time to come to terms with impending bereavement, acceptance of the patient's new self, encouragement of the sharing of grief between family members and to ultimately learn how to continue to love one another as life changes.

When illness dominates one's life, fear, anger and obsessive controlling thoughts tend to avoid thoughts toward coping and reframing expectations. Palliative Medicine can often assist patients and families by early referrals to supportive therapies such integrative medicine and therapies.

Preparatory grief and bereavement

Anticipating grief and bereavement of the loss of a family member is usually met by a multitude of uncertain events. Families usually have many differences of opinions and it is important in Palliative Medicine to let families know Part I

this is normal. Disagreements are usual and normal in families. There are differences about how each member of the family is participating in the dying process, different opinions about funeral arrangements and more often than not, fierce financial disputes. Irreparable damage of previously loving relationships can occur. Supporting those close to the patient and allowing the patient to be sick is one of the primary goals of Palliative Medicine. Preparatory grief is a normal reaction to perceived losses experienced by patients who are dying and their families [Periyakoil and Hallenbeck, 2002]. Being aware that patients and families may ask the same questions multiple times in order to absorb the reality of the patient's circumstances and facilitating family involvement in care may help alleviate guilt, help families to say goodbyes and manage concerns around impending death. Palliative Medicine can often facilitate preparatory grief and bereavement by regular family meetings to help support and gently move patients and their families toward mutually beneficial goals of care for all involved. "Membership in a family brings historical connection, a sense of kinship and duty, and a loyalty that can be called on at times of crisis" [Kissane, 2012]. In Palliative Medicine, family is often an asset rather than a liability, as it may be with patients who are without family. Avoiding the protectiveness of hoping for a future outcome that may never happen or unrealistic optimism at the cost of teamwork and cohesive mutual support is a primary function of Palliative Medicine. Preparatory grief and bereavement can be reduced in its intensity by the mentioning of a patient's accomplishments within family discussions in the medical record for the providers of care to the patient. This can be a way of reframing the value of the patient's life and an opportunity to sustain a meaningful life for the family as well as engaging medical providers in the ongoing creation of goals with a meaningful purpose to the patient and family. Focusing on the value of relationships and gratitude within the family and with medical providers may help to focus on living until death intervenes [Kissane, 2012].

Summary

In Aristotle's words, "The value of life is in awareness and our power of contemplation rather than upon mere survival" is a valuable thought when trying to have conversations with families about their understanding of human limitations and capacity for respect and tolerance of others. Trying to empower patients and families to make decisions together, to support one another and to love one another does not end. Even after death, there is much more the medical profession can do to achieve a much more meaningful acceptance of human limitations. It is through the medical professions own acceptance of the limits of medical science that this can be achieved.

In working with other specialties, Palliative Medicine has provided valuable information to clinicians who may not have the expertise or time to address suffering. The thought that one specialty or omnipresent medical provider can address all patient and family distress and suffering has long been antiquated and no longer state of the art care. Future studies in bereavement involving various disciplines and lifelong learning may help the medical profession to work together as a team to interact with patients and families authentically and with genuine empathy.

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Prognostication

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Introduction

The word "prognosis" is of Greek origin and means "foreknow". In modern medicine, physicians often overlook prognostication and it has become a lost art. For palliative care providers, when discussing goals of care and aspects surrounding end-of-life, the ability to prognosticate accurately is crucial. Prognostication truly blends the art and science of medicine by requiring practitioners' synthesis of known disease trajectories, symptom assessment, and biomarkers, and to effectively communicate that information to the patient and their family.

An accurate prognosis is necessary for the patient and their family to plan appropriately for the future and make informed decisions regarding goals of care and whether to intensify or discontinue certain treatments [Maltoni, 2009]. When patients and families are aware of prognosis they are more likely to forgo aggressive or inappropriate interventions and therapies [Mitchell *et al.*, 2009]. If a patient knows they have a limited prognosis it allows them to spend time getting their "affairs in order" (such as funeral arrangements, wills and other legal documents) and to spend time with family and friends while focusing on improving the quality of their remaining life. For those with a life expectancy of less than six months, an accurate prognosis is also necessary for appropriate and timely Hospice referrals.

Accuracy

Physicians often are not accurate prognosticators. Physicians

generally prefer not to discuss prognosis with their patients and avoid doing so. Physicians often avoid communicating a patient's prognosis because they are uncomfortable with the process of breaking bad news [Christakis and Iwashyna, 1998] and they also believe repercussions may follow when offering a prognosis. Believed repercussions include the fear of taking away patients hope or faith [Reinke et al., 2011; Daugherty, 2004], that giving a prognosis will lead to a self-fulfilling prophecy whereby the patient will in fact die because they know the prognosis [Rich, 2001] and concern that if the prognosis is incorrect the patient will lose faith in the physician's abilities. These fears are exacerbated by a general lack of training and knowledge in prognostication [Christakis and Iwashyna, 1998]. Over the past thirty years, there have been several studies detailing the problem of inaccurate prognostication. Despite this recognition, there continues to be a lack of medical education and rampant prognostic inaccuracy.

One study comparing prognoses of cancer patients among medical residents, an experienced physician and a tumor board, each prognosticated correctly only 61/55/63% of the time, respectively [Gripp *et al.*, 2007]. There is a great deal of skill involved in differentiating "dying" versus "reversibly sick" [Taylor and Johnson, 2011] which may come from greater experience. Overall, more experienced physicians are more accurate [Christakis and Lamont, 2000]. Even those with more skill, such as oncologists who prognosticate more frequently, are not always accurate and repeatedly more optimistic than their non-oncology counterparts [Christakis and Lamont, 2000]. Part I

When physicians or other practitioners do offer a prognosis, it is frequently an overestimate [Llobera *et al.*, 2000]. In the same study as above, medical residents, an experienced physician and a tumor board all overestimated the prognosis in patients with less than 1 month to live 96/71/87% of the time [Gripp *et al.*, 2007]. Physician predictions have been shown to be overly optimistic 80% of the time, by a factor of two or more [Parkes, 1972].

The duration and depth of the physician-patient relationship may affect the offered prognosis. Some studies have found that the longer the physician knows the patient the more likely the prognosis is an overestimate [Christakis and Lamont, 2000]. Other studies, however, suggest physicians are more likely to give an accurate prognosis if they know the patient well [Reinke *et al.*, 2011]. Accuracy may also relate to the confidence of the prognosticator, who may offer a less precise prognosis when less certain [Marcin *et al.*, 2004].

A patient's life expectancy also impacts a physician's ability to prognosticate accurately. When patients have a longer-predicted survival, the prognosis tends to be more inaccurate [Christakis and Lamont, 2000]. Predictions of less than one month are generally the most precise, and predictions greater than six months are not highly correlated to actual survival [Glare *et al.*, 2003].

Prognosis is a snapshot in time, and developing a prognosis is based on numerous fluctuating factors. A prognosis should not be a fixed assessment. Prognostication should be dynamic and evolving. When events occur and time passes, the prognosis should be reassessed and addressed with the patient and family.

Formulating a prognosis

Factors involved in prognostication include type and severity of illness, functional status, patient symptoms, biomarkers and psychosocial elements. It is inappropriate to assess prognosis on one factor alone. Models combining multiple elements are evolving to enhance prognostic accuracy. Often there are specific markers or criteria to help prognosticate in specific disease processes. Despite efforts to understand and enhance prognostic accuracy, little attention has been paid in the literature to how co-morbidities affect prognosis [Maltoni, 2009].

Staging

Staging and severity of a disease is a useful starting point

when formulating a prognosis (mild *vs.* advanced dementia, local cancer *vs.* widespread metastases). However, knowing stage alone is insufficient to develop an accurate prognosis. The advanced or end-stage disease trajectories will be discussed in more detail later in this chapter.

Symptoms

Several cardinal symptoms repeatedly represent a poor prognosis. For example, data from the National Hospice Study [Reuben *et al.*, 1988] showed that anorexia and eating problems, weight loss, dyspnea, xerostomia and dysphagia were all independent poor prognostic signs. Since that study, the symptoms that frequently recur in the literature as portending a poor prognosis are dyspnea, anorexia and weight loss, fatigue, dysphagia or difficulty eating and delirium or confusion. The presence of multiple symptoms is associated with a worse outcome [Llobera *et al.*, 2000; Teunissen *et al.*, 2006]. Much of the research on symptoms has been done in patients with cancer, but most symptoms are applicable to multiple disease states.

Dyspnea

Dyspnea, or the sensation of breathlessness, is very common in terminal illness. As many as one in four patients have moderate to severe dyspnea in the months leading up to death regardless of type of advanced illness [Currow *et al.*, 2010] even when there is no underlying heart or lung disease [Reuben *et al.*, 1988; Mitchell *et al.*, 2009]. Timing and severity of dyspnea can vary between patients with cancer and those with non-cancer diagnoses. Patients with cancer may exhibit more dyspnea at the very end of life (within 10 days) compared to those without cancer who may suffer from more severe dyspnea and of longer duration [Currow *et al.*, 2010]. In cancer patients, dyspnea is an independent prognostic factor for poor survival [Barbot, *et al.*, 2008; Gripp *et al.*, 2007; Maltoni *et al.*, 2005].

Anorexia and weight loss

Anorexia-cachexia syndrome is found in advanced cancer as well as end stage COPD, congestive heart failure (CHF), acquired immunodeficiency syndrome (AIDS), renal failure and liver failure [Del Fabbro and Bruera, 2006]. Cachexia is very common, affecting more than 80% of advanced cancer patients [Bruera, 1992]. Weight loss is an independent prognostic factor for mortality in cancer patients [Vigano

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et al., 2000a]. In patients with CHF, cardiac cachexia can occur. Anorexia is part of the Palliative Prognostic Score discussed further in this chapter.

Fatigue

Fatigue is a prevalent and under-recognized symptom, especially in advanced cancer patients. Patients with fatigue have great disturbances in quality of life which may cause more distress than pain or nausea [Morrow *et al.*, 1995]. Fatigue is a poor prognostic sign and is associated with decreased survival in cancer patients [Kikuchi *et al.*, 2007]. As many as 96% of pediatric cancer patients report fatigue in the last month of life, and it is frequently associated with suffering and poor quality of life [Ullrich *et al.*, 2010]. Fatigue is complex and closely related with other symptoms, as well as treatment for those other symptoms (such as opioids for pain), which may make fatigue more difficult to recognize and treat.

Dysphagia

Dysphagia is an independent prognostic factor for an increased risk of dying in cancer patients [Teunissen *et al.*, 2006] and is associated with poor survival in cancer patients as well [Vigano *et al.*, 2000a]. Evidence of dysphagia also has significance in patients with other illnesses, especially dementia. Frequently in end-stage dementia patients, dysphagia leads to aspiration pneumonia which often is a cause of death in this population [Mitchell *et al.*, 2009].

Delirium

Delirium, or an acute confusional state, is very common in the palliative care setting and the presence of delirium is a poor prognostic sign [Caraceni *et al.*, 2000; Inouye *et al.*, 1990; Vigano *et al.*, 2000b; Maltoni *et al.*, 2005]. Delirium can be precipitated by, among other things, infections, metabolic abnormalities, medications, constipation and uncontrolled pain. Though delirium can occur in any population, including children, patients with underlying cognitive deficits are at greater risk [Brietbart *et al.*, 1997]. Delirium is more often associated with male gender, central nervous system metastases, lower functional status, worse clinical prediction of survival (CPS) score, the presence of anorexia or dyspnea and steroid use [Caraceni *et al.*, 2000]. Delirium is included in the Palliative Prognostic Index (PPI). Part I

Functional status

A person's functional status is related to their ability to ambulate and complete their activities of daily living (ADLs). Functional status has better predictive capacity for patients with advanced cancer than other diseases and oncologists often use a measurement of functional status, the Eastern Cooperative Oncology Group (ECOG) to guide when patients are appropriate candidates for chemotherapy or continued aggressive treatment. The Karnofsky Performance Scale (KPS) and the Palliative Performance Scale (PPS) are other scales used for prognostication which incorporate functional status. Functional status has additional importance when used in combination with the presence of symptoms. Even when functional status is maintained fairly well, presence of multiple symptoms lead to a shorter lifespan [Reuben et al., 1988]. A poor functional status is fairly reliable for short term survival but it may be more critical to assess rate of decline in functional status rather than status alone [Maltoni et al., 2005]. A measure of functional status is included in both the PPI and the Palliative Prognostic Score.

Biomarkers

Combining biomarkers with functional status or disease state improves prognostic accuracy. Early studies looked at albumin and leukocyte count as prognostic indicators, while more recent attention is focused on lipids and inflammatory markers.

Leukocytes

Elevated leukocyte count [Gripp *et al.*, 2007] and a low lymphocyte percentage are related to a poor prognosis [Maltoni *et al.*, 2005]. Leukocyte count and lymphocyte percentage are included in the Palliative Prognostic Score.

Albumin

Low albumin is an indicator of a poor survival, often independently of other factors. [Horwich *et al.*, 2008; Barbot *et al.*, 2008]. Albumin less than 2 g/dL is shown to have increased mortality compared to controls [Hannan *et al.*, 2012] but generally it is suggested that levels less than 3 g/dL are indicative of a poor outcome [Kikuchi *et al.*, 2007]. Even when albumin falls within a normal range, variations or drops within that range can also have Part I

prognostic value [Horwich *et al.*, 2008]. Similarly, low albumin can be predictive of mortality in patients without identified disease [Goldwasser and Feldman, 1997]. Albumin is an independent prognostic factor for mortality in dialysis patients [Iseki, 1999].

Lipid

Low levels of high-density lipoprotein (HDL) are associated with increased inflammation [Kim *et al.*, 2012] and other markers of inflammation, such as an elevated CRP, are associated with higher mortality. High levels of lowdensity lipoprotein (LDL) are also associated with a worse prognosis [Vigano *et al.*, 2000a]. Cholesterol is a factor which is included in the Seattle Heart Failure model used for prognosis in CHF patients.

Uric acid

Specifically in cancer patients, uric acid has been investigated as prognostic aid. High uric acid may be related to declining renal function in end stage cancer or tissue damage from inflammatory processes. High uric acid levels, greater than 7.2 mg/dL, correlated with a shorter survival and were high 1-2 weeks prior to death [Shin *et al.*, 2006]. Uric acid also has prognostic significance in CHF and is included in the Seattle Heart Failure Model.

C-reactive protein (CRP)

CRP is a marker of inflammation, and has been studied as a prognostic tool in many populations, including patients with cancer, CHF, ESRD and COPD. In dialysis patients, CRP was shown to be an independent risk factor for mortality and may be related to disease progression and tissue damage [Iseki, 1999]. In COPD patients, elevated CRP >3 mg/L is associated with increased mortality, as well as reduced lung function and greater decline in FEV₁ [Dahl *et al.*, 2007].

B12

Elevated B12 levels are associated with a shorter survival in cancer patients, with levels greater than 600 pmol/L are linked to the shortest survival. B12 also has been studied in conjunction with CRP in cancer patients, in which if the product of B12 and CRP was greater than 60,000 it predicted the poorest outcome [Geissbuhler *et al.*, 2000].

Hyponatremia

In a study examining a middle-aged population, there was an increased risk of death or myocardial infarction with serum sodium less than 137 mEq/L [Sadadeij *et al.*, 2009]. Hyponatremia also has prognostic significance in end-stage liver disease described below. Levels less than 138 mEq/L are associated with shorter survival in cancer patients [Kikuchi, 2007]. Sodium also has predictive power of survival in CHF [Levy *et al.*, 2006].

Models

Several models have been developed that combine multiple prognostic factors together in an effort to improve prognostic accuracy. Some are based more on functional status such as the ECOG and Karnofsky scales, while more advanced models combine factors such as functional status, biomarkers and symptoms. Models are population based and not based on the individual [Taylor and Johnson, 2011], and it is important to consider all aspects of the patient and their situation when prognosticating.

KPS

The KPS was developed in the 1940s to assess the effects of chemotherapy on functional status. The KPS assigns a score based on functional status, where 100 is without evidence of impairment to 0 which is death. A KPS of less than 50% is associated with reduced survival [Gripp *et al.*, 2007]. The National Hospice Study showed a correlation between KPS score and length of lifespan, such that a KPS of 10-20 has a median 2-week life expectancy, 30-40 a median 7-week life expectancy and greater than 50, a median of 12-week in patients with advanced cancer [Maltoni *et al.*, 1994].

PPS

The PPS is a derivative of the KPS and includes disease extent, ambulation, activity, self-care, intake and level of consciousness. It was originally developed in British Columbia to assist with prognostication but also communication and assessing admissions and discharges to Hospice [Ho *et al.*, 2008]. Like the KPS, the PPS is broken into percentages of 10, where 100% is fully functional without symptoms of disease and 0 is death. Validation studies correlate associated median survival for each level of PPS [Anderson *et al.*, 1996; Morita *et al.*, 1999; Virik and

Prognostication

Glare, 2002]. PPS is a validated prognostic tool and may provide more information than the KPS.

CPS

CPS is a physician estimate of survival and is heavily criticized as physicians are poor prognosticators, as previously discussed. Despite this criticism, some studies show a positive correlation between CPS and actual survival, which indicates it does have some limited prognostic value [Glare *et al.*, 2003]. The CPS may suffer from the "horizon effect" in that the longer the estimated prognosis, similar to visualizing objects out on the horizon, it is more difficult to prognosticate or clearly identify the objects [Maltoni *et al.*, 2005]. The CPS likely is most effective when used in conjunction with other prognostic factors and not alone.

PPI

The PPI initially was validated in cancer patients in Japan and validated again in cancer patients in Ireland [Stone *et al.*, 2008]. Unlike other prognostic scores, it does not utilize biomarkers or CPS but rather the PPS, oral intake, presence or absence of dyspnea, edema and delirium. These factors are scored and tabulated and then the score is stratified into 3 groups predicting survival in the realm of less than 3 weeks, less than 6 weeks or greater than 6 weeks.

Palliative prognostic score (PaP)

The PaP was originally developed in Italy for patients with advanced solid tumors [Tarumi *et al.*, 2011]. This score incorporates symptoms, KPS, CPS and biomarkers. Values for each of the above factors are given points, which are tabulated for a total score. The total score is then risk stratified into three groups with an associated percentage of 30-day survival. This score is the best studied and validated of all prognostic scores [Pirovano *et al.*, 1999; Maltoni *et al.*, 1999]. However it has been criticized due to its inclusion of, and heavy emphasis on, the CPS, which is known to be unreliable [Gwilliam *et al.*, 2011].

Specific populations

Much of prognostic research and literature is based on patients with advanced cancer. Patients with dementia or end-stage organ failure such as CHF or COPD have a very different disease trajectory than cancer. These diseases often have their own specific prognostic factors based on the individual disease process and its assessment. It is critical to understand trajectories in these diseases to prognosticate accurately.

Pediatrics

There is limited published data on prognostication in pediatrics. Children with chronic illness often live much longer than what would be expected in adults with lifelimiting illness. The course of illness in children is not linear or predictable and therefore makes prognostication more difficult. Children with advanced disease do suffer similar symptoms to adults with advanced illness including fatigue, pain, dyspnea and poor appetite [Wolfe *et al.*, 2000]. The Lansky score is an assessment of functional status comparable to KPS developed for children with cancer in the 1980s which assesses functional status via activity and level of play [Lansky *et al.*, 1987].

Cancer

The "terminal cancer syndrome" is described as a KPS <50% (functional status requiring assistance with ADL's and frequent medical care) with associated symptoms of xerostomia, dyspnea, dysphagia or difficulty eating, weight loss and difficulty swallowing [Reuben *et al.*, 1988; Vigano *et al.*, 2000b]. In general lung cancer has a worse prognosis than other malignancies, as does the presence of liver metastases [Vigano *et al.*, 2000a]. As shown in *Figure 1*, patients with cancer often do relatively well until a particular point at which they decline quickly to death (*Figure 1*).

End organ disease

End organ diseases such as COPD, renal failure and CHF all have uncertain trajectories and often recurrent exacerbations with lack of return to prior baseline after each episode, shown in *Figure 2*. Uncertainty lies in which episode in particular will cause the patient's death. In these patients palliative therapies such as steroids in COPD or diuretics in CHF may reverse deterioration and help patients improve [Taylor and Johnson, 2011]. It is important to assess goals of care at the time of each episode and appropriateness for referral to Hospice (*Figure 2*).



Figure 1 'Cancer' trajectory, diagnosis to death [Youngworth, 2011] (Reprinted from: Youngwerth J. End-of-life care. BJM 2011. Permission is granted by Jean Youngwerth).

CHF

CHF is a complex and prevalent disease, affecting 1-2% of the general population and 10% of those older than 80 years [Anker et al., 2004]. CHF is staged by the New York Heart Association (NYHA) classification system based on functional status and level of symptoms, ranging from classes I to IV with IV being the most severe. Patients with advanced CHF often suffer from dyspnea, angina, edema and fatigue. Weight loss and wasting are also important features of advanced CHF, called "cardiac cachexia" and affects 10-15% of those with advanced CHF [Anker et al., 2004]. There are no strict criteria to diagnose cardiac cachexia, but a loss of >6% of body weight from nonedematous baseline over a period of greater than 6 months can be indicative [Anker et al., 2004]. Cardiac cachexia is associated with high mortality, and does not correlate with NYHA classification [Yin et al., 2004]. Mortality associated with cardiac cachexia is also independent of albumin [Horwich et al., 2008].

Another measure found to have prognostic significance in heart failure is CRP. CRP is frequently elevated in chronic heart failure and is associated with increased morbidity and mortality, the etiology of which is unclear, but likely is multi-factorial [Lourenco *et al.*, 2010].

The Seattle Heart Failure Model (SHFM) is a prognostic tool that has been validated to predict 1-, 2- and 5-year survival and mortality in patients with CHF [Levy *et al.*, 2006]. The SHFM combines demographic information (age and gender), CHF class and ejection fraction percentage, systolic blood pressure, weight, diuretic therapies, pharmacologic treatments (such as ACE inhibitors or beta blockers), biomarkers including hemoglobin, lymphocyte percentage, uric acid, cholesterol



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Figure 2 Organ system failure trahectory [Youngworth, 2011] (Reprinted from: Youngwerth J. End-of-life care. BJM 2011. Permission is granted by Jean Youngwerth).

and sodium. Seattleheartfailuremodel.org is an online tool, with web based and downloadable smart phone versions of the calculator.

Lung disease

End-stage lung disease, such as COPD, has an uncertain trajectory, with frequent exacerbations and hospitalizations for symptom management. Risk factors for respiratory failure within one year include a FEV₁ less than 30% predicted, declining functional status, recurrent hospitalizations (more than one per year), associated co-morbidities, and older age [Reinke *et al.*, 2011]. Lower self reported quality of life scores were associated with high mortality [Fan *et al.*, 2002].

Liver disease

Two prognostic models are in use for liver disease, the Child-Turcotte-Pugh (CTP) score and the Model for End-Stage Liver Disease (MELD), which largely has replaced the CTP score. These scores are utilized to assess patients for transplantation, but also are effective prognostic tools for mortality. The MELD is a formula that combines the serum bilirubin, creatinine and INR, resulting in a number that is then correlated to a percentage of 3-month mortality. The score was modified further to include serum sodium, which enhances prognostic ability [Kim et al., 2008]. The MELD has been validated in multiple populations of liver disease including cirrhosis, acute alcoholic hepatitis and patients with acute variceal bleeding [Kamath et al., 2001; Wiesner et al., 2001; Sheth et al., 2002; Chalasani et al., 2002]. Not included in the MELD, but also of prognostic significance, is the presence of hepatic encephalopathy, which is an



Figure 3 Dementia/frailty trajectory [Youngworth, 2011] (Reprinted from: Youngwerth J. End-of-life care. BJM 2011. Permission is granted by Jean Youngwerth).

independent predictor of mortality [Said *et al.*, 2004]. A version of the MELD called the Pediatric End-Stage Liver Disease score (PELD) exists for pediatric patients with liver disease.

Renal disease

End stage renal disease (ESRD) has a high 1- and 5-year mortality of 25% and 60%, respectively [Wittenberg and Cohen, 2009]. Many deaths in patients with ESRD are related to coronary artery disease (CAD) and ESRD is known to be an accelerating factor for CAD [Wittenberg and Cohen, 2009]. In patients with ESRD serum albumin has prognostic value, where less than 3.5 g/dL is associated with increased mortality. The Charlson Comorbidity Index (CCI) predicts 10-year mortality by assessing 19 comorbid conditions, and has been validated in patients with ESRD on hemodialysis [Hemmelgarn, 2003]. Nephrologists also have used the "Surprise Question" of "Would you be surprised if this patient died within 1 year?" which showed increased risk of mortality 3.5 times higher when the answer is "no" [Wittenberg and Cohen, 2009]. http://touchcalc. com/calculators/cci is is a web based calculator including both the CCI and SO.

Dementia

Patients with dementia often live for many years if no complications such as infections arise, however dementia is under-recognized as a terminal illness [Mitchell *et al.*, 2009] (*Figure 3*). As dementia advances and functional status

declines, risk for infections such as urinary tract infections or aspiration pneumonia increases. These dementiaassociated infections are often the cause of death in patients with advanced dementia. As dementia progresses oral intake (food and fluids) also decline, with subsequent weight loss. In the last three months of life, the rates of pneumonia, febrile episodes and eating problems were 37%, 32% and 90% respectively [Mitchell et al., 2009]. However, it can be difficult to determine when these life-threatening complications will occur. Prognostic models such as the Functional Assessment Staging Test (FAST) system used by Hospice are criticized for not predicting six-month mortality accurately. Often dementia does not progress in the linear fashion suggested by the FAST criteria [Mitchell et al., 2004]. It is thought that performance status and anorexia are better prognostic indicators in advanced dementia [Schonwetter et al., 2003].

Communication

Just as important as formulating an estimate about the likely course of an illness is communicating that information with the patient, their family and other practitioners involved in the patient's care [Glare and Sinclair, 2008]. When discussing prognosis, physicians often maintain optimism and focus on life-preserving treatment options rather than palliative treatments or end-of-life care and have difficulty discussing the truth [Reinke et al., 2011]. Often physicians are not sure when it is appropriate to initiate conversations about end-of-life care. Only 18% of health care proxies stated they received prognostic information from a physician in patients with advanced dementia [Mitchell et al., 2009]. Even when an accurate prognosis is formulated, physicians may communicate a more optimistic prognosis to the patient and family [Lamont and Christakis, 2001], though there is no data to suggest that there is harm caused by giving bad information in lieu of withholding information [Rich, 2001].

Most patients want full knowledge of their disease status and prognosis, but it is important to ascertain how much patients want to know about their diagnosis and prognosis before discussions begin [Ley, 1982]. Desire for full disclosure also holds true for parents of pediatric patients [Levetown, 2008].

Discussions with families about prognosis and goals of care may be difficult so it is helpful for providers to consider following a guideline. The SPIKES model was developed as a tool to assist in breaking bad news, however it can also be

Table 1 SPIKES	
Setting	Ensure everyone the patient wants present is available, timing is appropriate, quiet and comfortable environment, everyone seated
Perception	Inquire what the patient and family understand about the current situation and prognosis. Allows assessment of any knowledge gaps or misperceptions
Invitation	How much does the patient want to know about the disease and prognosis?
Knowledge	Share with the patient and family the course of illness, expected trajectory and prognosis. Speak in simple understandable terms. Say there is "no cure" if there isn't one
Empathy	Reflect on how the patient and family is responding to the news, provide support
Strategy/summary	Discuss goals of care and how best to accomplish goals moving forward. Discuss what patient wants to be doing with limited time
[Baile et al., 2000].	

useful as a template for family meetings and communication with patients and families regarding advanced illness [Baile *et al.*, 2000] (*Table 1*).

When discussing prognosis it is key to give a range, for example "hours to days", "days to weeks", "weeks to months", and "may be less than 6 months" and often it is not possible to be more specific. It also is important to remind patients and families that the range is an estimate and that patients may live longer or shorter than the estimate. When more specific numbers are given, patients can fixate on that number causing distress or lack of preparation. An example is a physician telling a patient he has "six months left to live", and when the patient is still alive after six months, he becomes distressed and confused. There is more likely to be patient distrust or suffering when very specific prognoses are given. A provider could instead phrase the information in this way:

"Based on what we know now, we feel your prognosis is in the realm of months, most likely less than 6 months. Some will live longer than this estimate, and some will live shorter. We hope that you live longer. What we can do now is hope for the best and plan for the worst."

Prognosis is not static and can frequently change as more information is gathered or patient status changes. A patient who was doing well but then develops a serious infection may have a much shorter prognosis than previously expected. At the time of an event, or even as time passes, the prognosis should be readdressed and discussed with the patient and family so they are fully aware.

Though discussing prognosis can be difficult for both the provider and patient, it is imperative that the patient is offered this information, and in a compassionate and sincere way. Often patients and families appreciate an honest and open discussion about their estimated survival. As patients face the end of their lives, in the midst of losing their health and independence, they may use this knowledge to plan for the future and accomplish their goals.

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Neuro-oncology

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Introduction

In developed countries, primary malignant brain tumors (BTs) have an annual incidence rate of 5.8 per 100,000 for males and 4.1 per 100,000 for females. Despite the use of aggressive multimodality therapy including surgery, radiotherapy and chemotherapy, the prognosis of these patients remains poor. Tumors of glial origin typically have the worst prognosis, with a predicted median survival of 12 to 15 months for glioblastoma multiforme (WHO grade IV) and two to five years for anaplastic glioma (WHO grade III) [Wen and Kesari, 2008; Stupp et al., 2009]. To date, the ongoing palliative care needs of neuro-oncologic patients between discharge and the terminal phase of disease are not well documented. From diagnosis to End of Life (EoL), the care needs of these patients are high, underestimated, and often neglected [Ford et al., 2012]. Care needs increase in the final stages of disease where there is a high incidence of neurological symptoms and psycho-social problems [Catt et al., 2008]. This will often induce caregivers and/or family members to hospitalize the patient.

BT patients are quite different from other cancer or neurological patients and require a specific palliative approach. Data reveal this to be a heterogeneous group of patients with complex needs [Ostgathe *et al.*, 2010]. There is a clear consensus on the need to improve the quality of care for neuro-oncologic patients, Education about palliative care and EoL decision-making in a neuro-oncology setting must be improved. There remains an absence of evidence-based guidelines for supportive care in BT patients.

While the development of more active therapies is ongoing, physicians caring for BT patients have the important role of providing effective and adequate supportive care for symptoms and complications that may result directly or indirectly from the tumor. Supportive care includes problems such as management of peritumoral brain edema, venous thromboembolism (VTE), seizures, rehabilitation, depression, opportunistic infections, psychological support/communication and EoL issues/ treatment decisions. The main goal of palliative care in neuro-oncology is the control of symptoms during the course of disease and particularly at advanced stages and at EoL. The needs of malignant BT patients at EoL require specific, multidisciplinary palliative interventions performed by a well-trained neuro-oncological team. These include effective management of pain, confusion, agitation, delirium, and seizure management with the overall aim being to allow the patient to experience a peaceful death.

In this chapter, we will address recent data that may provide a basis for strong clinical recommendations in the future.

Symptom management

Edema

The pathogenetic mechanism of peritumoral edema in BT patients is predominantly vasogenic, resulting from the flow of fluid into the extracellular space of the brain parenchyma through an incompetent blood-brain barrier (BBB) [Kaal and Vecht, 2004]. Several mechanisms have been postulated in order to explain the increased BBB permeability of BT patients, one of which is an abnormal secretion of the vascular endothelial growth factor (VEGF) from tumor cells [Criscuolo and Balledux, 1996; Kaal and Vecht, 2004]. Peritumoral brain edema is harmful to patients in that it exerts mass effect and increases intracranial pressure, thus causing relevant signs and symptoms of disease [Gomes *et al.*, 2005].

Vasogenic edema associated with BTs is extracellular

and results from increased brain capillary permeability [Criscuolo and Balledux, 1996]. Corticosteroids decrease capillary permeability and are the mainstay of the treatment of peri-tumoral brain edema [Gomes et al., 2005]. The most frequently prescribed corticosteroid in BT patients is dexamethasone, both for the long half-life (36-54 hours) and for reduced mineralcorticoid activity [French and Galicich 1964]. However, prolonged treatment with steroids has multiple adverse effects including iatrogenic Cushing syndrome with weight gain and moon facies, glucose intolerance, steroid myopathy, psychiatric disturbance, opportunistic infection [particularly Pneumocystis firovecii pneumonitis (PJP)], osteoporosis, psychiatric symptoms, and adrenal insufficiency secondary to suppression of the hypothalamo-pituitary-adrenal (HPA) axis [Kountz and Galicich 1997; Weissman et al., 1987; Kaal and Vecht, 2004]. The therapeutic dosage is empirical and the initial dose of dexamethasone is usually 4-16 mg, but even dosages up to 50-100 mg have been reported. Response is measured in terms of neurological improvement after 12-48 hours [Gomes et al., 2005]. In clinical practice, dosage of corticosteroid therapy should be adapted to a particular patient's needs and be slowly tapered according to neurological symptoms. Rapid tapering of steroids may induce a withdrawal syndrome with myalgia/arthralgia and bodily pain that require a dosage increase [Kountz and Galicich, 1997]. Therapeutic efficacy and side effects of corticosteroid therapy is also related to important interactions with enzyme-inducing anti-epileptic drugs (AED) and other concomitant treatments [Gattis and May, 1996].

In patients with rapid neurologic deterioration with impending herniation due to increasing brain edema, osmotic therapy with mannitol may be utilized. However, mannitol reduces brain edema only for few hours and may induce an increase of intracranial pressure after withdrawal. For this reason, treatment with mannitol is not recommended for more than 24-48 hours [Keyrouz *et al.*, 2008].

Thus, there is an urgent need for novel safe alternatives with similar efficacy to corticosteroids for the management of vasogenic edema of BT patients.

Corticorelin acetate (Xerecept[®]; CrA) is a synthetic peptide formulation of the endogenous neurohormone corticotropin-releasing factor which is under active investigation for the treatment of vasogenic edema of BT patients [Mechtler *et al.*, 2009; Recht *et al.*, 2009; Shapiro *et al.*, 2009]. CrA's mechanism of action appears to be independent of the functionality of the HPA axis [Tjuvajev *et al.*, 1996; Villalona-Calero *et al.*, 1998], rather resulting

from a direct effect of CrA on the vascular endothelium of the BBB [Tjuvajev et al., 1996]. Given its more benign side-effect profile compared to corticosteroids [Mechtler et al., 2009], CrA represents an appealing strategy for the management of peritumoral brain edema. In a recent randomized study allocating 200 patients with primary or metastatic BTs to CrA 1.0 mg (bid) subcutaneously or placebo, CrA led to a $\geq 50\%$ dose reduction of dexamethasone in a greater percentage of patients (57% for CrA versus 46% for placebo; P=0.12) [Recht et al., 2009]. Also, significantly more patients were able to discontinue dexamethasone in the CrA group compared with the placebo group (15% versus 6%, respectively; P=0.04). CrA was found to be at least as effective as incremental dexamethasone 4 mg [Recht et al., 2009]. In addition, patients on CrA experienced a significant reduction in dexamethasone-related adverse events such as myopathy and cushingoid symptoms [Recht et al., 2009]. Another randomized study compared CrA versus dexamethasone for the management of malignant glioma patients experiencing exacerbation of signs/ symptoms associated with peritumoral edema [Shapiro et al., 2009]. Despite this, the study was closed early due to slow accrual (only 37 patients randomized of the planned 120). However, despite the encouraging results of these studies, the exact role of CrA as an upfront therapy of peritumoral brain edema has yet to be determined.

Seizures

Seizures in patients with primary BTs are common, with more than one-third of patients having a seizure during the course of disease [Liigant et al., 2001; Lynam et al., 2007; van Breemen et al., 2008]. Seizures may be the symptom leading to the diagnosis of glioma but also may signal glioma recurrence or disease progression [Hildebrand et al., 2005; Scott and Gibberd, 1980; Wrensch et al., 2002]. For 30-50% of patients with BT, an epileptic seizure is the presenting clinical sign of a tumor; 10-30% will develop seizures later in the course of disease [Hildebrand et al., 2005; Sizoo et al., 2010]. Several factors affect epileptogenesis in patients with BT, including tumor histology, tumor location, changes in the peritumoural environment, and genetic factors [Scott and Gibberd, 1980; Wrensch et al., 2002; Lee et al., 2010]. Low grade gliomas (LGG) are the most epileptogenic and the incidence of seizures is reported in 60-88% of patients. Slow growing pattern of growth and cortical involvement may account to the high incidence of seizures in LGG [Rudà et al., 2010].

The frequency of seizures decreases significantly to

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30-50% in high grade gliomas (HGG) but seizures may occur at any time from onset to EoL (late-onset seizures) [Hildebrand et al., 2005]. In patients without seizures at the onset of disease, the probability of developing seizures is relatively low [Scott and Gibberd, 1980; Moots et al., 1995]. Patients who present with seizures as the first sign of a malignant glioma are at increased risk of recurrent seizures [Hildebrand et al., 2005]. Recurrent seizures are frequent (50-75%) in patients presenting with a seizure in spite of treatment with antiepileptic drugs (AEDs) [Hildebrand et al., 2005; Glantz et al., 2000]. Seizure control is an important issue in clinical management and supportive care in neuro-oncology. Quality of life (QOL) of BT patients is strongly influenced by the severity of the seizure disorder and by the intensity of anticonvulsant treatment. Uncontrolled seizures may result in major neurological, neuropsychological and psychological deficits [Glantz et al., 1996; Glantz et al., 2000].

Cognitive deficits seem to be related to the use of AEDs, whereas the low health related quality of life (HRQOL) scores have been reported to be mainly related to poor seizure control [Klein *et al.*, 2003]. Moreover, side effects of AEDs are more common among BT patients than in patients with non-tumoral epilepsy [van Breemen *et al.*, 2007].

The presence of epilepsy is considered the most important risk factor for long-term disability in BT patients [Taillibert *et al.*, 2004; Klein *et al.*, 2003]. Good seizure control can significantly improve the patient's psychological and relational sphere (i.e., social, personal, and professional) [Maschio and Dinapoli, 2012]. The evaluation of side effects of an AED is crucial in these patients, due to the fact that side effects can affect the patient's perception of QOL more than seizure frequency [Maschio and Dinapoli, 2012].

The selection of an AED therapy must take into consideration not only the drug's efficacy for seizure control, but also possible effects of the drug on important aspects of the patient's daily life, for example: cognitive function, sexuality, efficacy of systemic therapies, and the frequency of side effects [Van Breemen *et al.*, 2007].

VTE

Malignant glioma patients seem to harbor the second highest risk of developing VTE among all cancer patients, being in the range of 16-28% in the first year from diagnosis [Brandes *et al.*, 1997; Kayser-Gatchalian and Kayser, 1975; Marras *et al.*, 2000]. A recent meta-analysis estimated that cancers of the brain were associated with the second greatest

risk of VTE (48 per 1,000 person-years) among averagerisk cancer patients after cancer of pancreas [Horsted et al. 2012]. Direct secretion of pro-coagulants from the tumor and/or dysregulation of thrombogenic factors are much likely involved in the pathogenesis of VTE in this highrisk population. Clinically, it has been documented that surgical resection, age greater than 75, and glioblastomas are the most important risk factors for VTE in malignant glioma patients [Marras et al., 2000]. The use of low molecular weight heparin (LMWH) for the treatment of symptomatic VTE and the prevention of recurrent VTE is recommended, however, there is uncertainty on the benefits of primary prophylaxis for VTE in the general cancer population [Gerber et al., 2006; Lyman, 2009]. In fact, in malignant glioma patients, current data provide evidence against the use of LMWH in the primary prophylaxis of VTE. In a recent and prematurely closed randomized placebo-controlled trial a trend toward an increased risk of major intracranial bleeding was noted for patients allocated to the LMWH arm (5.1% for LMWH versus 1.2% for

The risk of VTE associated with newer anti-angiogenic therapies such as bevacizumab in these patients remains unclear. When VTE occurs in this patient population, concern regarding the potential for intracranial hemorrhage complicates management decisions regarding anticoagulation, and these patients have a worse prognosis than their VTE-free counterparts. Moreover, there is uncertainty on whether bevacizumab increases the risk of intracranial hemorrhages in the BT population [Kreisl *et al.*, 2009; Friedman *et al.*, 2009; Besse *et al.*, 2010]. Importantly, a retrospective study exploring the safety of using therapeutic doses of either warfarin or LMWH for the prophylaxis of recurrent VTE in malignant glioma patients suggested that anticoagulation therapy can be safely administered in bevacizumab treated patients [Nghiemphu *et al.*, 2008].

placebo, P=0.2) [Perry et al., 2007].

Depression

The prevalence and impact of mood disorders is not fully delineated in BT patients. The prevalence of depression in patients with glioma range from 0% to 93% [Litofsky and Resnick, 2009; Kilbride *et al.*, 2007; Pelletier *et al.*, 2002; Wellisch *et al.*, 2002]. In a recent review on depression and glioma, Rooney and coll. reported that clinically diagnosable depression occurred in roughly 15% of glioma patients [Rooney *et al.*, 2011; Rooney *et al.*, 2013].

The majority of studies of depression in adults with

glioma are small, cross sectional and retrospective. Also the instruments used to screen for depression appear to inflate depression frequency as compared with the clinical interview. A recent review reports that clinically diagnosable depression occurred in roughly 15% of glioma patients, and clinicians should anticipate this frequency of psychological morbidity among patients with glioma [Rooney *et al.*, 2011].

Depression results in functional impairment, cognitive dysfunction, reduced QOL and reduced survival [Pelletier et al., 2002; Mainio et al., 2006]. The association of depression with lowered HRQOL has been reported by several authors but unfortunately only a few studies have investigated the contemporary assessment of depressive disorder and HRQOL by clinically valid tools. Furthermore, longitudinal studies with repeated measurements during the evolution of disease are lacking. Pelletier et al. [Pelletier et al., 2002] showed that the presence of depression was the most notable single predictor of overall worse HRQOL among BT patients. Litofsky et al., in a large population of 598 glioma [Litofsky and Resnick, 2009], reported an impressive incidence of depression (93%) in patients enrolled in the glioma outcomes project. The incidence of mood disorders and the efficacy of methods of investigation in cancer patients are controversial. In the literature on cancer and depression, the main issue is the difficulty in distinguishing major depression from mild depression. Standard screening tools often fail to distinguish between demoralization and major depression. Situational or reactive depression should be considered a normal psychological response to the changes associated with diagnosis of cancer. This type of depression is essentially psychological in nature, rather than physiological, and is more responsive to supportive psychotherapy than medication [Weitzner, 1999; Litofsky and Resnick, 2009].

Several authors have reported that depression is not only a psychological reaction to the cancer but may be related also to biological factors [Brown *et al.*, 2005]. However, the absence of strong associations with other variables (including tumor location, histology, and extent of resection) implies that depression in glioma is primarily a psychologically mediated response to losses, including the loss of health.

Antidepressant medications and psychotherapy (particularly cognitive behavior therapy) have been shown to be of comparable efficacy in treatment of major depression [Caudill *et al.*, 2011]. Earlier studies among depressive cancer patients have reported that treatment of depression increased their survival [Spiegel *et al.*, 1989]. However, Litofsky *et al.* [Litofsky and Resnick, 2009] did not observe significant impact on survival among highgrade glioma patients treated for depression. Current evidence shows that many tumor-related and patientrelated factors may influence depression in BT patients. Larger studies are needed in order to identify the patients whose depression can be treated, as well as to determine appropriate treatment for depression in BT patients.

Rehabilitation

During the course of the disease, patients may have multiple neurological deficits that can be due either to primary tumor effects and/or the adverse effects of oncologic treatment. In general, rehabilitation in the early stages of disease aims at restoring function during or after cancer therapy, while in the advanced stages is important for maintaining patient's independence and QOL [Santiago-Palma and Payne, 2001]. Unfortunately, the role of rehabilitation in BT patients has been poorly investigated to date. Nevertheless, a significant effect of rehabilitation therapies has been demonstrated, especially in the acute phase with a functional gain comparable to that of other models of neurologic disability such as stroke or traumatic brain injury [Huang et al., 1998]. Despite this, rehabilitation in BT patients is still largely underutilized. Rehabilitation should be included in the management of BT patients given that its positive effect is not limited to functional outcome but strongly influences patients' QOL.

In recent years, cognitive disorders in BT patients have been receiving increased attention from the neurooncologic community. The percentage of neuro-oncological patients who suffer from cognitive deficits documented by formal neuropsychological evaluations range from 29% patients with low-grade glioma not receiving radiotherapy [Klein et al., 2002] to 90% observed in patients with BTs of other nature who underwent anti-cancer treatments [Tucha et al., 2000; Klein et al., 2001; Taphoorn, 2003; Meyers et al., 2004; van Nieuwenhuizen et al., 2007; Talacchi et al., 2011]. Data variability can be explained by the differences in inclusion criteria, treatment regimens, and neuropsychological tests used in these studies. The interest for cognitive alterations is related mainly to the QOL of patients and to the identification of cognitive rehabilitation strategies. A recent randomized trial performed in malignant glioma patients showed that cognitive rehabilitation training in glioma patients may help to improve significantly either short-term cognitive complaints and longer-term cognitive performances and mental fatigue [Gehring et al., 2009].

Psychological support/communication

A diagnosis of a BT induces emotional reactions of discomfort, future uncertainty, and depression in patients and their families [Davies and Higginson, 2003]. Communication of diagnosis and prognosis is considered an important step in palliative management and may help to facilitate coping strategies. Patients and their caregivers should be assisted in an adequate setting by a trained multidisciplinary palliative team that is dedicated to the management of psychosocial needs. However, physicians very often do not meet communication needs and avoid giving breaking bad news. A survey exploring the attitude and knowledge of neurologists and neuro-oncologists about palliative care reported that there is a great need for education for palliative care and communication skills [Carver et al., 1999]. Moreover, communication with patients and family is difficult even for the rapid evolution of neurological symptoms that can affect cognitive functions. Observational evidence suggests that patients' awareness about prognosis vary considerably and up to 40% are unaware [Davies and Higginson, 2003]. A study evaluating the medical decision-making capacity (MDC) in malignant glioma patients showed that more than 50% of patients have compromised MDC compared to controls [Triebel et al., 2009]. Also, this study investigated the relationship between cognitive functioning and consent capacity suggesting that MDC impairment may be associated with cognitive impairment [Marson et al., 2010]. However, not all patients may wish to be informed about prognosis and communication of bad news should be tailored to the coping styles of individual patients and relatives.

Very little is known about QOL and well-being in caregivers of patients with BTs. Usually, the caregivers' own needs are neglected because the focus is on the patients. Recent publication report that in the context of this severe and often devastating disease, the caregivers burden of suffering and despair is often neglected, suggesting a more global and comprehensive approach, possibly with pharmacological and psychological support, to the care of the affected family [Finocchiaro *et al.*, 2012]. Several programs of caregiver support including family consultation and internet or telephone-based support groups have been recently suggested as methods for supporting caregivers' emotional needs [Ford *et al.*, 2012].

EoL issues/treatment decisions

Neuro-oncologists devote most of their effort to seeking

active treatment against the tumor and, according to several authors, devote very little effort to what happens to patients with progressive disease when no further oncologic treatment options available. Little is known about symptoms and needs of BT patients at EoL, and too many patients do not receive adequate palliative care so that the burden of care often falls to the patients' family [Batchelor and Byrne, 2006; Carver et al., 1999; Pace et al., 2010]. A recent paper reported that BT patients at EoL have a high incidence of distressing symptoms that may influence the QOL during the process of dying [Oberndorfer et al., 2008; Sizoo et al., 2010]. In order to allow the patient to experience a peaceful death, specific palliative interventions are requested for the control of pain, confusion, agitation, delirium, and seizures [Sizoo et al., 2010]. The main goals of palliative care and EoL care in BT patients are to offer adequate symptom control, relief of suffering, to avoid inappropriate prolongation of dving, and to support the psychological and spiritual needs of patients and families. The lack of control of symptoms in patients not included in palliative care programs often lead to re-hospitalization with an increase in health system economic costs and a worsening of patient's QOL [Pace et al., 2012; Bausewein et al., 2003].

There is increasing attention to palliative care and EoL issues in neuro-oncology. From diagnosis to the EoL, care needs of BT patients are high and sometimes underestimated [Ford *et al.*, 2012]. In the last stage of disease, BT patients present both complex needs similar to the general cancer population. Furthermore, severe symptoms due to the growing tumor require adequate management from a multidisciplinary neuro-oncology team.

Recently, some studies have been focused on supportive care needs of BT patient in the last stage of disease. In a recent paper by our group, we observed a population of BT patients assisted until death with a neuro-oncological palliative home care program had a high incidence of distressing symptoms influencing the QOL during the last stage of disease and during the process of dving. Out of 231 patients who died, 169 (66%) were assisted at home until the EoL [Pace et al., 2009]. Among the 169 patients assisted at home until death, the most frequent symptoms observed in the last four weeks of life were: seizures 30%, headaches 36%, drowsiness 85%, dysphagia 85%, death rattle 12%, agitation and delirium 15%. Two other papers reported similar data about EoL symptoms in BT. In a small series of BT patients dying in hospital, an Austrian group found that the most frequent symptoms in the last weeks of life were decreased vigilance, fever, dysphagia, seizures, and pain [Oberndorfer

Part II

SymbolSizo at all based at a	Table 1 Rates of symptoms in patients with primary brain tumor at end of life							
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	Fatigue	25	-	44	-			

Ford E et al., 2012; Reprinted with permission from Oxford.

et al., 2008]. In the study of Sizoo and colleagues [Sizoo *et al.*, 2010] the clinical records of 55 patient deaths for high grade glioma were retrospectively examinated: the majority of the patients experienced loss of consciousness and difficulty with swallowing, often arising in the week before death. Seizures occurred in nearly half of the patients at EoL and in one-third of the patients in the week before dying.

Other common symptoms reported in the EoL phase were progressive neurological deficits, incontinence, progressive cognitive deficits, and headache (*Table 1*).

Given the lack of Class I study addressed on supportive care issues in BT, no guidelines can be drawn, however recent literature data may help to maximize the quality of care in the management of most frequent symptoms.

Symptoms in EoL

Seizures

Recent papers have reported a surprisingly high incidence of epilepsy in the last week of life of BT patients (37-50%) [Krouwer *et al.*, 2000; Oberndorfer *et al.*, 2008; Pace *et al.*, 2009; Pace *et al.*, 2012]. Epilepsy seems to be one of the more frequent symptoms in the last stage of disease, affecting even patients who had never had a seizure [Moots *et al.*, 1995].

In a small series of BT patients dying in hospital almost 50% of patients presented seizures in the last two weeks before death [Oberndorfer *et al.*, 2008]. In a previous study by our group on EoL issues in BT patients we reported that epilepsy represents a major issue in the management of dying patients, particularly in those assisted at home [Pace *et al.*, 2009]. Seizure occurrences in EoL may impact patient and family QOL and require adequate supportive care and treatment modifications. This may be especially complicated at EoL because of current depressed consciousness and dysphagia limiting oral intake of drugs [Pace *et al.*, 2013; Oberndorfer *et al.*, 2008; Sizoo *et al.*, 2010].

In a recent study by our group the incidence of seizures at EoL was evaluated in a population of 157 BT patients: seizures occurred in 51 patients (30%) in the last four weeks before death and with 85% of these being partial and 15% being generalized. Six percent of patients had status epilepticus. The incidence of seizures was higher in glioma patients than in patients with brain metastases (34% vs. 10% respectively). Most patients (53%) who had seizures in the last months of life had experienced seizures in the past and were on AEDs. In the remaining cases, seizure occurred in patients who had never had a seizure; 14 were on prophylactic AEDs and 10 on none.

Given the high incidence of seizures in the last period of life, the anticonvulsant treatment in this stage of disease needs to be optimized. Recommendations for the use of AEDs in neuro-oncology are available, but not specifically focused on the terminal phase of the disease [Krouwer *et al.*, 2000; Rudà *et al.*, 2010; Tremont-Lukats *et al.*, 2008; Wick *et al.*, 2005; Sirven *et al.*, 2004]. Various alternative methods of drug administration must be considered (intramuscular, rectal, transdermal, or subcutaneous). We prefer intramuscular phenobarbital in patients at home or intravenous levetiracetam in hospitalized patients. The lack of seizure control often led to re-hospitalization, increasing health care economic system cost and worsening of patient QOL. Correct management and providing proper information to the families may avoid inappropriate hospital readmission in the case of uncontrolled seizures.

Headache

The incidence of pain in the last hours of life is difficult to assess, but the presence of agitation and restlessness with moaning and grimacing is often interpreted as physical pain and requires appropriate treatment [Pace et al., 2009]. Literature reports that headache may be present in a large proportion of patients. In the large majority of patients, headache is mild, intermittent, due to increased intracranial pressure, and usually responding to steroid treatment. In some cases, headache may be severe and required a high dose of steroids and pain medication (opioid or non-opioid). In patients with meningeal syndrome due to meningeal involvement, both for neoplastic meningitis from systemic cancer and for meningeal spread from primary BTs, pain treatment required a multidrug approach with steroids, opioids, and neuropathic pain relievers (gabapentin, pregabalin).

Dysphagia

Dysphagia is reported to be one of the more frequent symptoms in the last weeks of life. Loss of the ability to swallow may induce pulmonary inhalation and may affect nutrition and hydration. Moreover, the patients' difficulty in the oral intake of drugs, liquids, and food requires appropriate modification of treatment and discussion with families and the home care team of issues concerning nutrition and hydration. In all patients presenting dysphagia in the last weeks of life, anticonvulsant therapy needs to be modified by changing oral treatment to other routes of administration [Pace *et al.*, 2009].

Consciousness deterioration

Most BT patients have a decline in level of consciousness in the last weeks of life. Lethargy, confusion, and night-day reversal may be early symptoms; the majority of patients enter into deep coma in the last days. Consciousness alterations are the result of multiple factors and may be managed by increasing antiedema treatments. However, the presence of delirium or behavioural disturbances may alter the usual "peaceful" pattern of dying. The occurrence of agitation, delirium, and confusion without a complete loss of consciousness may be very distressing for patients and their families, particularly in the home care setting. In these cases, pharmacologic sedation may help (neuroleptic, opioids and benzodiazepines) [Bonito *et al.*, 2005]; alternatively, agitation may be controlled by reducing steroid dosage.

Death rattle

Changes in breathing patterns in the last hours of life usually occur in unconscious dying patients. In some cases, difficulty in clearing upper airways leads to an accumulation of respiratory tract secretions. The death rattle may be very distressing for the family and home care professionals. However, it is important to explain to the relatives of a patient with decreased level of consciousness that death rattle is unlikely to be distressing for the patient.

Anticholinergic drugs (natural belladonna alkaloids: atropine, belladonna, hyoscyamine and scopolamine) may reduce the production of secretions and mild dehydration may help to control this symptom [Kompanje, 2006]. Other possible treatments of death rattle include gentle suction in the nasopharynx and trachea and postural drainage.

EoL treatment decision making process

EoL treatment decisions in neuro-oncology present unique features and require specific approaches concerning the decisions relating to medical treatment, including withdrawing-withholding of nutrition and hydration of patients in prolonged vegetative state, withholding of steroid treatment and palliative sedation [Ford *et al.*, 2012].

Withholding is a planned decision not to undertake symptomatic therapies that were otherwise warranted; withdrawal is the discontinuation of symptomatic treatments that have been started. Terminal sedation is defined as the pharmacologically-induced reduction of vigilance up to the point of the complete loss of consciousness with the aim of reducing or abolishing the perception of symptoms that would otherwise be intolerable ("refractory symptoms"). Few data are available on EoL decision making process in BT patients. The process of treatment decision making in the terminal stage of BT patients is often complicated by the presence of cognitive problems that may affect patient competence to express treatment preferences. Recent studies highlight that participation in EoL decision-making is only possible with advanced care planning.

A recent European study evaluating the EoL decision

making process in six European countries revealed that only 40% of competent patients are involved in EoL treatment decisions; fewer than 7% express their wishes in advance and more than 50% of decisions are made without involving the patients or their families [Pace et al., 2009]. However, considering that the large majority of BT patients become unable to participate in treatment decisions, it is of utmost importance to plan EoL treatment decisions by discussing this topic with patients and their families whenever possible. The aim is to obtain a consensus about the withholding-withdrawing decisions between all participants, respecting both patients and families values. There are wide disparities in the provision of palliative care in different countries. To receive good palliative care during the course of disease and particularly at the EoL is a human right and the access to the right care should be facilitated for every patient.

Currently, few countries invest in research into palliative care. For every €10 spent on cancer research, less than two cents in the UK and nine cents in the USA goes to palliative and EoL care research [Higginson et al., 2007]. Council of Europe Recommendation 24 of 2003 recommends that the governments of member states adopt the policies and other measures necessary for a coherent and comprehensive policy framework for palliative care. Palliative care is now understood as an approach to care concerned with caring for the whole person faced with a range of physical, psychological, and social needs. Recent studies reported that administrative data, and particularly hospital re-admission rate, in the last stage of disease may be considered a potential indicator of quality of EoL care [Pace et al., 2012]. However, studies specifically addressing palliative care and EoL issues in BT patients are lacking. Nevertheless, there is a great need for education in palliative care and EoL care for BT patients. Improved knowledge of clinical and ethical issues could help to improve the educational training and quality of care given by neuro-oncology services [Carver et al., 1999]. Palliative programs and home-care models of assistance may represent an alternative to in-hospital care for the management of patients with BT and may improve the quality of care, especially in the last stage of disease [Pace et al., 2012].

Ethical concerns

Considering that the large majority of BT patients lose the ability to participate in a shared decision making process, it is of utmost importance to plan in advance treatment

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decisions about nutrition and hydration by discussing them with families and with patients whenever possible [Sizoo et al., 2012]. According to a recent review of supportive care in neuro-oncology [Ford et al., 2012] only a small proportion of BT patients had established advance directives about EoL treatment, and progressive neurological deficits and loss of consciousness often meant that decisions had to be made on their behalf. A study exploring the decisionmaking process in the EoL phase of HGG patients reported that the physician did not discuss EoL treatment decisions preferences in 40% of patients. Since most cancer patients wish to be involved in decision-making at EoL, the results of this study underscore that EoL decision making process for BT patients warrants improvement and timely organisation of Advance Care Planning could contribute to improve ELD-making [Sizoo et al., 2012]. As the "shared decision" made together by physicians, nurses, and the patient's family may be the best approach to EoL decisions, common guidelines may be helpful.

Caregiver perspective at the EoL

Very little is known about OOL and well-being in caregivers of BT patients. The severity of symptoms is not only detrimental to patient QOL but also affects caregivers, who themselves report high levels of distress. Two recent studies surveyed relatives of deceased BT patients with the aim of exploring the caregivers' perspective. In the Dutch study [Sizoo et al., 2013] relatives were asked to fill a questionnaire regarding several aspects of the experience, including quality of care and quality of death. The results of this study indicate that, in the perception of their relatives, one quarter of patients did not die with dignity. The place of death and the satisfaction with EoL health care providers seemed to have the most effect on perception. In a similar study performed on 52 caregivers of deceased glioblastoma patients in Austria [Flechl et al., 2013], the most frequent complains reported by relatives were low QOL, burnout, financial difficulties, and perception of insufficient information.

Summary

Several barriers hinder the adequate provision of palliative care in the advanced stage of disease and at the EoL in BT patients:

• BTs represent a rare disease with peculiar symptoms during the course of disease and at the EoL with respect to other cancers;

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- Lack of evidence-based guidelines on BT supportive care and symptoms management;
- Poor training of health care workers;
- Lack of information for patients and care-givers.

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Cancer induced bone pain

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Introduction

The number of patients diagnosed with cancer is on the rise with 12 million new cases diagnosed in 2008, with 7.6 million deaths related to cancers. Seventy-five percent to 90% of these patients were found to have advanced stage cancer with metastases and significant pain related to that.

While pain is taken as a common end-of-life issue related to cancer and bone metastases, and in most cultures is an expected entity, it is now known that pain can be controlled, usually without much sedation, by involving a team composed of members with experience in different areas related to end-of-life issues and pain. In the SUPPORT study (Study to Understand Prognoses and Preferences for Outcomes and Risk of Treatment) [JAMA, 1995], an outstanding finding was that nearly half of the patients with an overall 6-month mortality rate of 47% were found to have moderate to severe pain during the final three days of life. Understanding the source of pain related to bone metastases is key in the formulation of appropriate management of these issues in palliative care.

The most common cancers, which metastasize to bones, are breast cancer in female patients and prostate cancer in male patients. Lung, thyroid, and renal cancers are the other types of cancers that affect the male and female population equally as far as bone metastases are concerned. Bone metastases may cause severe, debilitating pain affecting patients and their caregiver's lives, and can result in added stress. In addition to these cancers, carcinomas are more likely to metastasize than sarcomas. Due to presence of bone marrow in the axial skeleton, these skeletal structures are more prone for metastases, which can cause complications including intractable pain, fractures, spinal cord compression, bone marrow aplasia, and hypercalcemia. These terms are generally, and collectively, referred as "Skeletal Related Events". Pain related to bone metastases usually fall in two groups: baseline pain that is usually constant and incidental breakthrough pain. A study by Laird and colleagues [Laird *et al.*, 2011] showed that breakthrough pain was present in 75% of cases with cancer induced bone pain (CIBP), causing significant interference on mood, relationship, sleep, activity, and general enjoyment of life. Forty-five percent of patients with breakthrough pain had patterns of pain that were unpredictable and made management profoundly challenging.

Pain associated with bone metastases often resulted in the patients' admission to the hospital or initiation of hospice, placing a burden on the families and patients. This pain was also associated with a downfall of the patients' level of functioning, more physical dependence, depression and anxiety. A systematic review of music interventions for improving psychological and physical outcome in cancer patients indicated that music interventions might have beneficial effects on anxiety, pain, mood and quality of life in cancer patients [Bradt *et al.*, 2001].

Cellular bases of bone metastases

There are four stages in which cancer cells metastasize to bone, including communication, adherence, osteoplastic activity and bone resorption. In the process of communication, tumor cells interact with the hematopoietic stem cells, followed by the attachment of osteoclasts to the bone during the process of adherence, which initiates the process of osteoplastic activation. Osteoplastic activation is the main reason for osteolytic erosions and lesions. The final stage of the process of forming bone metastases involves bone resorption with both organic and inorganic matrices, with inorganic matrix bone resorption being an active energy-driven process [Khor *et al.*, 2013].

Management of pain related to bone metastases

Involvement of a multidisciplinary pain team is crucial for the appropriate management of pain related to bone metastases. This approach includes both nonpharmacological measures and pharmacological measures.

Non-pharmacologic conservative measures

In this area of treatment, there is active involvement of other specialties such as Behavioral Sciences with behavioral therapy, including hypnosis and relaxation therapies, Physical Medicine & Rehabilitation and acupuncture. Traditional non-invasive approaches are useful in this setting, as well such as yoga, tai chi, stretching, and thermal techniques (heat & cold). As discussed earlier, music modalities have shown some beneficial effects on mood, anxiety and overall quality of life. The outcomes of two different studies that were conducted show that massage therapy has beneficial effects on pain, sleep quality and muscle relaxation [Jane et al., 2011; Toth et al., 2013]. Jane et al. indicated, in a randomized clinical trial of Taiwanese patients with metastatic bone pain, the beneficial effects of massage therapy on pain, mood status, relaxation, and sleep [Jane et al., 2011]. Toth and colleagues showed in their pilot randomized, controlled trial concerning metastatic cancer that providing therapeutic massages improves the quality of life for end-of-life patients and may be associated with further beneficial effects such as improvement in pain levels and sleep quality [Toth et al., 2013].

Pharmacological measures

The foundations of pharmacological measures are based on the World Health Organization's (WHO) analgesic stepladder; a guideline based on recommendations from international WHO expert committee on cancer pain and was published by WHO in 1986 [Burton and Cleeland, 2001].

Analgesics, which are considered in the WHO-based established guidelines, are:

- (I) Non-opioid analgesics such as acetaminophen, NSAIDs, cyclooxygenase-2 inhibitors;
- (II) Adjuvants such as muscle relaxants, alpha-2 adrenergic agonists, NMDA receptor antagonists, antidepressants and anticonvulsants;
- (III) Opioids and/or opioid-like analgesics [Zech et al., 1995].

Non-steroidal anti-inflammatory drugs (NSAIDs)

Use of NSAIDs has been in practice for long time, although there is a lack of strong evidence to support their use in cancer-related bone pain. Experience shows that they are particularly helpful in helping cancer pain related to inflammation due to metastatic process and less in neuropathic component of cancer pain [Vielhabe and Portenoy, 2002].

Eisenberg and colleagues conducted a meta-analysis of published randomized controlled trials to assess the effects and safety of NSAIDs. It was determined that better pain management was achieved with NSAIDs than placebo with 15-36% pain relief with a single-dose placebo compared to 31-60% pain relief with NSAIDs [Eisenberg *et al.*, 1994].

A review study of 3,084 patients in 42 trials was conducted to evaluate the effects of NSAIDs or paracetamol, alone or combined with opioids, for cancer pain [McNicol *et al.*, 2005]. McNicol and colleagues concluded that, based on limited data, NSAIDs appear to be more effective than placebos for cancer pain. There was no supportive evidence of one NSAID being better than another. There was either "no significant difference" or a "slight but statically significant advantage" of using either a single use of NSAIDs or an Opioid, or combination of the two [McNicol *et al.*, 2005].

Newer generations of NSAIDs including Cyclooxygenase-2 (COX-2) inhibitors also contain antitumor or anti-angiogenic properties, which gives them an additional advantage over the other traditional NSAIDs and, at least, theoretically with better potential in some patients. Sabino *et al.* showed in their study of sarcoma model that chronic inhibition of the COX-2 enzyme due to use of selective COX-2 inhibitors causes reduction in both spontaneous and movement related to bone pain in the cancer population. It also results in some neurochemical changes, which shows central and peripheral sensitization [Sabino *et al.*, 2002].

Steroids

Methylprednisolone, dexamethasone and prednisone are corticosteroids commonly used in the management of pain related to bone conditions. Dexamethasone has a high antiinflammatory property with low mineralocorticoid action making it the most commonly used and the preferred oral steroid for this purpose. Reduced mineralocorticoid quality results in a smaller chance of salt and water retention via the kidney compared to other corticosteroids at the same dosage. While the exact mechanism of action is still uncertain, it is widely believed that reduction in edema and their action on the prostaglandin and leukotriene synthetic pathway play a major role.

Bruera and colleagues found in their study that severity of pain was significantly lower after methylprednisolone compared to the baseline pain level or with a placebo, with 68% of patients reporting better pain control with prednisolone by the end of the treatment phase. Additionally, the chances of better response after five days of treatment were poor [Bruera *et al.*, 1985].

Antiepileptic drugs

Cancer pain has been associated with neural structure changes and damage to the central and peripheral nervous systems. Changes in the sensory neurons due to metastatic cells cause sensory nerve injury. These changes can be evident at the cellular level in the form of the sprouting of sensory nerve endings into bone, hypertrophy of satellite cells surrounding the dorsal root ganglion, or by increasing level of activating transfer factor-3 in the sensory neuron's nucleus of the innervations of bone [Peters *et al.*, 2005; Jimenez-Andrade and Mantyh, 2010].

Antiepileptic drugs (i.e., Gabapentin) work by their calcium-channel-blocking effects. In animal studies, it was shown that these antiepileptic drugs reverse neurological changes in the dorsal root ganglion related to metastatic bone pain. These studies suggested that there is a neuropathic component of metastatic bone pain. The unique quality of Topiramate as a calcium channel blocker, sodium channel blocker, Glutamate inhibitor, GABA agonist, and its potential effects of NMDA receptor makes it a valuable drug of choice in this class for treating bonemetastases-related pain [Donovan-Rodrigues *et al.*, 2005].

Opioids

Opioids are the cornerstone of management of osseous metastatic pain. While there are a variety of options in this class to choose from, there is no clear clinical evidence to support one opioid over other. Opioids are an effective therapy for baseline pain, but have not been a useful tool for breakthrough pain. Titration of opioids to obtain good breakthrough pain control can be challenging and can result in unacceptable side effects [Portenoy *et al.*, 1999].

Opioids taken orally usually go through significant changes by the liver into inactive metabolites via "first pass",

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which makes oral route relatively not efficient. Patients who are terminally sick with a considerable amount of pain often consider the parenteral route better due to its rapid pain control.

In palliative settings, physicians should consider the fastest, safest and most effective delivery system for the opioids in the management of pain issues if these medications are being considered. If traditional routes are ineffective or are not a suitable option, intrathecal delivery of opioids should be considered, which requires special training and expertise. Extensive research in the area of opioid receptors in search of "ideal" analgesics in this class has been disappointing so far, with ongoing new areas that need to be studied [Swarm, 2013].

Various factors usually implicate opioid responsiveness including: type of pain (neuropathic *vs.* somatic and break through), tolerance, progression of disease, patient related specific demographic factors, and specific opioids metabolism. Adequate understanding of these factors is essential to optimize therapy [Mercadante and Portenoy, 2001].

Bisphosphonates

Bisphosphonates are classified into nitrogen-containing and non-nitrogen-containing groups. Nitrogen-containing bisphosphonates (i.e., clodronate) act by attaching to the bone matrix with a metabolic end result including ATP analogs, causing osteoclastic apoptosis [Costa and Major, 2009].

Non-nitrogen-containing bisphosphonates such as pamidronate and zoledronate inhibit the enzyme "farnesyl pyrophosphate synthetase" (FPP). This enzyme, which is mandatory for posttranslational modification of GTPase, is required for proper osteoclastic bone resorption function. There is indirect osteoclastic apoptosis resulting from accumulation of isopentyl pyrophosphate (IPP) by nitrogencontaining bisphosphonates as well [Mönkkönen *et al.*, 2006].

Several studies have shown beneficial effects of bisphosphonates in pain relief related to bone metastases. These studies included: bisphosphonates in multiple myeloma models [Berenson *et al.*, 2002], disodium pamidronate in non-Hodgkin lymphoma model [Pistevou-Gombaki *et al.*, 2002], (zoledronic acid in metastatic bone cancer [Santini *et al.*, 2006], zoledronic acid treatment in metastatic breast cancer model [Amir *et al.*, 2009], *aoedronic acid* in mouse breast cancer metastatic model [Hiraga *et al.*, 2004], zoledronic acid palliation in bone metastatic breast cancer [Furlow, 2006], and Fulfaro's zoledronic acid with bone metastatic from a prostate carcinoma [Fulfaro *et al.*, 2005]. Zoledronate is the most effective of the nitrogencontaining bisphosphonates and is also particularly effective in inhibiting FPP synthetase activity, resulting in reducing bone resorption in breast cancer patient studies [Amir *et al.*, 2009; Higara *et al.*, 2004], and in reducing metastatic bone pain in prostate models [Fulfaro *et al.*, 2005].

In addition to its role in bone resorption prevention, zoledronate has been reported to have direct anti-tumor properties in non-clinical trials by inducing tumor cell apoptosis and inhibiting cancer cell invasion [Rachner *et al.*, 2010; Woodward *et al.*, 2005]. Before a patient can be administered zoledronate, a thorough initial dental evaluation and follow-up is required to monitor risk of jaw osteonecrosis. Other complications associated with zoledronate are renal impairment and flu-like symptoms, which demand close observation.

Hormonal therapy

Not all cancers respond to hormone therapy. However, prostate and breast cancers are among the types of cancer that may respond to hormonal treatment. Surgical or medical approaches can be utilized to achieve androgen deprivation therapy by bilateral orchiectomy or synthetic gonadotropinreleasing hormone agonists respectively in prostate cancer. Synthetic gonadotropin-releasing hormone agonists cause persistent stimulation of the pituitary, causing downregulation of gonadotropin releasing hormone receptors with subsequent reduction of luteinizing and follicle-stimulating hormones, necessary for testosterone production.

Radiation therapy

The benefits of using external radiation therapy are reduction in bone metastatic-related pain and reduction in the use of other analgesics with improvement in function, ambulation and related fractures especially in weightbearing bones. Tong *et al.* reported in a multi-institutional randomized trial that 80% of patients receiving radiation therapy experienced complete or partial pain relief related to osseous metastases within 10 to 14 days [Tong *et al.*, 1982]. Efficacy of single and/or multi-fraction regimens of radiation therapy have been evaluated and confirmed by multiple meta-analyses including: single-fraction external beam radiation for localizing metastatic bone pain [Jeremic, 2001], dose fractionation radiotherapy trials for palliation of painful bone metastases [Wu *et al.*, 2003], single-fraction

versus multifraction radiotherapy [Sze *et al.*, 2003], and palliative radiotherapy trials for bone metastases [Chow *et al.*, 2007]. Nomiya and colleagues conducted a study in which complete pain relief was reported in 49% of cancer patients and partial relief in 91% of cases, where the mean time to obtain 50% relief was 13 days and complete relief was 24 days [Nomiya *et al.*, 2010].

Radiopharmaceutical agents

Properly trained physicians should administer radiopharmaceutical drugs. Pregnancy and patient refusal are the absolute contraindications for this mode of therapy. Benefits of these agents over the external beam radiation therapy are: ease of administration intravenously, treatment of multiple diffuse sites, less bone marrow suppression, and fewer side effects. Strontium-89 was the first radioisotope approved by the FDA for bone pain palliative treatment [Paes et al., 2010]. A bone-specific isotope is incorporated in the bone after intravenous injection. Robinson et al. reported pain relief in two weeks and maximum relief by six weeks of treatment effective for 4-15 months [Robinson et al., 1992]. Eighty percent of patients presenting with mild leukopenia or thrombocytopenia and were treated with strontium had a complete recovery of thrombocytopenia in 3-6 months after treatment. The FDA approved Samarium-153-lexidronam in 1987 for patients with osteoblastic bone metastases [Samarium-153, 1997]. Significant decreases in pain scores (P<0.002) were observed at week 4 after each of the first three doses and maintained at week 8 after the first two doses (P<0.003) but not after the third dose. Decreases in pain scores were observed in 70%, 63%, and 80% of patients, respectively at week 4 after the first three administrations [Sartor et al., 2007].

Interventional and invasive approaches

Interventional approaches for metastatic bone pain included vertebral augmentation procedures such as vertebroplasty/ kyphoplasty, intrathecal delivery system of medications, radiofrequency and cryoablation techniques.

Vertebral augmentation techniques

The consequences of bone metastases are compression fracture, bone pain, radiculopathy, instability and myelopathy. Vertebral augmentation procedures, such as balloon kyphoplasty and vertebroplasty, may result in

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immediate pain relief in patients with compression factures of the vertebral structure.

Vertebroplasty procedures involve injection of surgical cement through a percutaneously-placed needle or trocar with the help of X-ray image inside the vertebral body, specifically in the area of the compression fracture. Lee and colleagues reported that 84% of individuals treated with this technique at 1-3 levels experienced short- or long-term improvement [Lee *et al.*, 2009]. An unique feature which differentiates the study conducted by Saliou and colleague is that they evaluated 51 patients with an epidural extension of tumor cells with a total of 74 vertebroplasty procedures and reported that this procedure provided effective analgesia in patients with pain related to a spinal tumor with epidural extension [Saliou *et al.*, 2010].

Balloon kyphoplasty claims to have advantage of restoring the height of the vertebral body in addition to analgesia related to compression fracture. This procedure involves the placement of a balloon device inside the vertebral body and inflating it, which creates a cavity into which cement is injected. A retrospective review by Qian *et al.* on 48 patients with multiple spinal metastases treated with balloon kyphoplasty demonstrated decreases in VAS significantly with improvement in both physical and social functioning [Qian *et al.*, 2011].

Ablation techniques (cryoablation and radiofrequency ablation)

If a patient reports moderate to severe pain that is limited to 1-2 focal areas and the affected area is reachable by the ablation device, this technique may be beneficial for painful metastases. If a lesion is close to structures such as major motor nerves, the spinal cord, brain, bowel, bladder and/ or artery of Adamkiewicz, this procedure carries higher risks than benefits. In one study, radiofrequency ablation followed by radiotherapy was more effective and safe compared to radiotherapy alone [DiStaso *et al.*, 2011].

Cryoablation reportedly has advantages over radiofrequency ablation in treating pain related to metastases due to its ease in monitoring the zone of the lesion with intermittent imaging such as CT scan or MRI [Callstrom and Charboneau, 2007]. Additionally, cryoablation can treat larger lesions than RFA.

Intrathecal delivery system for cancer bone pain

Intrathecal delivery system has emerged as an important

option for management of cancer-related pain. Usually, it is reserved for the cases that have failed other modes of management, which include less invasive measurements or patients on high dosage of opioids or with significant side effects related to opioid therapy. A multicenter, randomized, prospective study on intrathecal delivery of pain medications conducted by Smith *et al.* showed improvement in opioid-related complications such as cognitive slowing, sedation and generalized fatigue along with improvement in pain scores compared to patients who received conventional comprehensive medication management [Smith *et al.*, 2002].

While intrathecal delivery system has its own advantages, it has limitations in that only a certain number of specific medications can be used. Medications suitable for this mode of delivery include: morphine sulfate, hydromorphone, local anesthetics, and ziconotide. In addition to these limitations, thorough knowledge, training and proper patient selection are the key requirements. Intrathecal delivery system is not fail-proof and does not eliminate drug-related complications or side effects and may have potential for mechanical error or malfunction due to the mechanical nature of these devices as well as surgical complications related to the procedure.

Future experimental and potential approaches

Cannabinoid agonists

Most data supporting potential beneficial effects of cannabinoids relates to animal studies. Lozano-Ondoua and colleagues reported reduction in bone-induced pain, bone loss and breast cancer cell proliferation with a cannabinoid-2 (CB-2) receptor agonist, JWH-015, via systemic administration. These effects were reversed *in vivo* by treatment with a CB-2 antagonist but not with a CB-1 antagonist. These results suggest CB-2 agonists as a promising treatment for breast cancer-induced bone pain, in which disease modifications include a reduction in bone loss, suppression of cancer growth, attenuation of severe bone pain and increased survival without the major side effects of current therapeutic options [Lozano-Ondoua *et al.*, 2013].

Gu and colleagues demonstrated beneficial effects of intrathecal administration of the CB-2 agonist JWH-015 in another animal study with dose-dependent attenuation of tactile allodynia and thermal hyperalgesia. The effect was prevented by intrathecal injection of CB-1 antagonist AM-630 thirty minutes prior. Their conclusion was that intrathecal administration of a CB-2 agonist might relieve cancer-related pain likely due to NR2B-dependent activity in the spinal cord [Gu *et al.*, 2011].

RANK-RANKL inhibitors

The receptor activator of nuclear factor kappa-B (RANK) and receptor activator of nuclear factor kappa-B ligand (RANKL) system plays an important role in the development and progression of bone metastases by its role in the maturation and function of osteoclasts. This makes it a logical reason to explore the inhibition of this system in order to discover possible treatment for osteolysis and metastases [Papachristou et al., 2012]. It was determined that most of the bone pain in metastatic lesions is as a result of osteoclastic activity. Interaction between the RANK receptor and osteoprotegerin ligand (OPGL) is crucial in activating the process of osteoclastic activity and bone resorption. Any treatment that inhibits this interaction will impair RANK activation, and thus will impair bone resorption and related pain [Kong et al., 1999]. There are some experimental trials in progress in an effort to find a treatment that specifically targets this area.

T-Cell related proteins inhibitors

Hang *et al.* demonstrated the relationship between T-cell death-associated gene 8 (TDAG8) and the initiation and maintenance of cancer-related bone pain [Hang *et al.*, 2012]. A bone cancer pain model was created by inoculation of Walker-256 cells into the intramedullary space of a rat tibia. Intrathecal administration of TDAG8 attenuated bone cancer pain behaviors during the initiation and maintenance phases with decrease in TDAG8a and mRNA protein levels in the spinal cord. On days 6, 12 and 18 after inoculation, the relative levels of spinal TDAG8 and mRNA were significantly and time-dependently increased in bone cancer pain rats compared to sham and normal saline rat groups [Hang *et al.*, 2012].

Purinergic modulators

It appears that purinergic modulators have the capacity to affect nociceptive process. Kaan *et al.* demonstrated that pain related behavior was improved with an increase in phosphorylation of ERK ½ protein expression levels in the spinal cord and dorsal horn/dorsal root ganglion (DRG) in bone cancer rat modules relative to the sham group. They also demonstrated attenuation of bone cancer pain-related behavior, reduction in bone cancer-induced dorsal horn hyperexcitability *in vivo* on oral administration of a strong selective P2X2 and P2X2/3 receptor antagonist, AF-353 [Kaan *et al.*, 2010].

Chen and colleagues demonstrated in their published study that intrathecal injection of the P2Y1R antagonist, MRS 2179, not only decreases P2Y1R mRNA and p-ERK ½ protein expression in the spinal cord dorsal horn and DRG, but also reduces pain-related behavior including tactile allodynia, spontaneous pain and ambulatory-evoked pain [Chen *et al.*, 2012].

Summary

Cancer-related bone metastases are a devastating condition associated with various cancers. It is usually associated with suffering and unbearable pain. In certain situations, it leaves patients wheelchair-bound with very limited functional capacity and several other complications in last stages of life. A team approach consisting of multidisciplinary areas will not only provide better pain control, but will also make it possible for the patient to remain somewhat functional in the last stages of life. Knowledge related to these issues is rapidly evolving as treatment approaches continue to emerge. A better knowledge and understanding of the pathophysiology of metastatic bone lesions and associated pain will lead to better analgesia and lesser side effects. As new approaches are emerging, there is a hope that future agents and approaches will bring safer options with more effective pain control and better quality of life in the last days of a patient's life.

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HIV and AIDS

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Introduction

There was a time, not so very long ago, when a diagnosis of Acquired Immunodeficiency Syndrome (AIDS) was commensurate with death. The relentless nature of the Human Immunodeficiency Virus' (HIV) destruction of the immune system left patients vulnerable to life-threatening opportunistic infections and malignancies and, ultimately, death. Since the advent of highly active antiretroviral therapy (HAART) in the middle 1990s, patients' immune systems have been restored to the point where a nearnormal lifespan is possible, even expected.

This chapter will review the role of palliative care in HIV infection and AIDS, and how patients and their health care providers have adapted to the changing treatment paradigms. The reality of HIV medicine is that HIV infection has evolved from an inevitably terminal disease to a chronic condition, one that is eminently treatable, enabling patients to survive into their senior years. The story of the HIV/AIDS epidemic is one of hope and courage that arose from a state of panic and desperation in a little over thirty years. This chapter will summarize that journey and will explore the role of palliative care in the pre- and post-HAART eras, both in the developing and western worlds.

The history of the HIV epidemic

It was 1981 when reports from Los Angeles and New York City surfaced of an unusual infection, *Pneumocystis carinii*, now *Pneumocystis jirovecii*, causing pneumonia, and an uncommon malignancy, Kaposi's sarcoma, in homosexual men [CDC, 1981]. Patients with *Pneumocystis jirovecii* pneumonia (PJP) started filling up intensive care units in hospitals across the United States and Europe. The usually indolent skin cancer, Kaposi's sarcoma, typically seen in men of Mediterranean descent, was appearing in a disseminated form in the skin, lymph nodes and lungs of patients at the same time [CDC, 1982a]. Physicians were starting to understand that these cases were clustered among sexual contacts of men who have sex with men (MSM) [CDC, 1982b]. By July of 1982, reports emerged concerning cases of PJP among patients with hemophilia A [CDC, 1982c] and, by the end of that year, in infants [CDC, 1982d]. By January of 1983, reports of women, partners of the HIVinfected men, also were reported to have developed HIV infection [CDC, 1983].

In 1984, evidence for antibodies to a retrovirus was found to be etiologically associated with clinical AIDS [CDC, 1984]. The U.S. Food and Drug Administration (FDA) approved the first test for HIV antibodies in 1985. This screening test has been refined over the years. The fourth generation tests now include antibodies for HIV-1 groups M and O, HIV-2 and p24 antigen, to also detect HIV in patients earlier, as they are seroconverting [Pandori *et al.*, 2009].

The case definition for AIDS has evolved since the CDC first defined this in 1982 [CDC, 1982e], with a major revision occurring in 1993 [MWR, 1992]. The CDC expanded the list of typical AIDS-defining conditions to include cervical carcinoma, pulmonary in addition to extrapulmonary tuberculosis, and recurrent bacterial pneumonia. Further, a laboratory definition of AIDS was added, to include a CD4 cell count less than 200 cells/cmm, or a percent CD4 less than 14%. This revision was the last, and is the version we still use for classification of HIV infection today.

HIV epidemiology

Between June 1981 and September 1982, there were 593



Figure 1 AIDS diagnoses and deaths of adults and adolescents with AIDS. (1985-2009: United States and six U.S. Dependent Areas).

cases of AIDS reported, with 243 deaths (41%) [CDC, 1982e]. There have been an estimated 659,000 deaths with an AIDS diagnosis in the United States since the beginning of the epidemic [CDC, 2011a]. Over 1.1 million people are thought to be currently infected with HIV in the U.S., with approximately 50,000 new infections occurring each year (*Figure 1*). Approximately 18% of these are thought to be undiagnosed and unaware of their infection. This group of undiagnosed patients may contribute disproportionately to new cases of HIV transmission [Koopman *et al.*, 1997]. Men who have sex with men continue to be the most common risk group for HIV infection in the U.S., and African Americans continue to be disproportionately affected by the epidemic [CDC, 2006].

HIV treatment

In March 1987, the first therapy to treat HIV infection, zidovudine, was FDA-approved [Food and Drug

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Administration. HIV/AIDS Historical Timeline]. This drug is an inhibitor of reverse transcriptase, and was our first therapy in a long list of drugs that have now been approved to treat HIV infection. A generic form of zidovudine became available in 2007 [Food and Drug Administration. HIV and AIDS Activities]. Since that time more than 25 drugs from six classes of therapy have been FDA-approved to treat HIV infection in the United States. These drugs work by impairing the replication of HIV, resulting in suppression of the amount virus that we can detect in the blood, with subsequent improvement in CD4+, T-helper cells, the target cells of HIV. Combination therapy works better than singledrug therapy, and three active drugs are the most effective in maintaining durable viral suppression [Hammer et al., 1998]. Guidelines exist for the treatment of HIV infection, as well as for the prevention and treatment of opportunistic infections, and these are updated regularly [DHHS, 2012]. There are two major sets of treatment guidelines in the United States, those of the Department of Health and Human Services
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[DHHS, 2013], and those of the International Antiviral Society-USA [Thompson *et al.*, 2012].

Palliative care in the pre-HAART era

For the first half of the epidemic, up until 1996, survival with HIV infection depended upon the successful use of life-prolonging, prophylactic antimicrobials to prevent PJP and Mycobacterium avium complex (MAC). As CD4 cells counts, or T-helper cells, drift below 200 cells/cmm, people become much more susceptible to life-threatening infections or cancers. Guidelines exist for recommendations for the prevention and treatment of opportunistic infections in adults and adolescents [Kaplan et al., 2009]. Antiretroviral therapy played a significant role in the pre-HAART era, but lacked the potency for durable viral suppression in most patients. Palliative care and hospice care were critical in helping patients die with dignity [O'Neill et al., 2003]. AIDS advocacy, as portrayed in And the Band Played On [Shilts, 1987], gave voice to the urgency of the crisis at hand. This type of advocacy pushed the politicians and scientists and demanded integrity and transparency in clinical trials and research for HIV and AIDS. The author himself, Randy Shilts, typified the culture of the day, where many gay men had moved to large, urban areas, where their lifestyle was more accepted. Embodied in this was the fact that for many, their only support system was their friends, as they were not "out" to their families back home. Many did return home to be with their families during their final days, but others either had no family, or did not feel welcome back in their communities of birth.

There was much uncertainty in the early days of the epidemic. What was the cause? Was it an infection? If so, how was it transmitted? Were caregivers at risk of getting it? There were many unsung heroes in AIDS wards across the United States. As time marched on, it became clear that HIV was transmitted via blood and by sex. Nurses, doctors, and practitioners from various disciplines rose to the occasion to care for these many men, women and infants in the U.S, Europe and Australia. In the developing world, especially Sub-Saharan Arica, the epidemic grew to be the largest region of the world impacted by HIV and AIDS [UNAIDS, 2005]. The mortality rates there have been the highest in the world, and only more recently has antiviral therapy become available in many of these regions.

A unique aspect of the HIV epidemic is the wide variety of backgrounds from which many of the caregivers arose. Immunologists, oncologists, family practitioners, internists Part II

and infectious disease specialists stepped up to provide care for these many patients affected by HIV and AIDS. And from the start, the care was multi-disciplinary, out of necessity. Nursing units in hospitals became second homes to these individuals, who may have been shunned by their families. Depression and substance use were also commonplace, so mental health professionals and substance use counselors have been part of the care teams from the beginning. Injection drug use had become recognized as an additional risk factor for HIV infection. These people had even fewer supports, and often relied on public health facilities for any outpatient health care they received. Attention to the spiritual needs of the patient was addressed by hospital chaplains, as the hospital was the setting where much of the early epidemic played out. When medical providers would round on these patients, fevers abounded, and providers chased one opportunistic infection after another. Cytomegalovirus caused blindness, toxoplasmosis caused encephalopathy, PJP caused fever, shortness of breath and cough, and cryptococcus caused headaches and meningitis, to name a few. Kaposi's sarcoma darkened the skin and filled the lungs of some patients, lymphomas caused startlingly high fevers in others, and cervical carcinoma became common among the women, who often lacked comprehensive gynecologic care. Care teams also developed from the community, and patients and their friends supported each other, both in the hospital and after discharge. The vast majority of these patients' outcomes were the same, however, with death resulting after months and sometimes years of struggle. Nearly everyone died.

Because HIV causes severe wasting, good nutrition has been a constant and important element of the care of the HIV-infected patient. Food requirements of some of the antiviral regimens are significant, and early on, patients would set their alarms to take their zidovudine every four hours. The gastrointestinal (GI) side effects of some of the antiviral therapies are well known. These side effects are on top of the effect of the many opportunistic infections, including HIV itself, on the GI tract. The relentless weight loss seen in those early years was discouraging, not only for the patients themselves, but also for the caregivers. Single drug, antiviral therapy gave way to dual, combination therapy, which helped with control of viral replication to some degree, but ultimately failed, leading to wasting syndrome and death for the patient. Even after zidovudine was FDA-approved, new drugs came slowly, each with its own, unique side effects, such as peripheral neuropathy. One set of challenges was replaced by another. Pain control was an important aspect of the management plan for each patient, though specific pain management programs were not as available as they are today. And so it went, for another decade, until the approval of the first protease inhibitor, saquinavir, in December 1995 [Food and Drug Administration HIV/AIDS Historical Timeline].

Palliative care in the HAART era

With the development of two new classes of antiretroviral therapy, the protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs), a rather abrupt change took place in the lives of many people living with HIV and AIDS. Dying patients reversed their course, felt better, gained weight, and literally rose from their deathbeds, in some instances. These two drug classes heralded what has been called the era of Highly Active Antiretroviral Therapy, or HAART. Finally, sustained, complete viral suppression to the lower limits of detection was feasible, and became commonplace. Immune systems, as measured by CD4+ cell counts, improved, sometimes to normal levels, with one caveat. Patients had to strictly adhere to their regimens at a level no prior disease had demanded, indefinitely, and without interruption. These new medications were not without their own side effects, and the GI side effects were, and continue to be, often the most disabling. Relentless diarrhea becomes intolerable, even if it means stopping the medications and allowing viral replication to resume. The protease inhibitors-based HAART required 95% or better adherence to maintain complete viral suppression [Paterson et al., 2000]. Any less adherence risked virologic breakthrough, drug resistance and, ultimately, antiviral failure with subsequent immune failure.

In the HAART era, the role of adherence counseling has become paramount. Adherence programs have become an integral part of the care team, to work with patients and help them be successful with their medications. This team often includes a nurse, a pharmacist or Doctor of Pharmacy, a peer, and the medical provider. As patients' health improved, prior issues often resurfaced, including depression and other mental health problems, substance use relapse, and financial stress, to name a few. Some patients, who were dying, had cashed in their life insurance policies, and later found themselves improving in regards to their health, but financially impoverished. Newer therapies, to include protease inhibitors boosted with ritonavir, another PI, and newer classes of drugs, such as entry inhibitors and integrase inhibitors, which have been approved in the past decade, now make complete viral suppression the norm. These therapies still demand high degrees of medication adherence, but their potency and half-lives have enabled single-tablet regimens. These combination regimens help patients be much more successful with adherence [Llibre and Clotet, 2012] and enjoy complete viral suppression with immune restoration.

The epidemic slowly has shifted over the last decade to a chronic illness, one that is now largely managed as an outpatient. In-patient AIDS units are smaller, and some have closed entirely [Ofri, 2012]. Hospitalized patients now have different sets of problems including coronary heart disease, diabetes, and renal failure, to name a few. Our in-patient multi-disciplinary care teams still exist, but have evolved. Inpatient stays are shorter, and patient needs have shifted. In New York State, hospitals were given financial incentives early in the epidemic to become Designated AIDS Centers, to ensure appropriate care of individuals with HIV and AIDS New York State Department of Health: Designated AIDS Centers (DAC) Clinic Contacts. Accessed April 2013]. Now that the epidemic has shifted to an out-patient, manageable, chronic illness, reimbursement structures have also changed to try to adjust to the changing care delivery system.

In-patient HIV care

So what do in-patient units look like now in the United States? Patients with HIV and AIDS increasingly are hospitalized with non-AIDS defining illnesses. These include complications from chronic hepatitis C, such as cirrhosis, from end-stage renal disease, heart disease and malignancies. Also, hospitalizations related to substance use and mental illnesses remain significant. The international SMART trial, Strategies for Management of Antiretroviral Therapy, compared continuous versus interrupted therapy, guided by CD4 cell counts in over 5,000 HIV-infected individuals, and was the first trial to demonstrate an increased risk of death from non-AIDS defining events, to include heart disease, liver disease, and kidney disease, in patients with higher CD4 cell counts [The SMART Study Group, 2006]. In addition, this trial was the first of now several trials to prove the value of continuous antiviral therapy. Continuous therapy without treatment interruptions, or drug holidays, as they were called, provided longer viral suppression and improved survival, in patients with higher CD4 cell counts, above 350 cells/cmm, well above the AIDS-defining threshold of 200 cells/cmm.

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Increasingly, our in-patient HIV units look more like traditional hospital units. Put simply, HIV-infected patients are living long enough to suffer diseases and complications similar to those of the general population, albeit at a somewhat higher rate. Some of this increased risk seems to stem from the chronic inflammatory state incited by HIV itself, due to the microbial translocation of bacteria from "leaky" gut mucosa [Brenchley et al., 2006]. Regardless, patient needs have shifted, even on our in-patient units, to expectations for living rather than dving. We still have our care teams, but they need not be as specialized on the in-patient side. Our social workers, case managers and discharge planners work with the nursing staff and medical providers to develop safe discharge plans for our patients. The importance of the pharmacist's input cannot be overstated, in minimizing negative drug-drug interactions, such as QTc interval prolongation, serotonin syndrome, or unintended methadone withdrawal, to name a few examples. Complex drug interactions can occur as a result of the cytochrome P450 mechanism of metabolism of many of the antiretroviral medications.

Additionally, we use chaplains, peer counselors, ethicists, and other team members as the need arises. To be clear, we still have patient deaths, though increasingly these are not from the traditional, AIDS-defining causes. Those that occur related to AIDS are typically from patients who are diagnosed late in the course of their illness and present to the emergency room with a life-threatening opportunistic infection or malignancy. These "late testers" have been a challenge, and why, in 2006, the Centers for Disease Control called for the routine testing of everyone between the ages of 13 and 64 years [Branson et al., 2006]. Centers for Disease Control data from 1996-2005 from 34 states that utilized confidential, name-based HIV and AIDS reporting indicated that 38.3% of patients had or developed AIDS within one year of their HIV diagnosis [CDC, 2009]. Peer counselors can be especially important to engage patients, help them to cope with their new diagnosis, and help them get into care upon discharge from the hospital. However far we have come in treating HIV and turning it into a chronic, manageable illness, a new diagnosis is always a shock for the individual. Patients always remember the date of their diagnosis, and need the support of the care team to get through this difficult time. The one message that we want patients to hear at the time of diagnosis is that, while not curable, HIV is eminently treatable, and can now be associated with near normal life expectancy. In a study from the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD), a cohort of over 23,000 treatment-naive individuals living with HIV who are at least 20 years of age or older, HIV-infected people would be expected to live an additional 47.1 years, as of 2006-2007 [Hogg et al., 2012].

Out-patient HIV care

Most of the care delivery for patients living with HIV infection in the U.S. occurs now in the outpatient setting. The care team ideally includes adherence nurses, case managers, nutritionists, substance use counselors, mental health counselors and/or psychiatrists, and peer counselors, in addition to the medical providers and pharmacists. Specialists are needed on a referral basis for the wide variety of conditions that patients develop over a lifetime.

For adolescents transitioning from the pediatric clinic to the adult practice, transitional services are important to ensure uninterrupted care [DHHS, 2011]. Medical and support staff, who have known these patients from birth, can be critical to the successful transfer of patients to adult providers. Adolescent HIV providers care for patients who have been both perinatally infected and behaviorally infected with HIV. The reduction in perinatal transmission of HIV as a result of antiretroviral therapy has been one of the major success stories of the epidemic [CDC Figure 2]. Risk of perinatal transmission of HIV to the newborn of an HIV-infected mother is less than 2%, with fully suppressive HAART in the mother [Cooper et al., 2002]. HIV therapy is so successful that women living with HIV request family planning services. Well-coordinated care between those caring for the mother and the neonatologist, who will be caring for the newborn, is essential. Enormous efforts and resources are deployed to help these mothers be successful in their antiretroviral therapy, so they may have healthy, HIV-negative babies.

For adults, HIV-infected patients are seen every three to six months for follow-up visits and laboratory monitoring. A more intensive visit once per year is helpful for a complete physical exam, case management assessment, update of medical releases, and other services as dictated by the patient. Coordinated, integrated health care is the goal. Models of care delivery differ depending on the community. In some, the patient has a primary care provider and then sees an HIV specialist for their HIV-related care. In others, the HIV specialist is also the primary care provider for the patient. Coordinated care is especially important for people living with HIV or AIDS, and the care team model

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Figure 2 Estimated numbers of perinatally acquired AIDS cases by year of diagnosis. (1985-2007: United States and Dependent Areas).

is critical for those patients with complex needs. The epidemic has increasingly impacted minority and poorer communities. As an example, among 33 states reporting HIV/AIDS cases from 2001-2004, blacks accounted for 51% of the HIV/AIDS population, while representing only 13% of the U.S. population [CDC, 2006]. Complicating HIV infection is substance use, mental illness, poor oral health, chronic hepatitis B or C and other challenges. Much has been written about the triply diagnosed patients with HIV, mental illness and substance use problems, and the challenges they present to the treatment team [Sacks et al., 2011]. Oral health care is limited or non-existent for many people living with HIV/AIDS across the United States. Funding for some programs is provided by Health Resources Services Administration (HRSA) through the Ryan White Care Act (RWCA), but is insufficient to meet the oral health needs of many patients due to its limited distribution [HRSA: Oral Health. Accessed April 2013a].

HIV care has also included complementary therapies to include acupuncture, massage therapy, Reiki, and herbal

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therapies, as examples. Some herbal therapies, such as St. John's wort used for depression, interact negatively with protease inhibitors, affecting their levels in the blood [Henney, 2000]. HIV care providers should ask patients for all of the medications they are taking, including supplements and herbal or other complementary therapies. This allows for the optimal care of the HIV-infected patient. In as much as complementary therapies relieve stress, provide pain relief, or reduce drug side effects, they can be a useful adjunct to HAART.

It is important to recognize that there is a subset of patients living with HIV infection, whose immune systems seem to handle HIV without antiretroviral therapy [Gaardbo *et al.*, 2012]. Long-term non-progressors have had their infection for years, with normal CD4 cells counts and stable viral loads. Elite controllers control their virus, with completely undetectable viral loads and normal CD4 cell counts, without HAART. These individuals probably represent less the 1% of the HIV-infected population, and have been of intense academic and research interest as to

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Figure 3 HIV Care Cascade; CDC, July 2012.

how their immune systems handle the infection, so as to inform possible future treatments.

HIV/AIDS funding

The Ryan White Care Act provides congressionally appropriated grant funding, as the "payer of last resort," to help the multi-disciplinary core team meet the complex needs of many of their patients [HRSA: HIV/AIDS Programs, Accessed April 2013b]. This Act was originally authorized in 1990, in honor of the hemophiliac from Indiana, Ryan White, who died from AIDS, to fill funding gaps for HIV and AIDS care. It has been re-authorized four times since then, and was up for re-authorization again in the fall of 2013. How health care reform and the Affordable Care Act will impact re-authorization and future funding remains to be seen. Another important component of the Ryan White legislation authorizes the AIDS Drug Assistance Programs (ADAP), with dollars appropriated to each State to pay for the expensive medications for those individuals who financially qualify. The Designated AIDS Center care model of NY State is truly an example of what is being emulated for other chronic conditions, in the Patient-Centered Medical Home of the National Committee for Quality Assurance [NCQA, 2013]. These centers have been this home for people living with HIV and AIDS for decades, and will need to align themselves with the national models in order to sustain their funding.

HIV/AIDS in developing countries

HIV/AIDS has had a devastating impact on the developing world. According to the Joint United Nations Programme

on HIV/AIDS (UNAIDS), of the approximately 40 million people living with HIV/AIDS in Africa in 2005, 26 million, or 64%, live in Sub-Saharan Africa [UNAIDS, 2005]. This compares to an estimated 1.2 million people living with the virus in the U.S. The lack of availability of antiretroviral therapy for people living with HIV in Sub-Saharan Africa, for example, has led to high mortality rates. AIDS is the most common cause of death in the region. In 2003 the President's Emergency Plan for AIDS Relief (PEPFAR) authorized 15 billion dollars over five years to implement HAART in countries hit hardest by the epidemic [Institute of Medicine Press Release, 2013]. By World AIDS Day in December 2012, 5.1 million people were estimated to be on HAART through the PEPFAR program [PEPFAR: World AIDS Day, 2012]. Community supports and palliative care vary by region and country, from no support and actual shunning from society to a full complement of medical and psychosocial, supportive services. Africa is not the only region struggling, as the epidemic has exploded in Asia and eastern European countries, as well.

The HIV care cascade

One of the great challenges remains getting people diagnosed and into consistent HIV care. The HIV Care Cascade is an analysis from the CDC looking at how many people in the U.S. are diagnosed and consistently linked to and engaged in care, with fully suppressed HIV (Figure 3) [CDC Fact Sheet, July, 2012; CDC Press Release, 2012]. As of July 2012, CDC estimated that 82% of the 1.2 million people living with HIV in the U.S. were actually diagnosed. Only 66% were estimated to be linked to care, and only 37% were retained in care. Thirty-three percent were prescribed antiretroviral therapy, and only 25% of those living with HIV in the U.S. enjoyed undetectable viral loads. The conclusion of the CDC is that we need to reduce disparities of race and age, and get the some 200,000 HIV-infected, but yet undiagnosed, tested, linked to and retained in care, and stabilized on antiretroviral medications. Given the convincing data that lowering HIV viral load through successful antiretroviral therapy is linked to decreased sexual transmission, guidelines have moved toward recommendations to treat everyone with HIV with HAART, regardless of CD4 cell count [Cohen et al., 2011]. Some have captured this in the phrase, "treatment as prevention." There is a newer concept of "community viral load," meaning the mean or median viral load of all those living with HIV in a given community. If this were lowered

enough, in all communities, spread of the epidemic could theoretically be halted [CDC, 2011b].

If any of this is to happen, a comprehensive approach of outreach for HIV testing and linkage to primary HIV care is necessary. HIV providers should utilize a multidisciplinary care team approach to meet the needs of their patients, especially for those patients with unstable housing, mental illness and/or substance dependence, to help them stay in care and on effective antiretroviral therapy. Co-located services are beneficial to help patients access all the care they need with as few barriers as possible. Palliative care implies caring for the patients' physical, medical, emotional, spiritual and psychosocial needs, to the extent possible. If we are successful in this regard, progress can be made in curbing HIV transmission and promoting healthier communities.

Summary

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The ultimate goal of HIV care is to meet all of the needs of the patient. These include the psychosocial, spiritual, and emotional as well as medical needs. Whatever challenges an individual had before the diagnosis of HIV infection are magnified by the reality of a life-threatening illness. Whether it is emotional or physical pain, our goal as HIV caregivers is to alleviate suffering. Antiretroviral therapy is an important part of the treatment plan for a person infected with HIV, but it is not the only part, and in some ways not the most important part. People require food, clothing and shelter, and without a sense of security it is difficult to move forward with any other treatment plans. There is more to HIV care than viral suppression, and that is where the *art* of medicine comes into play.

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End stage liver disease

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Introduction

End-stage liver disease (ESLD) is a clinical syndrome characterized by systemic manifestations of liver dysfunction. ESLD results from both acute liver failure and chronic liver disease progression. There are many etiologies for both acute and chronic liver disease, including viral infection, alcohol consumption, obesity, malignancy, trauma, and drug toxicity. Regardless of the etiology of ESLD, the manifestations of the liver dysfunction are remarkably consistent and affect every system in the body [Rahimi and Rockey, 2013].

The sole cure for ESLD remains in liver transplantation [Lee *et al.*, 2008]. However, many liver transplant candidates will die on the waiting list as a result of a worsening organ shortage. By 2011, the most ill patients waiting on the list faced a mortality rate per patient per month in excess of 80% [SRTR, 2011]. For these patients, as well as those who are unable to undergo liver transplantation for medical or personal reasons, palliative medicine (PM) is a humane treatment option. The goal of PM is to relieve medical, psychosocial, and spiritual suffering.

The timing of PM

For patients with acute liver failure, the rapid progression of disease is dramatic. Most of these patients survive to reach ESLD only because of life-sustaining interventions and heroic care provided in an intensive care unit. In that setting, many providers have experience in providing PM or in consulting PM specialists. PM is considered as soon as the option of liver transplantation is exhausted. In this setting, it is often difficult to differentiate hospice care from PM. For patients living with chronic liver disease progression, which can occur over months to years, the timing of the institution of PM may be challenging. Patients with ESLD face a slow physical and mental decline as they struggle to maintain their autonomy. PM is often only considered following an acute event, which mandates inpatient hospital evaluation and treatment [Wigg *et al.*, 2013]. For a patient with a complication of ESLD, such as hepatic encephalopathy or gastrointestinal bleed, this may be the first time that they are offered PM. However, many patients with ESLD may benefit from PM in the outpatient setting. For example, when dialysis is considered for the treatment of chronic kidney disease, PM should also be considered. In many cases, PM can be provided in addition to heroic measures, to improve the quality of life of the patient.

Hospitalization for complications of ESLD is an indication for PM consultation. By that time, symptoms of ESLD already have a measurable impact on the patient's quality of life. Early referral allows the PM team as much time as possible to establish and cultivate a relationship with the patient and the patient's family, while collaborating with medical and surgical specialists. Despite the best of intentions, suboptimal care is often delivered to patients with chronic diseases, such as ESLD, at the end of life [SUPPORT trial, 1995]. Nonthreatening explanations of hospice services can be introduced early, so that patients and families have the opportunity to decline treatments with a low probability of a desired outcome, without feeling as though they are "giving up".

The role of the PM specialist

PM providers specialize in the management of the symptoms of ESLD. Many of these symptoms decrease the

patient's quality of life, but are often overlooked during the medical and surgical management of acute manifestations of ESLD, which are more immediately life-threatening. From the perspective of the patient, the management of symptoms is often overlooked; poor sleep, pruritus, nausea, anxiety, abdominal pain, and muscle cramps may not be addressed by clinicians. Although liver transplant may be an eventual option for some patients with ESLD, many are "too well for a transplant but too sick for life" [Larson and Curtis, 2006]. These patients require a team approach, which helps them to cope with the decreased quality of life they experience and the decreased life expectancy associated with it [Kanwal et al., 2004; Schomerus and Hamster, 2001; Bianchi et al., 2003]. The effect of the integration of PM into programs with curative and life-prolonging intent is unknown [Song et al., 2009].

The PM specialist can recommend symptom management options to the primary treating team. For example, opioid use in ESLD can be challenging, especially in the setting of a history of prior ethanol or substance abuse. The provider and the patient may have different goals of therapy; providers often aim to relieve discomfort, while the patient hopes for relief of pain, suffering, and anxiety. The provider's goal may be to return the patient to a functional status which allows them to achieve activities of daily living in an independent manner, while the patient may wish to be heavily sedated to avoid any further suffering. Discrepancies in the goals of providers and patient often results in frustration for all parties involved. In addition to analgesic therapy, the PM specialist can help to identify these discrepancies and address them, to optimize the comfort of the patient and the efficacy of therapy.

A successful collaboration with both the patient and patient's family is built on trust, over time. The patient, patient's family, and patient's providers often fear the suffering which is associated with the end of life. In doing so, they commonly delay the institution of palliative therapies for patients who need them most. Physicians often overestimate the patient's prognosis in the setting of a terminal illness, such as ESLD. In one study, patients with ESLD were rarely referred for PM consultation, despite being removed from the transplant waiting list [Poonja et al., 2013]. Clinical practice guidelines contain little information to guide physicians to consider PM. Attention to end-of-life concerns should be part of the treatment plan as early as possible [Mast et al., 2004]. For these reasons, a PM consultation should be considered for all patients who suffer from complications of ESLD.

A PM specialist can facilitate the most difficult medical decision-making. An early evaluation of the family structure and its decision-making process can help the medical team to provide optimal care while ameliorating the distress of the patient and patient's family. For example, hepatic encephalopathy is often perceived as a threat to a patient's independence; it is a distressing symptom for patients and families to experience and it complicates communication efforts [Younossi *et al.*, 2001; Arguedas *et al.*, 2003]. In such a setting, a PM specialist is particularly helpful in guiding the patient and family through a challenging time, while ensuring the patient's comfort.

A PM specialist can facilitate the transmission of bad news and poor prognoses to patients and families. Most providers fear the discussion of a patient's prognosis as much as the patient and the patient's family. When a provider is unable to successfully treat or cure an illness, such as a complication of ESLD, it may result in the provider experiencing a sense of failure and inadequacy. However, patients often do not associate honest prognostic information with the loss of hope, especially when such prognostic information is delivered in a caring manner, in a private and calm environment [Curtis et al., 2008]. Contrary to popular misconception, patients' hopes do not depend exclusively on the desire for cure [Benzein et al., 2001]. A PM specialist will explore the patient's philosophical outlook on life and death, interpersonal connections to those important to them, and spiritual orientation, allowing for a more comprehensive understanding of the needs of the patient.

Pathophysiology of ESLD

The liver is an essential organ. It synthesizes plasma proteins, lipids, and clotting factors. It detoxifies the blood by extracting ammonia, bilirubin, proteins, and vasomotor mediators [Berry *et al.*, 2013]. It also serves as a passive reservoir of blood in the abdomen. When one of these functions is disrupted, the resulting illness may be lifethreatening. ESLD is heralded by systemic manifestations of liver failure, as well as the complications associated with these conditions. Many of these conditions, and their therapies, can result in patient suffering. At this time, liver transplantation remains the sole cure of ESLD.

Hepatic encephalopathy

When the liver fails to adequately filter toxins and vasogenic

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mediators from the bloodstream, abnormal brain function, or hepatic encephalopathy, ensues [Sass and Shakil, 2005]. A spectrum of clinical manifestation, ranging from mild irritability and subtle cognitive dysfunction (stage 1) to coma (stage 4), may be observed [Rahimi and Rockey, 2013]. Factors that precipitate hepatic encephalopathy include gastrointestinal bleeding, dehydration, sepsis, administration of sedatives, portosystemic shunting, and liver injury [Shawcross and Wendon, 2012].

Hyperammonemia

The primary toxin of clinical concern is ammonia, which is the breakdown product of protein metabolism and gut bacteria metabolism. A failing liver is unable to clear ammonia from the blood, resulting elevated levels of blood ammonia (*byperammonemia*). The treatment for hyperammonemia is to decrease ammonia production, increase ammonia excretion, and modify its portosystemic circulation [Bajaj, 2010]. Caution is advised in the interpretation of blood ammonia levels; encephalopathy may occur in the setting of normal blood ammonia levels, and normal mentation may occur in the setting of elevated blood ammonia levels.

In the past, dietary protein was restricted in effort to minimize protein metabolism and thereby the production of ammonia. This approach is less favored today, as it may contribute to protein malnutrition. Instead, the ingested protein content can be altered to include more plant- or dairy-based protein, which may be better tolerated because of its more favorable calorie-to-nitrogen ratio, as well as refined amino acid substitutes [Krenitsky, 2003].

To increase ammonia excretion from the gut, lactulose, neomycin, and rifaximin may be used. The therapeutic effect of lactulose is achieved by mass evacuation of gut bacteria; to be effective, it must result in three to five generous bowel movements per day. It can be challenging for providers to reach a therapeutic balance with lactulose, as the resulting diarrhea may contribute to dehydration, renal dysfunction, and electrolyte imbalance. Rifaximin is better tolerated, as it acts locally in the gut as an antibiotic against the gut bacteria that generate ammonia. In the ICU setting, lactulose is often administered as an enema or as a continuous feeding tube infusion in conjunction with either a rectal tube or a fecal incontinence appliance to maintain a hygienic environment, track the volume loss for replacement purposes, and to prevent skin breakdown until the patient's encephalopathy improves.

Portal bypertension and portosystemic shunt-associated encephalopathy

Patients with ESLD undergo progressive liver fibrosis, which results in portal hypertension. Portosystemic shunting ensues, which is often inadequate to prevent complications of portal hypertension. Portosystemic shunts can be created surgically and through minimally invasive procedures to decompress portal blood into the systemic circulation. Patients who undergo shunting procedures may develop encephalopathy, as ammonia and other toxins bypass the liver and are emptied directly into the systemic circulation. This may result in new or worsening encephalopathy.

Directed tumor therapy- and infarction-associated encephalopathy

Patients with hepatocellular carcinoma (HCC) or metastatic disease in the liver may undergo medical or surgical therapy to control the tumor burden and/or tumorassociated symptoms. However, in the setting of ESLD, even small changes in functional liver volume may result in encephalopathy. Whereas a patient with normal liver function only needs 10-20% of their liver to survive, the opposite may be true for a patient with ESLD, who may require 80-90% of their minimally functional liver to survive. ESLD patients undergoing directed therapy, be it surgical excision or minimally-invasive tumor lysis, should be closely observed for at least 12 to 24 hours for new or worsening encephalopathy.

Cerebral edema (CE)

CE commonly accompanies fulminant hepatic failure and is present in most cases of death due to fulminant hepatic failure [Sass and Shakil, 2005]. In the setting of ESLD, CE is likely the result of elevated blood levels of vasorelaxants and cytokines, including nitric oxide, carbon monoxide, endothelin-1, and tumor necrosis factor α . In cases of moderate to severe encephalopathy, this diagnosis should be considered early on. If it is unrecognized early on, CE may progress to intracranial hypertension, resulting in brain herniation, brain death, and circulatory arrest.

The most helpful diagnostic and therapeutic maneuver in the evaluation and treatment of CE is the insertion of a decompressing intracranial pressure (ICP) monitor. Medical therapies, including elevation of the head of the bed, osmolality regulation, and hypertension control may also help to regulate the ICP [Sass and Shakil, 2005]. Anticonvulsant therapy is often employed in the prophylaxis and/or treatment of seizure associated with CE.

Ascites

The pathologic accumulation of fluid within the peritoneal cavity is termed *ascites*. In most patients (85%) with ESLD, ascites is a manifestation of portal hypertension. Other causes include portal vein thrombosis, lymphatic obstruction, peritoneal malignancy, and peritoneal infection [Moore and Van Thiel, 2013]. Ascites can easily be identified by physical examination, and its identity can be confirmed through an ultrasound examination. In ESLD patients, who often suffer from coagulopathy, thrombocytopenia, and abdominal wall varices, paracentesis can be dangerous. Careful correction of coagulopathy and/or thrombocytopenia, as well as ultrasound imaging guidance, may help to avoid bleeding complications of paracentesis.

Early on, ascites is often manageable medically with the introduction of sodium restriction and diuretic therapy. However, with progressive ESLD, the volume of ascites becomes difficult to manage with diuretics. Hospital admission and mechanical drainage with large volume paracentesis become necessary, eventually resulting in volume depletion and renal impairment. By this time, the patient's quality of life is usually poor. For cases of refractory ascites, insertion of a transjugular intrahepatic portosystemic shunt (TIPS) or a permanent percutaneous catheter may alleviate nausea, pain, and hiccups [Moore and Van Thiel, 2013]. Hospice referral is indicated at this time.

Spontaneous bacterial peritonitis (SBP)

Gut permeability is impaired in ESLD. SBP occurs through bacterial translocation across the gut into the peritoneal space in the setting of ileus, bacterial stasis or bacterial overgrowth [Leber *et al.*, 2012]. If SBP is identified, antibiotic therapy is warranted.

Heart failure and respiratory failure

Systemic vasodilation, hypotension, and a low systemic vascular resistance are observed in ESLD. To compensate for these vasodilatory events, an increase in the cardiac output occurs, resulting in a hyperdynamic state. Early on, volume loading may help to counteract this issue. However, symptoms of heart failure, including dyspnea and edema, will ultimately result in a poor quality of life.

Hepatopulmonary syndrome (HPS)

As vasoactive mediator levels rise, vasodilation and angiogenesis occur in the pulmonary vascular bed. This results in hypoxia through at least three mechanisms. First, ventilation-perfusion mismatch occurs. Second, oxygen diffusion is impaired due to dilation of the pulmonary microvasculature, which impedes oxygen transport. Finally, arteriovenous shunts may develop spontaneously, resulting in decreased oxygenation [Grace and Angus, 2013; Karcz *et al.*, 2012].

ESLD patients with dyspnea should be further evaluated for HPS. Clubbing of the fingers and cyanosis may be observed. Pulse oximetry is useful in establishing a diagnosis of hypoxia. The most definitive diagnostic maneuvers include arterial blood gas and bubble contrast echocardiography. In cases where contrast echocardiography is not helpful, radioactive macro-aggregated albumin (MAA) scanning may be used to make the diagnosis. In cases of HPS, supplemental oxygen is most helpful, and some patients may require home oxygen if they sufficiently recover to leave the hospital [Sass and Shakil, 2005]. The prognosis for ESLD patients with cirrhosis and HPS is poor compared to their counterparts. Patients with ESLD and a PaO₂ <60 mmHg are expected to die within six months [Grace and Angus, 2013]. Hospice referral is indicated at this time.

Hepato hydrothorax (HHT) and spontaneous bacterial empyema

Approximately 5% to 10% of cirrhotic patients will develop HHT, which is the pooling of ascites in the chest in the absence of cardiopulmonary disease. Most patients will develop HHT on the right side as a result of the development of fenestrations in the diaphragm. As ascites accumulates in the abdomen, it increases the pressure on the diaphragmatic muscle fibers. As the intraabdominal pressure rises, peritoneal blebs bulge through these fenestrations, rupture, and release ascites into the chest. Negative intra-thoracic pressure generated during normal respiration draws ascites into the chest, where it accumulates [Krok and Cardenas, 2012].

In most cases, lymphatic drainage of the chest will

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increase as much as twenty-fold to prevent ascites from collecting in the chest. However, in the setting of ESLD, chronic ascites may exceed the capacity of lymphatic drainage, thereby accumulating and compressing the lung. With increasing compression, atelectasis and hypoxemia ensue, and can be complicated by pneumonia and empyema [Moore and Van Thiel, 2013].

The diagnosis of HHT can be made with the combination of an imaging study of the chest, such as chest X-ray or CT scan, and thoracentesis. Thoracentesis will be diagnostic and therapeutic; evacuating >500 mL of pleural fluid will allow for lung expansion and improved oxygenation, while pleural fluid can be collected for analysis. Malignancy, infection, and cardiac disease should still be ruled out. If there is evidence of infection in the pleural or abdominal fluid, antibiotic therapy is indicated. Caution is advised regarding tube drainage of the chest or abdomen; ESLD patients often have chest wall varices and/or coagulopathy, making the likelihood of procedureassociated bleeding greater. In the absence of gross purulence, most authors advise against the placement of a longstanding tube thoracostomy or abdominal drain. However, if the empyema is chronic, and gross purulence is encountered, tube drainage, and possibly surgery, may be needed. Short-term use (12 to 48 hours) of such drains is often more reasonable.

In most cases of HHT, management should be focused on sodium restriction and diuretic therapy, to minimize ascites production. Combined thoracentesis and paracentesis can be performed for symptomatic relief. However, the evacuation of large volumes of ascites from the chest and abdomen can result in hypotension and re-expansion pulmonary edema, and may not be tolerated in volumes exceeding 2 L from the chest, or 3 to 4 L from the abdomen, or more frequently than once every two to three weeks. Regular loss of large volumes of protein-rich fluid can result in further malnutrition, renal failure, and electrolyte disturbance.

Alternative drainage options should be considered for symptomatic relief in the outpatient setting. Cuffed thoracostomy tubes, such as the PleurX[®] (CareFusion; San Diego, CA), can be implanted for short- or longterm drainage of the chest, and can be used in both the inpatient and outpatient setting. Pleurodesis is rarely effective. In some cases, TIPS has been attempted in effort to decompress the mesenteric venous system in hopes of decreasing ascites production and transit into the chest. (See section on ascites.) However, the mortality associated with TIPS or surgical intervention is high, ranging from 25-40% [Krok and Cardenas, 2012].

Cholestasis and pruritus

The poor filtration function of ESLD results in progressive cholestasis and hyperbilirubinemia. Accumulation of bilirubin occurs in the skin (jaundice) and sclera (icterus). Pruritus results from the deposition of bile salts, bile acids, bilirubin, and cholephiles in the tissue. Elevated endogenous opioids also result in itching [Wang and Yosipovitch, 2010]. The insatiable itch of pruritus is exhausting for some patients to endure because it limits sleep, thereby contributing to depression.

Pruritus associated with cholestasis can be challenging to treat. Cholestyramine, rifampicin, naltrexone, UV phototherapy, ursodeoxycholic acid, and serotonin reuptake inhibitors have been used in trials with varying results. In cases of mechanical biliary obstruction, such as cholangiocarcinoma or metastatic pancreas cancer, symptomatic relief may also be achieved through temporary external tube drainage of the biliary tree, or permanently through endoscopic stent placement or surgical drainage [Bolier *et al.*, 2012].

There are several classes of agents available for the relief of pruritus. Cholestyramine binds bile salts in the gut and prevents their enterohepatic circulation. Rifampicin (10 mg/kg/day) has shown to alleviate cholestasis pruritus; however, because of hepatotoxic properties, it is only used for short-term treatment. Selective serotonin reuptake inhibitors (SSRIs) may ameliorate pruritus. Paroxetine is noted to be effective, but must be administered for several weeks before its therapeutic effect manifests fully. Other medications, including antihistamines and opioid antagonists, may also be effective. Agents such as mirtazapine, hydroxyzine, doxepin, naltrexone and naloxone may be used to treat intractable pruritus with some success, but their use is limited by their side effects [Wang and Yosipovitch, 2010].

Malnutrition and deconditioning

In excess of 80% of patients with cirrhosis will progress to a malnourished state [Krenitsky, 2003]. For example, in a study of liver transplant candidates on the waiting list, 65% were found to have protein-calorie malnutrition [Lautz *et al.*, 1992]. The etiology of this pronounced malnutrition is likely multifactorial; inadequate intake, malabsorption, altered energy expenditure, and protein loss explain this phenomenon. It is characterized by cachexia, which includes generalized wasting, muscle loss (sarcopenia), fatigue, anorexia, and deconditioning [Montano-Loza *et al.*, 2012; Dasarathy, 2012].

Inadequate food intake

One of the most important contributors to malnutrition in ESLD is inadequate food intake. In ESLD, circulating levels of leptin and tumor necrosis factor result in anorexia and early satiety. Similarly, ascites is associated with anorexia and early satiety, and contributes to the sensation of fullness. Encephalopathy may result in decreased mental and motor function, resulting in a patient's inability to feed independently. Finally, providers may restrict intake around the time of procedures.

It is important to discuss the use of appetite stimulants with the patient and patient's family. In the setting of ESLD, significant side effects may be observed with the use of appetite stimulants. In this situation, the benefit and risk will vary with the patient's condition. Meta-analysis demonstrated improvement in appetite and weight gain with the use of megestrol acetate in patients with chronic conditions [Ruiz Garcia *et al.*, 2013].

Malabsorption

Malabsorption of food intake may also contribute to malnutrition. In ESLD associated with cholestasis, such as with biliary obstruction (e.g., primary biliary cirrhosis), a decreased volume of bile is delivered to the gut, resulting in malabsorption of fat-soluble vitamins and fat. In alcoholics with ESLD, alcohol-induced pancreatic exocrine insufficiency results in decreased pancreatic enzyme production, which limits food digestion and absorption. In such cases, bile acid or pancreatic enzyme replacement therapy is useful. Fecal fat assessment may aid in the identification of fat malabsorption [Krenitsky, 2003]. Finally, for patients who receive lactulose therapy to increase gut emptying of ammonia-generating bacteria, the transit time of nutrients is decreased, leaving less time for absorption. In that situation, an oral antibiotic, such as rifaximin, may be preferable to lactulose.

Alterations in fuel metabolism

The metabolic state of a patient with ESLD can be quite

variable. Patients suffering from sepsis or acute liver failure are expected to be hypermetabolic. However, for those who are not in a high-stress state, and who are relatively inactive (e.g., patient with encephalopathy, oxygen-dependent HPS patient), the daily energy expenditure is low. Furthermore, fuel metabolism is altered; glycogen stores are limited, and gluconeogenesis is diminished, resulting in a diminished capacity to tolerate interruptions in intake. Further metabolic derangement results from hormonal imbalance; insulin resistance, for one, results in glucose intolerance [Krenitsky, 2003; Nompleggi and Bonkovsky, 1994].

Protein loss

Protein loss can be accelerated by the evacuation of large volumes of protein-rich ascites and hepatohydrothorax. Albumin replacement is commonly employed for immediate intravascular oncotic and volume replacement, though its effect is short-lived; its "intravascular residence time" is approximately four hours [Boldt, 2010].

Estimation of nutritional requirements

Caution is advised when employing conventional nutritional assessment techniques for patients with ESLD. Daily weight trends can be terribly inaccurate in patients with ascites, because the volume of ascites can vary by liters per day. Serum pre-albumin and serum albumin levels may fall as a result of decreased protein synthesis in ESLD. Many patients are hospitalized in acute stress states, such as SBP or variceal bleed, resulting in the synthesis of acute phase reactants rather than albumin. Careful estimates of intake and output may be most helpful when correlated with clinical estimates of muscle mass. Estimation of the nitrogen balance and stress state can be factored in. Tracking the success of interventions over time, with adjustments as needed, is more helpful than one single assessment. One traditional strategy employed in the prevention of encephalopathy has been to limit protein intake; however, caution is advised in restricting protein intake without regard to the patient's overall clinical status.

Placement of permanent feeding tubes

Caution is advised regarding the placement of permanent tubes (e.g., gastrostomy, jejunostomy). These procedures are fraught with complications, from bleeding secondary to portal hypertension, to ascites leak at the tube site.

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Whenever possible, the gut should be fed, as it promotes the maintenance of intestinal brush border health and it prevents bacterial overgrowth and translocation, which can result in SBP [Krenitsky, 2003]. Caution is advised with regards to supplemental feeds; in ESLD, the loss of lean body mass may not be reversed simply by increasing nutritional intake [Dasarathy, 2012].

Nutritional supplementation as life support

In patients for whom ESLD is not curable with liver transplantation, the provider is encouraged to consider the long-term goals of supplemental nutrition. The use of tube feeding is considered an artificial life support by many, and it may be an overly heroic intervention for a patient who is dying. In fact, it may perturb physiologic mechanisms that allow for a suffering-free death.

In the past, eating was commonly associated with a purpose: to nourish and to "stay alive" [Ochs and Shohet, 2006]. For patients with ESLD, a PM specialist can be helpful in initiating a discussion about the loss of this natural eating behavior, which is upsetting to the patient and patient's family. Artificial nutrition that is delivered through a feeding tube is often associated with undesirable and unanticipated consequences, which can also be addressed. For most patients, the social aspect of eating is eliminated. In most cultures, the consumption of food with family or friends is a routine aspect of daily life; when the patient is unable to participate in the meal, it can be isolating. A sense of loss may ensue, which saddens the patient. Additionally, the loss of gustatory pleasure, which accompanies ESLD, worsens the patient's anorexia, and may result in decreased eating. The patient often seeks isolation during meal times to avoid guilt and further inquiry. Social isolation can dramatically impact the quality of life of the patient, who is already suffering from a loss of dignity, which is acquired as the patient struggles and fails to overcome ESLD.

Most patients, families, and providers do not understand the physiology of starvation. They harbor unwarranted fears of extreme thirst and hunger [Pasman *et al.*, 2005]. Most patients who suffer from prolonged malnutrition do not suffer from hunger. However, many patients continue to experience a sensation of "starving" with continuous artificial feedings, which is likely due to the loss of expansion and contraction of the stomach from oral intake. Likewise, with intravenous hydration, dying patients or those with advanced illness are more likely to have satisfaction of thirst by small amounts of oral liquids, good mouth care, and moistening of the lips [Buiting et al., 2011].

Anorexia

Progressive ascites accumulation is associated with appetite suppression. Small intestinal motility is impaired, leading to ileus, nausea, and vomiting. Cachexia, abdominal pain, and respiratory compromise are commonly observed in patients with substantial ascites. For symptomatic relief, paracentesis may be employed.

Nausea and emesis

The only symptom more dreaded than pain is nausea. Medical providers may tend to focus more on emesis rather than nausea because it is observable and quantifiable. However, nausea is reported by 50-62% of terminally-ill patients [Abernathy et al., 2009; Wood et al., 2007]. Several physiologic mechanisms contribute to ascites in ESLD. First, ascites applies a direct, mechanical pressure on the upper gastrointestinal track and abdominal wall. With a generous volume of ascites, a patient will experience a sensation of bloating or fullness due to abdominal wall stretch and compression of the gastrointestinal track. Second, centrally-mediated nausea results from elevated levels of bilirubin, as well as toxins and metabolites, which are not filtered from the blood stream. Many drugs are metabolized poorly in ESLD; accumulation of these drugs and their active metabolites contribute to nausea as well [Rhee and Broadbent, 2009].

A thorough evaluation of nausea is indicated when it is identified. There are many causes for this symptom other than ESLD, including medications, bowel obstruction, constipation, gastritis, hepatitis, and pancreatitis. It is best to identify the etiology of the nausea, which will facilitate the targeted use of anti-emetic therapy. In many cases, the etiology of nausea can be determined through careful history-taking alone. For example, opioids, cardiac medications, anti-convulsants, and anti-depressants are notorious triggers of nausea and should be considered for discontinuation. A careful physical examination is also helpful; in some cases, abdominal distension may be due to a bowel obstruction. Additional imaging, such as X-ray or computer tomogram, is often warranted.

In the absence of a bowel obstruction, non-pharmacologic management of nausea can be facilitated with the use of small frequent meals, good oral hygiene, avoidance of unpleasant odors, and the use of aromatherapy. Cool foods are usually better tolerated than warm foods.

In the setting of mechanical bowel obstruction, relief of nausea is achieved solely through mechanical decompression, which can be achieved with nasogastric tube decompression. There is no anti-emetic which will achieve the same degree of relief as mechanical decompression. The discomfort associated with a nasogastric tube is often substantial; topical anesthetic sprays and lozenges help to ease this discomfort. Sprays can be used in the nose as well as the oropharynx. In the setting of near-obstruction of the bowel or biliary tree, stent insertion may be a palliative alternative to surgery. Venting tube gastrostomy allows for the pleasure of eating and drinking and can be employed intermittently for decompression. Needle paracentesis, as well as the insertion of an indwelling percutaneous peritoneal catheter, may provide intermittent relief from ascites.

Consideration should be given to use of intravenous or sublingual administration of anti-emetics in the setting of nausea/vomiting. Intravenous and sublingual therapies have a more rapid onset of effect than oral agents. Additionally, the retention and absorption of oral agents is unreliable.

There are several neurotransmitters involved in the signaling of nausea, including serotonin, dopamine, and NK1. 5-HT3 receptor antagonists are often very effective in the relief of nausea/vomiting. For refractory cases of nausea, propofol, a 5-HT3 receptor antagonist, may be helpful. Its added benefit of sedation provides further patient comfort [Lundström *et al.*, 2005]. Ondansetron, palonosetron, granisetron and dolasetron are popular; long half-lives and prohibitive cost limit their utility. Ondansetron may be the most widely used; it is available in pill and intravenous forms and has a half-life of 3.9 hours. To be maximally effective, the drug should be dosed every four hours. However, reduced clearance of ondansetron has been demonstrated in hepatic insufficiency; as such, dose adjustment may be needed [Figg *et al.*, 1996].

There is little data on the use of D2 receptor antagonists, such as haloperidol, droperidol, prochlorperazine or metoclopramide, in ESLD. However, metoclopramide is considered safe in liver failure patients [Uribe *et al.*, 1985]. Anti-psychotics, especially droperidol, are avoided due to the possibility of QT interval prolongation, which is a dose-dependent effect [Lishke, 1994]. Though anti-psychotic medications can often significantly relieve intractable nausea, the risk of cardiac complications may outweigh the benefit. Atypical anti-psychotic agents, such as olanzapine, which blocks multiple neurotransmitter receptors, can be very effective when started at a low dose at bedtime and increased as tolerated. Thorazine also blocks multiple receptors and may be useful. Aprepitant, a NK1 receptor antagonist, is available in oral or intravenous forms, but is also expensive.

The treatment of central nausea is typically achieved through the use of benzodiazepines, dronabinol, nabilone and corticosteroids. Benzodiazepines and cannabinoids are likely to accumulate and increase confusion or hallucinations in ESLD patients and should be used with caution. Scopolamine, hyoscyamine, meclizine, promethazine, hydroxyzine, and diphenhydramine must be used with caution; these medications cross the blood-brain barrier and may contribute to hepatic encephalopathy. H1 receptor antagonists, such as Hydroxyzine may cause less sedation and/or confusion in ESLD patients. Dexamethasone's mechanism of action is unclear, but it has intrinsic anti-emetic properties and can enhance the effect of other anti-emetics. Corticosteroid is a very effective anti-emetic, despite its side-effect profile, which includes agitation and psychosis.

Opioid-induced nausea may occur with the initiation of opioid or with opioid dose escalation. This may resolves in three to five days with continued use. D2 receptor antagonists, such as droperidol, haloperidol or metoclopramide, can be helpful in patients with a history of nausea due to opioid use [Abernathy *et al.*, 2009].

In PM, it is appropriate to employ rapid maximization of the dosage before adding a new agent or changing agents. Inpatient hospital pharmacies are often very accommodating in preparing single bags of multiple anti-emetics for easier intravenous administration.

Portal hypertension

Complications of portal hypertension define the morbidity and mortality experienced by most patients with ESLD. In cases of acute liver failure (e.g., acetaminophen overdose), portal hypertension is uncommon. However, in cases of chronic liver disease, longstanding inflammation results in progressive liver fibrosis and eventually cirrhosis. As the liver becomes less compliant with fibrosis, blood from the mesentery is less easily able to empty via the portal vein into the liver, generating mesenteric venous hypertension, or *portal hypertension*. This silent process occurs over years, and commonly goes unnoticed until complications of portal hypertension result. With increasing mesenteric venous pressures, decompression of blood occurs through the spleen (resulting in splenomegaly) and portal venous

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tributaries (varices), including the esophageal, rectal, paraumbilical, and retroperitoneal veins. With worsening portal hypertension, portal pressures exceed 10 mmHg and pathology appears. Rising levels of vasoactive mediators, such as nitric oxide, result in splanchnic vasodilation and angiogenesis [Ashkenazi *et al.*, 2013].

Splenic sequestration, or platelet destruction, occurs in the enlarged spleen, resulting in thrombocytopenia and contributing to spontaneous bleeding in the gut, nose, skin, eyes, and brain. Varices, most commonly esophageal, enlarge and spontaneously hemorrhage. Despite coagulopathy and thrombocytopenia, the portal vein and superior mesenteric vein may thrombose, thereby worsening portal hypertension. Gastropathy may manifest as gastric antral vascular ectasia (GAVE), or watermelon stomach (termed such for its endoscopic appearance, which resembles that of a watermelon), a phenomenon of the stomach associated with diffuse oozing [Probst et al., 2001]. Ascites forms, a manifestation of decompensation and a poor prognostic indicator; approximately half of patients with portal hypertension-associated ascites will die within three years [Gordon, 2012].

The mortality associated with esophageal variceal hemorrhage used to be at least 40%. With improvements in endoscopic and medical management, this mortality rate has fallen to 20% in specialty centers. Re-bleeding remains a common problem following endoscopic management. In these cases, a TIPS may be employed to decompress the mesenteric system [Garcia-Pagan *et al.*, 2012]. Surgical shunts are rarely employed, as their morbidity and mortality profile is inferior to that of TIPS.

Physical examination is useful in identifying portal hypertension. Varices of the abdominal wall, ascites, and splenomegaly are often readily apparent. Varices can also be visualized with ultrasound or CT scan. In addition to medical management, patients with ESLD suspected of having portal hypertension should be considered for pre-emptive endoscopic screening and banding of varices, to avoid an acute bleeding event [Ashkenazi *et al.*, 2013]. However, pre-emptive TIPS is not advised. In the past, the long-term patency of TIPS was poor. A combination of newer devices and improved placement technique has resulted in higher patency rates, at the cost of increased encephalopathy. Despite this progress, survival after TIPS is not improved [Riggio *et al.*, 2010].

Caution is also advised with regards to activity in the setting of portal hypertension. Encephalopathic patients suffer from motor dysfunction and are prone to falls, which are often associated with life-threatening bleeding from the spleen, liver, skin, and brain.

HCC and metastatic tumors of the liver

Surgical resection is the only potentially curative therapy for most malignant and metastatic tumors of the liver. Treatment outcomes for hepatobiliary malignancies are typically defined by patient survival, morbidity of the procedure, and, to a lesser extent, symptom control. Better patient selection and improved surgical techniques have improved patient survival following hepatobiliary surgery. Despite these advances, though, most patients (85%) with hepatobiliary tumors are not candidates for curative resection. In these cases, and many more, palliation is a major goal of treatment [Barbarisi *et al.*, 2001].

For most patients with combined ESLD and hepatobiliary malignancy, the prognosis is poor. It is customary to discuss palliative medical and surgical options with all patients suffering from ESLD and hepatobiliary malignancy. Patients with a large tumor burden may suffer from a myriad of tumor-related symptoms, including pruritus, nausea, vomiting, anorexia, weight loss, fatigue, hot flashes, and pain. For these patients, palliation of symptoms is a major goal of treatment [de Rooiji *et al.*, 1991; Van Heek *et al.*, 2003].

The indications for palliative surgery for hepatobiliary malignancy includes: control of loco-regional disease, treatment of gastrointestinal obstruction, and relief of biliary obstruction. The "surrogate end point," or objective clinical benefits, of this therapy are: improvement in performance status, weight gain, and relief of pain. For example, a decrease in analgesic consumption is considered a tangible manifestation of relief of pain [Burris *et al.*, 1997]. Many studies have reported outcomes after hepatic resection for primary and metastatic cancer [Cha *et al.*, 2004]. However, the literature available for palliative care in patients with extensive tumor burden causing ESLD is sparse, and it is limited to HCC.

When choosing a therapy for a patient with HCC, several factors are considered: tumor stage, liver functional status, physical status, and cancer-related symptoms. Few patients suffer from HCC in the absence of cirrhosis. For these rare patients, who suffer from HCC in the absence of ESLD, hepatic lobectomy is well tolerated and resection is the best therapeutic option for cure [Regimbeau *et al.*, 1999]. By contrast, most patients with HCC also suffer from cirrhosis and ESLD. In these patients, the degree

of functional impairment of the liver may preclude safe surgery. In ESLD patients, the first-line treatment of HCC is liver transplantation. If liver transplantation is not an option for a patient, palliative interventions should be considered, including percutaneous ethanol ablation, radiofrequency ablation, cryotherapy ablation, or microwave ablation. These options are thought to offer palliation of symptoms, though they are less effective in achieving a long-term cure. The sole palliative approach that has been shown to have a positive impact on survival is transarterial chemoembolization [Llovet and Bruix, 2003].

Outcomes of percutaneous and surgical interventions vary with the patient's stage of disease. Outcomes are best for patients who undergo therapy at an early stage of disease, with solitary tumors (usually <5 cm), or two to three nodules (none >3 cm). Patients may benefit from curative therapies, such as resection, transplantation, or percutaneous ablation. The 5-year survival ranges from 50% to 70%. Patients in the intermediate stage suffer from large or multifocal tumors, with preserved liver function, and no cancer-related symptoms or vascular invasion. They may benefit from transarterial chemoembolization and enjoy a 50% survival at three years. Only one study evaluated quality of life in patients with HCC treated with transarterial chemoembolization and found that patients had an increased survival and better quality of life prior to death [Steel et al., 2004].

Patients in the advanced stage have cancer-related symptoms, vascular invasion, or extra-hepatic tumor spread; their median survival is less than one year. There is no effective treatment for patients with advanced disease. These patients may only find hope for cure in aggressive research trials. Finally, patients with end-stage disease suffer from major impairment of liver function or major cancer-related symptoms and severe deconditioning. Their short-term prognosis is poor, and they should receive PM [Bruix *et al.*, 2004].

Neuroendocrine tumor metastasis to the liver may manifest as symptoms of ESLD in non-cirrhotic patients. Management of metastatic neuroendocrine tumors to the liver is usually multi-modal, but hepatic arterial embolization is the mainstay of disease and symptom control. Two studies reported a decrease in hormone and pain symptoms following arterial embolization. Chamberlain and colleagues reported excellent palliation of symptoms with surgical resection combined with embolization [Chamberlain *et al.*, 2000]. Wu and colleagues concluded that hepatic arterial embolization alone was effective in controlling pain and hormonal symptoms; the procedure provided a durable response of 16 to 17 months [Wu *et al.*, 2013]. In this patient population, all treatment is palliative; survival is often only extended by the combination of a variety of therapies.

Other metastatic tumors to the liver, such as colorectal carcinoma, cause ESLD symptoms when the tumor burden is extensive and is unresponsive to chemotherapy. In these cases, the patient's survival depends on the primary tumor's physiology. These tumors result in ESLD through one of several mechanisms. First, tumors that impede normal blood flow by invading the inflow (resulting in ischemia) or outflow (resulting in congestion) can result in ESLD. Second, tumors that obstruct the biliary tree result in biliary obstruction and ESLD. All of these patients should be considered for PM.

Renal failure

Caution is advised when using the serum creatinine (S_{Cr}) to describe renal function in the setting of ESLD. The S_{Cr} is notoriously inaccurate in the setting of muscle wasting and ESLD. Creatine is an energy substrate made by the liver. Creatine is transported in the blood, taken up by muscle, and metabolized by muscle to form creatinine. Muscle releases creatinine into the blood stream, to be filtered out of the blood by the kidneys. In the setting of muscle wasting, loss of muscle mass results in decreased energy demand by the muscle, thereby resulting in less creatinine production and a falsely low creatinine. The glomerular filtration rate (GFR) may be a better estimate of renal function in patients with ESLD, but it also tends to overestimate renal function. The GFR relies on the patient's ideal weight; in the setting of ESLD, the patient's weight may be substantially inaccurate due to edema or ascites [Nadim et al., 2012].

Renal dysfunction is commonly observed in the setting of ESLD. ESLD is associated with poor clearance of vasoactive mediators, which leads to systemic vasodilation, hypovolemia, and renin production. In response to renin, renal artery constriction occurs. Renal hypoperfusion ensues and results in the rapid decline of renal function. This pathologic process is known as type-1 hepatorenal syndrome (type-1 HRS). The prognosis for type-1 HRS is dismal; the median survival is two weeks. Similarly, in the setting of refractory ascites, HRS is seen as renal dysfunction which becomes progressively worse with serial paracenteses, leading to volume depletion, hypotension, and further renal artery constriction. The

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prognosis for this type-2 HRS is poor; the median survival is four to six months.

The treatment of HRS includes limitation of systemic vasodilation and reversal of hypovolemia. To limit systemic vasodilation and interrupting renal artery constriction, terlipressin may be used. Terlipressin interrupts renin production by increasing systemic vascular resistance, thereby decreasing cardiac output and increasing renal perfusion [Rajekar and Chawla, 2011]. Hypovolemia is reversed with short-acting volume expansion agents, such as albumin [Angeli and Gines, 2012].

The diagnosis of HRS is largely one of exclusion; evaluation for other types of organic renal disease, such as urinary tract infection, is helpful [Lata, 2012]. Extreme caution is advised when considering renal biopsy; both percutaneous and transvenous approaches are fraught with bleeding risk. Regardless of the etiology of renal dysfunction, in the setting of progressive ESLD, recovery of renal function is rare. A PM consultation is appropriate in this setting.

Psychiatric illness, psychosocial destabilization, substance abuse, and pain

Many patients with ESLD struggle with acute and/or chronic psychiatric illness and addiction. In fact, many ESLD patients self-treat their anxiety and/or depression with ethanol, sedatives, hypnotics, and narcotics. For many of these patients, their liver disease is the result of selfmedication; alcoholics repetitively consume liver-injuring ethanol, while intravenous drug addicts may acquire viral hepatitis from needle-sharing. These issues prove particularly challenging to address in the hospital setting for providers who are not experienced in the treatment of addiction and substance withdrawal.

Substance withdrawal

Acute substance withdrawal may be difficult to identify in the setting of other acute complications of ESLD [DiMartini *et al.*, 2008]. Consultation with an addiction specialist is very helpful, both in determining the appropriate maintenance therapy as well as addressing new issues.

To avoid acute withdrawal from alcohol, opioids, or sedatives, patients should be monitored for sympathetic activity, which manifests as hypertension, hyperthermia, and tachycardia. Providers should consider delirium tremens prophylaxis for alcoholics, along with Wernicke-Korsakoff Syndrome prophylaxis with thiamine. Methadonedependent or opioid-dependent patients usually require narcotic maintenance therapy, which should be prescribed after confirmation of outpatient dosing. Patients will require close mental status and physiologic monitoring during this time, as many suffer concurrent hepatic encephalopathy exacerbation, sepsis, ICU-associated sleep deprivation, and acute renal failure-associated uremic encephalopathy, all of which cloud the clinical picture [DiMartini *et al.*, 2008].

Recidivism

Alcoholism is one of the rising causes of chronic liver disease, both in the United States and abroad [Berry *et al.*, 2013]. In order to become a liver transplant candidate, a patient is usually required to abstain from ethanol consumption or illicit drug use for at least six months. In order to remain sober or drug-free, most patients will require further treatment in a formal rehabilitation program in order to gain insight into their addiction, and to develop coping skills that will help them to avoid recidivism. Incorporating an addiction specialist into their care early on will be helpful, and it is recommended in a consensus statement by the American Association for the Study of Liver Diseases [DiMartini *et al.*, 2008].

Overdose and suicidality

In some cases, the ESLD patient is hospitalized following acetaminophen overdose or a drug overdose. It is important for an addiction specialist to be involved, to determine whether or not the overdose was a suicide attempt. In such cases, psychosocial dynamics are often challenging to manage, as is the determination of medical decision-making power. Recognizing underlying depression or psychosocial destabilization will be helpful. In many cases, mental illness plays a role in the events that led to hospitalization [Rosenberger *et al.*, 2012].

Psychosocial destabilization

Nearly half of all patients with ESLD suffer from a psychiatric illness, most commonly depression and/or anxiety. Most of these patients are debilitated by the combination of their mental and physical illness, limiting their ability to work and socialize. These limitations impair the patient's quality of life through isolation, limitation of their independence, and by increasing the psychosocial stress within their home environment. For example, a former alcoholic patient with new onset hepatic encephalopathy and ascites will likely be unable to work or drive. Such a patient would lose the ability to visit with friends and family and would likely suffer from an impaired appetite. The family, already alienated by chronic alcoholic behavior, may reluctantly take on the burden of continued medical care, frequent hospitalizations, and medical bills, leading to further discord and resentment. Many ESLD patients who are drug-dependent or alcohol-dependent have already alienated their support system; family and friends withdrew following repetitive social insults, medical complications, legal infractions, and financial decline. Such dynamics are best addressed by a psychiatric specialist, as they are often very complex [Dimartini *et al.*, 2008].

Mental illness assessment and treatment

A psychosocial evaluation can be performed by all members of the care team. A nonjudgmental approach from multiple perspectives allows for shared responsibility in decisionmaking, information sharing, and the identification of inconsistency. Nurses, providers, social workers, and psychiatry/psychology specialists all provide useful assessments and observations in this regard [DiMartini *et al.*, 2011]. Specifically, discussion on the use of tobacco, illicit and prescription drugs, and alcohol should occur. Exploring how patients pay for these substances will often provide insight into dysfunctional psychosocial dynamics. The legal associations of these behaviors may also be explored to determine the extent of the illness.

Addiction rehabilitation is available for the treatment of substance abuse disorders following substance withdrawal. Rehabilitation programs incorporate counseling (individual or in a group setting), medication, and abstinence monitoring. Alcohol-, tobacco-, and opioid-replacement therapies are widely available [DiMartini *et al.*, 2011]. For ESLD patients awaiting transplantation, this is problematic; they are less likely to report recidivism for fear of being removed from the waiting list. For example, interview alone may not be adequate in screening for recidivism. Random blood, urine, hair, and breath analysis for alcohol have been employed for on-the-spot testing [DiMartini and Dew, 2012].

Pain

The patient with ESLD may suffer from pain or discomfort for a variety of reasons. Ascites results in abdominal distension, which can cause abdominal pain. Severe leg edema associated with peripheral vasodilation and hypoalbuminemia can cause leg pain. Often, the patient may have abused ethanol, narcotics, or sedatives to self-treat chronic pain conditions, such as a prior herniated disc-associated back pain or chronic headache.

Many factors should be considered when prescribing analgesics. First, decisions need to be made about whether the patient is opioid tolerant or naïve, which will help the prescriber with dosing requirements. Establishing a chronicity of pain and prior therapy will also guide the prescriber in choosing an appropriate starting dose and frequency of analgesic. The type of pain should be considered; for example, neuropathic pain may respond better to a non-narcotic analgesic, whereas incisional pain immediately following surgery is well managed with narcotic.

Caution is advised with the institution of narcotics and the escalation of their dosing in patients with ESLD. A dysfunctional liver will not metabolize opioid and active opioid metabolites of opioids in a normal manner. Similarly, renal dysfunction that accompanies liver dysfunction often results in decreased clearance of active metabolites [Chandok and Watt, 2010]. Elevated levels of these compounds can result in sedation and confusion, which may cloud the evaluation and treatment of hepatic encephalopathy. Opioids are primarily metabolized in the liver by the enzyme cytochrome CYP P450-3A4. Co-administration of CYP 450-3A4 inhibitors or drugs that are similarly metabolized by the P450 system can alter opioid levels in the body [Smith, 2013]. These drugs include immunosuppression agents, anti-convulsants, anti-psychotics, calcium channel blockers, and macrolide antibiotics. In opioidtolerant patients, providers must consider the possibility of under-dosing or inadequate frequency of medication administration. If so, adjustment in the patients around-theclock medication may be appropriate first [Smith, 2013].

A wide variety of narcotics are available to the provider. Combination medications, such as hydrocodoneacetaminophen, are also available. In most cases, the regular use of acetaminophen in patients with ESLD is frowned upon, as acetaminophen can contribute to liver toxicity over time. Similarly, most patients with ESLD have or will develop renal insufficiency. As such, the use of combination medications which contain a non-steroidal anti-inflammatory or acetaminophen, such as hydrocodone ibuprofen, are not advised.

Fentanyl or hydromorphone are less likely to produce

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toxic metabolites [Chandok and Watt, 2010]. Fentanyl is a very short-acting narcotic, which is available in intravenous, pill, lozenge, tablet, film, nasal spray, and patch form. The systemically absorbed dose of intranasal fentanyl spray bypasses hepatic first-pass metabolism, can be administered by caregivers, has a rapid onset of action, and can be used by ESLD patients who are often unable to swallow or have nausea [Smith, 2013].

Hydromorphone is metabolized in the liver by glucuronidation and is safe to use in renal failure. It is available in oral pill or liquid, rectal, intravenous forms, but may be expensive. Oxycodone has multiple unpredictable metabolite levels, but it is a cheap oral alternative to the above-mentioned narcotics and is available in pill or solution form.

Methadone has used primarily after the failure of other opioids or in the setting of narcotic addiction. However, in some instances, it may be used in opioid naïve patients with careful titration due to its long half-life [Gelfman *et al.*, 2013]. Methadone is a mu opioid agonist and N-methyl-paspartate (NMDA) receptor antagonist which is metabolized in the liver. Its metabolites are inactive, and it is believed to be safe in the presence of renal failure. Methadone is primarily used for around-the-clock medication pain relief [Gelfman *et al.*, 2013]. Patients and families need education about its use and that it is often used in complex or terminal pain syndromes.

Summary

Both acute and chronic liver disease may result in ESLD. The patient with ESLD suffers from a host of systemic manifestations of liver disease, which limits their quality of life and life expectancy. Even with liver transplantation, many patients will suffer from, and die of, liver failure. Palliative care for the patient with ESLD ensures a humane approach to the care of the patient with progressive liver failure.

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New treatments for symptomatic severe aortic stenosis

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Introduction

Aortic stenosis (AS) is the most frequent valvular heart disease in western industrialized countries. It is more frequent as the average age of the population increases. Its incidence correlates directly with the age. Once symptoms occur AS is considered significant. Average survival in patients with severe AS and symptoms is only 2-3 years and there is a high risk of sudden death. The treatment of symptomatic AS is surgical replacement of the aortic valve. Medical treatment is often utilized in optimizing patients before surgery but has limited utility in treating symptoms. Until recently palliative management of symptomatic AS was appropriate for patients who were not candidates for aortic valve surgery. Non-surgical candidates included patients with co-existing medical conditions and in patients who have refused aortic valve replacement (AVR) or patients deemed high risk for operative mortality and morbidity. Non-surgical candidates include patients with comorbid conditions that made the risk benefit ratio of operation adverse and those who refused surgery. New percutaneous treatments have been developed for care of patients with severe symptomatic AS in patients who previously would have been deemed inoperable. This new approach is discussed in this chapter [Carabello and Paulus, 2009; O'Gara and Loscalzo, 2011].

Etiology

AS is caused by age related degenerative calcific disease. The mechanism is believed to be similar to that of atherosclerosis. The initial plaque of AS is like that of coronary artery disease.

Both these conditions can co-exist in the same patient. Studies have shown that as in atherosclerosis the valve tissue of the patient with AS display lipid infiltration, inflammation, neoangiogenesis and calcification. Statins seem to retard the progression of AS [Rosenhek, 2005].

Rheumatic heart disease can also lead to AS. The mitral valve is almost always affected in this situation. Commissural fusion of the aortic valve leaflets is usually present as a result of chronic rheumatic valve disease. Calcific changes that progress to AS may also develop in patients with congenital bicuspid aortic valves (about 1%). Stenosis arises because of less favorable hemodynamics of bicuspid valves. Turbulent flow across the valve disrupts the endothelium and collagen matrix of the leaflet resulting in gradual calcium deposition.

Pathophysiology

Decreases in valve area result in increased left ventricular pressure overload. The normal aortic valve area (AVA) is 2.5 to 3.5 cm². Peak transvalvular pressure gradients higher than 50 mmHg and an AVA of less than 0.8 cm² are characteristic of severe AS. ASE guidelines now call severe AS below 1 cm². Pressure overload increases left ventricular afterload, impairing ejection performance. Afterload is quantified as wall stress. Since afterload is a key determinant of ejection performance, the normalization is important in maintaining normal ejection fraction and stroke volume (SV). Left ventricular hypertrophy (LVH) occurs as a compensatory mechanism of increased wall tension. Hypertrophy also impairs coronary blood flow reserve and reduces diastolic function. Decreased oxygen reserve

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may cause angina. Increased diastolic pressure increases congestion and dyspnea. Patient with AS and LVH have higher prevalence of heart failure secondary to impaired relaxation and reduced compliance which manifests as an elevated left ventricular end diastolic pressure (LVEDP).

Clinical presentation

The classic clinical symptoms of critical AS are angina pectoris, syncope and dyspnea on exertion.

Angina

An imbalance of myocardial oxygen supply and demand may occur even in the absence of significant coronary artery disease. The combination of LVH and wall tension increases systolic myocardial oxygen requirement while a reduction in coronary perfusion pressure decreases myocardial oxygen supply. In addition myocardial oxygen delivery is decreased because of compression of subendocardial blood vessels by increased left ventricular pressure.

Syncope

Syncope typically occurs on exertion. Cardiac output is limited by a stenotic valve and there is inability to compensate during an exercise induced peripheral arterial vasodilation. Ventricular dysrhythmias are another potential cause of syncope.

Dyspnea

Increased LVEDP causes higher left sided filling pressure, which leads to pulmonary congestion and dyspnea. Decompensation arises when the wall tension can no longer be maintained by systolic wall thickening and the left ventricle (LV) dilates. LV dilation is associated with increased wall tension.

Disease progression

In adults with valvular AS, obstruction to left ventricular outflow develops gradually over many years. In many patients AS is coincidentally diagnosed when echocardiography is performed for other reasons or after finding of a systolic murmur on examination. In some patents a substantial decrease in valve area and an increase in transaortic velocity occur before symptom onset. The occurrence of symptoms presents a turning point in the natural history of the disease. About 75% of symptomatic patients will die within 3 years if they do not have a valve replacement.

Patients with congenital AS may become symptomatic in early childhood. Rheumatic AS becomes symptomatic over a wide age range with patients presenting between 20 and 50 years of age. In the adult patient with degenerative calcific valve disease, symptoms may occur at 50 years of age but usually occur in the elderly patients aged 70-90 years.

Asymptomatic patients

Predictors of symptom onset include older age, male gender, AS severity and functional status. One of the most important predictors of outcome is the degree of stenosis which is directly related to the peak aortic jet velocity on Doppler echocardiography. Rate of increase in aortic jet velocity over time is a strong predictor of clinical outcome. The combination of calcified aortic valve with rapid hemodynamic progression, defined as an increase in peak aortic jet velocity of more than 0.3 m/s within 1 year identifies a patient group at particularly high risk.

In the updated guidelines from American Heart Association a valve area of less than 1.0 cm² is used to define severity. The severity of gradient measured by Doppler echocardiography and cardiac catheterization proposed is a mean gradient greater than 40 mmHg by American College of Cardiology and 50 mmHg by the European Society of Cardiologists.

Symptomatic patients

Once definite symptoms of AS are present outcome is very poor without surgical intervention. In adults with symptoms of AS, predictors of survival are transaortic velocity or gradient, functional status, left ventricular systolic function, co-morbid disease and gender. When symptoms due to severe AS are present, prognosis is better in the presence of a high gradient or jet velocity. A low gradient and transaortic velocity in the setting of severe valve narrowing is a reflection of a reduced cardiac output and a worse prognosis.

Difficulty of low gradient, low output AS

A subset of patients with severe AS, LV dysfunction and low transvalvular gradient suffer a high operative mortality rate and poor prognosis. It is difficult to accurately assess the AVA in this low-flow, low-gradient AS because the calculated valve area is proportional to forward SV. Some Part II

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patients with low flow, low gradient aortic stenoses have a decreased AVA as a result of inadequate forward SV rather than anatomic stenosis. Surgical therapy is unlikely to benefit these patients because the underlying pathology is a weakly contractile myocardium. However, patients with severe anatomic AS may benefit from valve replacement despite the increased operative risk associated with low flow, low gradient hemodynamic state. A dobutamine echocardiographic evaluation can be done to distinguish patients with fixed anatomic AS from those with flow dependent AS with LV dysfunction. Low flow, low gradient AS is defined for a mean gradient of less than 30 mmHg and a calculated AVA less than 1.0 cm² [Zile and Gaasch, 2003].

Diagnosis

The patient presents with a history of decreased exercise tolerance, exertional angina and syncope. On examination auscultation reveals an ejection systolic murmur best heard in the aortic area, which may radiate to the neck and mimic a carotid bruit.

Investigations

In advanced cases, electrocardiogram (ECG) features of hypertrophy and down sloping of ST segments and T wave inversion (strain pattern) is seen in leads reflecting LVH. Nevertheless, especially in old age, the ECG can be normal despite severe stenosis. Chest radiography may show a prominent ascending aorta due to post-stenotic dilation.

Echocardiography

Findings on echocardiography include identification of leaflets, calcification and restricted mobility of the aortic valve opening, LVH and assessment of diastolic function. Doppler assessment permits calculation of the systolic gradient across the aortic valve, from which the severity of stenosis can be assessed. In patients with impaired LV, velocities across the aortic valve may be diminished because of reduced SV, while in those in whom aortic regurgitation is present, velocities are increased because of increased SV. Echocardiography is usually recommended in asymptomatic patients every year for severe AS, every 1-2 years for moderate AS and every 3-5 years for mild AS.

Exercise stress testing may be an additional strategy to evaluate asymptomatic patients with moderate to severe AS to identify those with poor exercise tolerance and or an abnormal blood pressure response to exercise. Patients with exercise-induced symptoms might benefit from AVR. Cardiac catheterization and coronary angiography may be necessary when severity of AS cannot be determined by echocardiography or to elucidate underlying coronary artery disease.

Timing of surgery

In asymptomatic patients with AS it appears to be relatively safe to delay surgery until symptoms develop, but outcome vary widely. The presence of moderate or severe calcification along with a rapid increase in aortic-jet velocity identifies patients with a very poor prognosis. These patients should be considered for early valve replacement. AVR is indicated in patients with severe AS with symptoms of angina, syncope or dyspnea. AVR is also indicated in patients with severe AS who are undergoing coronary artery bypass grafting (CABG), patients with severe AS who are undergoing surgery on the aorta or other heart valves [Otto, 2006].

Replacement is possibly indicated for patients with moderate AS who require coronary artery bypass surgery or surgery on the aorta or heart valves. Other indications include asymptomatic patients with severe AS with EF of no more than 50 percent, hemodynamic instability during exercise and ventricular tachycardia.

Functional outcome after AVR in patients older than 80 are excellent, operative risks limited and late survival rates are good. Operative mortality is relatively high in older adults with rates of 5-15%. There is a higher rate of complications in elderly patients including perioperative myocardial infarction (3-8%) and cerebrovascular events up to 11%.

Medical management of symptomatic AS

AVR is the mainstay of treatment of symptomatic AS. AVR offers improvement of symptoms and life expectancy. Medical therapy may not prolong life in patients with AS and has limited utility in treating symptoms. The goal of medical therapy is to treat concurrent cardiovascular conditions and treat symptoms. This includes medical therapy for coronary artery disease and atrial fibrillation [Otto, 2012].

Treatment of concurrent illness

Hypertension is treated and volume status is maintained. Heart failure is treated with a combination of diuretic and ACE inhibitors. Diuretics are used with caution since it

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Table 1 Indications for ballon aortic valvuloplasty		
Indications for aortic valvuloplasty		
As a bridge to surgical AVR		
Palliation in patients with serious comorbid conditions		
Bridge to delivery in symptomatic pregnant women		
Urgent non cardiac surgery		
Abbreviation: AVR, aortic valve replacement.		

may reduce preload on which the patient may depend for maintenance of cardiac output. Vasodilators in the presence of a fixed valvular stenosis may reduce systemic blood pressure and reduce coronary artery perfusion pressure. Positive inotropic drugs can be used in the short term but may cause tachycardia and myocardial ischemia.

Medical therapy can optimize hemodynamics in the preoperative setting. Long-term palliative medical management of symptomatic AS is appropriate in a setting where patients are not candidates for aortic valve surgery such as malignancy, patients with high risk for operative morbidity and mortality and patient refusal.

Severe symptomatic inoperable AS

The goal of medical therapy is to treat concurrent cardiovascular conditions, prevent or treat superimposed diseases, maintain optimal loading conditions and treat symptoms of heart failure. In addition, the physician provides the patient and family counseling about the expected disease process, treatment options and end of life preferences. Evaluation of associated cardiovascular risk factors, e.g., hyperlipidemia is recommended. At present statin therapy is reserved to prevent progression of AS. Medical therapy for coronary artery disease and atrial fibrillation should be continued.

Supportive care is offered during acute illness. Medical therapy focuses on decreasing cardiac workload by reducing fever, controlling heart rate and blood pressure, correction of anemia and administration of oxygen. Volume status should be carefully monitored with cautious replacement of fluid or gentle diuresis as needed.

Percutaneous balloon valvuloplasty

Percutaneous aortic balloon valvuloplasty (PABV) is the only surgical palliation for severe AS. It may reduce aortic valve gradients and can improve symptoms. Interest in the procedure has waned because of high recurrence rate (50% within 6 months) and absence of any mortality benefit. Lack of benefit in adult with acquired disease stems from diffuse calcification of the valve preventing balloon dilatation from substantially altered valve leaflet morphology. Possible indications for aortic valvuloplasty are as a bridge to more definitive surgical replacement who present with hemodynamic compromise and patients requiring high-risk percutaneous coronary intervention (*Table 1*). While PABV did not show long-term survival benefit it has recently been shown to improve one year survival. Increasingly PABV is being used in severe AS and as a preliminary treatment strategy before transcatheter aortic valve replacement (TAVR) [Lieberman *et al.*, 1995; Hamid *et al.*, 2010].

Surgical management

Currently open surgical AVR is the most commonly used modality of treatment and offers excellent long-term improvement of symptoms [Bonow et al., 2008]. Even though most patients with AS are elderly, the risks of valve replacement surgery are acceptable unless there are also serious co-morbid diseases that can worsen outcome. The mortality difference for people with symptoms of AS treated with AVR vs. those not undergoing this procedure is striking. Valve replacement relieves the symptoms of AS and the ejection fraction usually increases. A biological valve in the elderly is often preferable to a mechanical because this obviates the need for anticoagulation (less thrombogenic), and the durability of biological valves exceeds the patient anticipated life expectancy. Most operations on the aortic valve are performed using a heart lung machine with the patient on cardiopulmonary bypass. The aorta is clamped and myocardial protection is assured. An aortotomy exposes the diseased valve, which is excised. The annulus is debrided and measured with the appropriate sizing device and the valve is sutured in. More liberal indications for an AVR are: asymptomatic patients with severe AS [Vlahakes, 2007] (Table 2).

TAVR: help for the high risk

Open heart AVR has been traditionally recommended for severe AS. This approach affords most patients excellent prognosis and good long-term outcome. Unfortunately there is a subgroup of patients that cannot be treated with traditional AVR. These patients are elderly with significant medical problems making them high risk for open surgery.

Table 2 ACC/AHA indications for AVR in patients with severe AS
ACC/AHA indications for AVR in patients with severe AS
Patients with symptomatic severe AS (Class I)
Patients with severe AS undergoing CABG surgery (Class I)
Patients with severe AS undergoing surgery on the aorta or other heart valves (Class I)
Patients with severe AS and an LV ejection fraction <50% (Class I)
Patients with moderate AS undergoing CABG surgery or surgery on the aorta or other heart valves (Class IIa)
Abbreviations: AVR, aortic valve replacement; AS, aortic stenosis; LV, left ventricle; CABG, coronary artery bypass grafting.

Table 3 Inclusion criteria	Table 4 Exclusion criteria
Indications	Contraindications
Severe symptomatic aortic stenosis	Native aortic annulus size <18 mm or > largest annulus size
High risk for conventional AVR	for which TAVR device is available
Porcelain aorta	Severe iliofemoral disease
Previous chest surgery	Bicuspid aortic valve, non-calcified
Frailty	Patients whom relief will not improve QOL or prolong life
Abbreviation: AVR, aortic valve replacement.	Abbreviation: QOL, quality of life.

In November 2011, the Food and Drug administration (FDA) approved the SAPIEN transcatheter heart valve (Edwards Lifesciences, Irvine, CA) for patients with severe AS who are not suitable candidates for AVR. The FDA approved this valve based on the Placement of Aortic Transcatheter Valve (PARTNER) trial, which enlisted 21 centers in the US (*Tables 3,4*). At one year the mortality in the TAVR group was 30%—significantly lower than 50% in the group that received balloon valvuloplasty and medical therapy [Leon *et al.*, 2010].

Cribier and colleagues described the first implantation of a percutaneous heart in a patient who was declined surgery because of excessive operative risk [Cribier *et al.*, 2002]. Ye *et al.* described the first Transapical aortic valve implantation in humans in 2006. The field of percutaneous aortic valve implantation since has rapidly evolved [Ye *et al.*, 2006].

TAVR—the procedure

TAVR has emerged as an option for patients who are considered inoperable via standard open-heart surgical approach. This catheter-based technology avoids large incisions. The SAPIEN heart valve is a bovine pericardial tissue valve supported on a stent. The calcium bed of the native valve and the outward force of the blood flow

hold the valve secure. The new valve is delivered through
the arteries that lead to the heart (Femoral approach) or
directly through the left ventricular apex of the heart.
Patients are thoroughly screened for this procedure
by cardiologists, cardiothoracic and vascular surgeons.
Preoperative screening involves echocardiography,
angiography and computer tomography scans. A functional
assessment is done where all medications and laboratory
tests are reviewed.

Criteria for high-risk patients are based on EuroSCORE and the Society of Thoracic Surgery (STS) risk calculator. Patient criteria include high operative risk scores (EuroScore and STS score), advanced lung disease, and who have been denied surgery by 2 cardiac surgeons or had previous sternotomy with functional coronary artery bypass grafts [Zajarias and Cribier, 2009].

The TAVR procedure is performed in a hybrid operating room or catheterization laboratory. A general anesthetic is usually preferred. However, in certain situations the procedure can be performed under a regional anesthetic. Invasive monitoring and a Transesophageal echocardiogram (TEE) are used routinely. Heparin is given to maintain activated clotting time greater than 250 seconds. Short acting vasopressors are used to maintain adequate perfusion pressure. The importance of skilled anesthesia management in these procedures cannot be overestimated. New treatments for symptomatic severe aortic stenosis



Figure 1 Edwards Sapien.

Transfemoral approach

A transfemoral sheath is inserted through the femoral artery. Under fluoroscopic and echo guidance a standard balloon aortic valvuloplasty (BAV) is performed using rapid ventricular pacing. The bioprosthetic heart valve crimped into a balloon catheter is advanced across the native valve, rapid ventricular pacing is achieved and the valve is deployed. The bioprosthetic valve expands secured by the underlying annulus. Heparin is given during the procedure.

Transapical implantation

Transapical implantation is performed through a left antero-lateral mini thoracotomy in the 5th intercostal space. Purse-string sutures are applied at the apex with the heart continuously beating. The apex is punctured and a soft guide wire is passed. Then a valvuloplasty is done under fluoroscopic and echo guidance. BAV performed under rapid ventricular pacing. This is then followed by valve insertion through a delivery system. Correct valve position is confirmed and the valve is instantaneously implanted using rapid balloon inflation. Rapid ventricular pacing is used for deployment. The sheath is removed and apex is closed with the purse-string sutures. Postoperatively patients are fast tracked and extubated early if they remain hemodynamically stable. The patients are usually recovered in the intensive care unit (ICU). Antiplatelet therapy is continued for 6 months after the procedure.

Structural heart team

This procedure requires a multidisciplinary team including interventional cardiologists cardiothoracic surgeons, vascular surgeons, cardiac anesthesiologist and intensive care staff.

Devices

Edwards Sapiens (Edwards Lifesciences, Irvine, CA)

The balloon expandable valve consists of 3 pericardial leaflets. Now the valves are made of bovine tissue. The valve is mounted within a stainless steel frame balloon expandable stent. The Edwards Sapien valve is commercially available in two sizes: a 23 mm and a 26 mm valve which can be used for either through a transfemoral or transapical approach (*Figure 1*).

CoreValve (CoreValve, Irving, CA)

CoreValve consists of 3 pericardial leaflets mounted and sutured into a nitinol stent. The valve is crimped on a delivery catheter into a loading system. A sheath is necessary to deliver the valve which is placed via the transfemoral approach. Using the body temperature, the valve stent automatically expands (*Figure 2*).

Clinical trials

The PARTNER trial was a multi-center randomized study involving patients with severe AS and with cardiac symptoms New York Heart Association (NYHA) functional class II or higher who were considered not suitable candidates for surgery because of clinical or anatomical factors.

Leon *et al.* published the results of the PARTNER trial in *New England Journal of Medicine* in October 2010 suggesting that in patient with severe AS not suitable for surgery, TAVR showed significantly reduced rates of death from any cause. There was a higher incidence of major strokes and vascular events. A total of 358 patients with AS who were not suitable candidates for surgery underwent randomization at 21 centers. At 1 year the rate of death from any cause was 30.7% with TAVR as compared to 50.7% with standard therapy (Balloon valvuloplasty and medical management). There was however, a higher incidence of



Figure 2 CoreValve.

strokes (5% vs. 1.1% and major vascular complications (16.2 % vs. 1.1%). In the year after TAVR there was no deterioration in the functioning of the bioprosthetic valve as assessed by evidence of stenosis or regurgitation [Leon *et al.*, 2010].

Standard medical therapy including BAV, which was performed in 83. 8% of the patients did not alter the natural history of severe AS. At the end of 1 year the rate of death from any cause was 50.7% and the rate of death from cardiovascular causes was 44.6%. Transfemoral TAVR was superior to standard therapy marked reduced rate of death from cardiovascular causes and the rate of repeat hospitalization. TAVR was associated with significant reduction in symptoms assessed by NYHA and 6-minute walk test. There were however more neurological events, major vascular complications and major bleeding events in the TAVR group than standard therapy. Hemodynamic performance was excellent with no deterioration in the first year [Grube *et al.*, 2007].

Kodali reported in a multicenter randomized trial TAVR had similar mortality, reduction in symptoms and improved hemodynamics. Paravalvular regurgitation was more frequent after TAVR and even mild paravalvular regurgitation was associated with increased late mortality [Kodali *et al.*, 2012]. 30-day stroke rate was more in the TAVR group 4.6% *vs.* 2.4% in the surgical group. The increase in early stroke frequency was believed to be

liberation of thromboembolic debris from the valve or aorta causing embolic ischemic strokes. Aortic regurgitation severity was evaluated by echocardiography. The factors that underlie paravalvular aortic regurgitation include the ratio of the transcatheter valve size to the size of the annulus, the position of the prosthetic valve, and the pattern of calcification in the native valve. Better selection of properly sized valves is required [Trippoli and Messori, 2011]. The negative effect of prosthetic regurgitation has been reported in studies of SAPIEN and CoreValve devices. Mitral valve regurgitation is a risk factor for poor treatment response after TAVR [Kodali *et al.*, 2012].

Makkar reported that in this 2-year analysis of the PARTNER trial TAVR was associated with a substantial, sustained and incremental decrease in mortality. The report also showed a sustained improvement in qualityof-life measures, including NYHA class, the rate of repeat hospitalization, and the number of days alive and out of the hospital [Makkar *et al.*, 2012]. There was however an increased incidence of early ischemic stroke (<30 days) but little change in late ischemic strokes (>30 days) and sustained improvement in hemodynamic performance of the valve, with no significant deterioration over time [Gotzmann *et al.*, 2011].

The results of the FRANCE 2 trials looked at 3,195 patients enrolled between January 2010 and October 2011 at 34 centers. Rate of death at 30 days and 1 year were 9.7% and 24% and incidence of periprosthetic aortic regurgitation was 64.5%. The incidence of stroke was 4.1%. It was concluded that the TAVR approach was a reasonable option. Higher EuroSCORE, NYHA functional class III or IV, the use of transapical approach and higher periprosthetic regurgitation was significantly associated with reduced survival [Gilard *et al.*, 2012].

Treatment with the CoreValve prosthesis was also shown to be feasible and was associated with a lower mortality rate [Gilard *et al.*, 2012]. The SOURCE registry, the largest enrolled registry demonstrated transcatheter valve implantation had excellent 1-year survival in high-risk patients [Thomas *et al.*, 2011]. Similar results were seen with the Transapical approach [Kempfert *et al.*, 2011].

Quality of life (QOL)

A prospective analysis of 186 patients with symptomatic severe aortic valve stenosis ineligible for conventional AVR underwent TAVR with either the Medtronic CoreValve or Edwards Sapien device. A total of 106 patients completed

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the 1-year follow-up protocol. The QOL was measured using the Medical Outcomes Study short-form health survey questionnaire. Scores at baseline and at 3 months and at 1 year were analyzed. At one year of follow up data were analyzed for physical functioning, bodily pain, general health, vitality and mental health. At 1 year the various physical and mental scores were comparable to an age matched standard population. It demonstrated that TAVR could improve the QOL status. Significant improvement in NYHA functional class was seen at 3 and 12 months of follow up. No significant improvement could be detected for social functioning and emotional role [Krane *et al.*, 2012].

A similar study by Georgiadou with 36 consecutive patients showed marked 1 year clinical benefit in functional status and physical and mental health in patients who underwent TAVR [Georgiadou *et al.*, 2011]. Cost analysis life expectancy at an incremental cost per life year gained was within accepted values for current cardiovascular technology [Reynolds *et al.*, 2012].

Future developments

Further studies are being done evaluating TAVRs role in low-risk patients which will determine a broader use in the near future. Studies also show ventricular remodeling after its placement. The long-term properties and durability of the newer devices continue to be followed up.

Summary

TAVR has become an established treatment for symptomatic severe AS. Careful patient selection, valve sizing, and meticulous technique results in good outcomes. QOL and cost effectiveness are acceptable for current cardiovascular technology but remains uncertain in lower risk patients. Stroke, paravalvular leak, and vascular injury are major complications of this procedure.

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End stage pulmonary disease

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Introduction

End-stage lung disease resulting in severe dyspnea and debilitation is a common indication for palliative care referral. Chronic obstructive pulmonary disease (COPD) is a leading cause of mortality and ranks third behind only heart disease and cancer in the US [Hoyert and Xu, 2012]. COPD and other chronic lower respiratory conditions are responsible for close to 150,000 deaths a year in the US alone. Lung cancer claims even a higher number of deaths and is by far the number one cause of cancer-related mortality. End-stage lung disease imposes an enormous emotional and financial burden on patients and patient families. Progressive respiratory conditions frequently lead to respiratory failure and persistent distressing symptoms such as severe dyspnea.

Dyspnea is a highly unpleasant subjective perception of difficulty breathing. Pain and dyspnea are the most taxing symptoms in the terminally ill. Their management has been and remains an important aspect of palliative care. The treatment of dyspnea remains challenging and it is often undertreated. A detailed discussion on dyspnea and cough including treatment options can be found elsewhere in this book and will not be covered in this chapter.

Palliative care initially focused on the end-of-life care [Saunders, 2001]. Subsequently, the scope of palliative management expanded to improving quality of life for patients and families regardless of the stage of disease. Even though it is commonly viewed as the next logical step after restorative therapy has failed, ideally, palliative care should be delivered concurrently with curative intent efforts [Lanken *et al.*, 2008]. End-of-life management is generally focused on palliative care.

COPD

COPD is a lung disease most commonly caused by tobacco

smoke exposure. COPD is characterized by an obstructive pattern (flow limitation) evident on spirometry. The airflow obstruction is progressive and irreversible. Chronic bronchitis is a clinical syndrome of chronic cough and sputum production closely related to COPD. Emphysema is another aspect of the same smoking-related pathology characterized by histological or radiological evidence of alveolar destruction. In clinical practice, COPD, chronic bronchitis and emphysema are often used interchangeably as they reflect different aspects of the same underlying, most commonly tobacco-related, lung pathology. The palliative management of other obstructive lung conditionsbronchiectasis, bronchiolitis obliterans and severe fixed bronchial asthma- is similar to that of COPD.

The prevalence of smoking has steadily declined in most of the Western world since the 60-70s but tobacco use still remains quite prevalent worldwide. With an aging population and the progress made in cardiovascular prevention and early cancer detection, the importance of COPD to health care, especially end-of-life care, is growing. COPD is a progressive disease and further loss of function is often observed after smoking cessation. The affected individuals are frequently unaware of their condition for many years. It is not uncommon for the symptoms to develop decades after quitting smoking due to the natural loss of lung function with aging. Continuous tobacco exposure, however, results in accelerated lung function deterioration. The relationship between the severity of COPD measured by airflow impairment on spirometry and symptoms is not quite predictable and varies from person to person. Once the pulmonary reserve is exhausted and depending on the individual's level of activity, symptoms will develop. The course of COPD is characterized by disease exacerbations with relatively quiescent periods in between. An exacerbation can lead to unexpected death.

Subsequent recovery may not be complete, resulting in a step-wise deterioration of lung function. For this reason, the prognosis is quite variable and expected survival may be difficult to accurately predict even in severe cases. The BODE index is a popular way to estimate long-term survival in COPD [Celli et al., 2004]. It takes into account the Body mass index, airflow Obstruction, Dyspnea severity and Exercise capacity. The BODE index ranges from 0-10. The highest quartile (BODE 7-10) carries mortality of 80% at 52 months. However, even in this most severe group, the 1-year survival exceeds 90%. Therefore the BODE index is inadequate to identify candidates for end-of-life care. Frequent exacerbations, general functional decline and worsening symptoms will alert a vigilant health care professional of the high likelihood of the patient entering the terminal stage of their disease. The impact of symptoms of end-stage COPD on quality of life and functional status is comparable to that of cancer [Edmonds et al., 2001]. Although palliative and hospice care have been traditionally viewed as part of cancer management, more attention is paid today to non-malignant yet equally debilitating conditions. When faced with an advanced disease, providers should discuss palliative care strategies along with disease specific restorative therapy and prevention. The patient's attitude toward intubation and mechanical ventilation should be explored. Living wills and advanced directives may need to be encouraged if not already in place. Clinicians often avoid these unpleasant topics, which may deprive the patient of early palliative intervention and proper preparation with regards to their personal affairs [Sullivan et al., 1996]. Fears that this discussion will cause undue distress are generally unfounded. The patients by and large want to be well informed and most will appreciate a frank discussion about end-of-life care. The patients' attitudes to mechanical ventilation and resuscitation cannot be predicted based on age and disease severity [Gaber et al., 2004]. Patients' information needs, however, are variable and an individual approach should be undertaken in each case [Jones I, 2004].

In severe, end-stage cases, chronic respiratory failure sets in with persistent and debilitating symptoms. Dyspnea is invariably present and often dominates the patient's life. It requires aggressive management, especially in the terminally ill. Since flow limitation and difficulty ventilating are a hallmark of COPD, bronchodilators constitute an important component of therapy. β_2 -sympathomimetic agonists (albuterol, salmeterol) and anticholinergic agents (ipratropium, tiotropium) are used for this purpose. Brochodilators relax the smooth muscles in the airways

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and improve airflow. Inhaled corticosteroids have been widely used in COPD for maintenance therapy. Their role in bronchial asthma is well established but the effectiveness of inhaled steroids in COPD is controversial. Enteral and parenteral steroids may be needed in severe cases of persistent symptomatic bronchospasm or during exacerbations of otherwise less severe disease. Oxygen is almost always needed in end-stage COPD and often in less severe cases due to hypoxemia. Oxygen improves survival in COPD and may alleviate dyspnea in hypoxemic patients [NOTTG, 1980].

Theophylline may be of some value for symptomatic relief in COPD. It is believed to have bronchodilator and anti-inflammatory properties [Barnes, 2006]. Unfortunately, the narrow therapeutic window and potential for adverse effects limit its use.

Smoking cessation is of utmost importance for all COPD patients but the terminally ill. Eliminating tobacco exposure results in mild but rapid improvement in lung function. The rate of further decline in nonsmokers is half of that in those who continue to smoke [Scanlon *et al.*, 2000]. Smoking cessation in the setting of end-of-life care is more controversial. The benefits for the terminally ill are likely minimal. Safety considerations may be of higher importance, as oxygen use is universal in this patient population. The fire hazard is real and the patient and his caretakers need to be educated and advised against the use of open fire when oxygen is in use [West and Primeau, 1983]. Fortunately, smoking is not very common among individuals dying of lung disease and suffering from severe dyspnea.

Respiratory rehabilitation is increasingly recognized as an effective method to maintain functional status and manage symptoms in COPD [Lacasse et al., 1996]. As the focus shifts to palliative care in progressive respiratory failure, high intensity endurance training to maintain functional ability may become less feasible. However, several low-intensity protocols, including interval training and single-leg ergometry, have demonstrated ability to improve dyspnea and functional capacity [Sachs and Weinberg, 2009]. As mentioned earlier, the disease trajectory in COPD is defined by slow progression punctuated by exacerbations. This is in contrast to the precipitous decline observed in lung cancer and other rapidly progressive conditions [Lynn and Adamson, 2003]. Thus, pulmonary rehabilitation remains an important tool in the management of COPD even after the focus shifts to palliative care. Other aspects of pulmonary rehabilitation including education (breathing strategies, energy conservation and work simplification, end-of-life education), psychosocial and behavioral intervention (coping strategies, stress management) become more relevant in this patient population [American Thoracic Society, 1999]. A Cochrane review concluded that rehabilitation "relieves dyspnea and fatigue, improves emotional function and enhances patients' sense of control over their condition. These improvements are moderately large and clinically significant." [Lacasse *et al.*, 2006] COPD patients with severe dyspnea benefit as much from pulmonary rehabilitation as patients with less severe disease [Lizak MK, 2008]. These individuals should not be excluded from rehabilitation programs.

Noninvasive ventilation may be helpful for symptomatic relief of breathlessness in COPD. It decreases the need for intubation, shortens the hospital stay and improves in-hospital mortality rate in patients with COPD exacerbation requiring intensive care admission [Brochard et al., 1995]. Intubating and placing the patient on mechanical ventilation is often a psychological line that both the patient and the clinicians are reluctant to cross when the established goal of care is comfort. Noninvasive ventilation is an acceptable temporary solution to treat symptoms and bridge the patient over an acute complication such as COPD exacerbation or pneumonia. This mode of ventilation, however, generally requires an alert and, to some extent, cooperative patient and can be, in and of itself, a source of discomfort. It should never be offered as a permanent solution and its use should be discouraged if no improvement in the patient's condition is expected. Noninvasive ventilation can be used in respiratory failure of any etiology, not just COPD. It is particularly beneficial in pulmonary edema as positive pressure ventilation decreases venous return to the right ventricle and thus improves pulmonary congestion [Barach et al., 1938].

Depression and anxiety often complicate both malignant and non-malignant end-stage lung disease and are especially frequent in patients suffering from constant dyspnea [van Manen *et al.*, 2002]. Management of mood disorders and anxiety is an integral part of the palliative management of these patients. Pharmacological treatment and/or psychotherapy can be of help. If needed, consultation should be sought from a psychiatrist.

Lung cancer

Currently, bronchogenic carcinoma is the most common cancer causing death. Due to the unique role they play in the circulation, the lungs are also a common location for metastatic hematogenous spread of other malignancies. The disease trajectory of lung cancer and most other types of cancer is characterized by initially preserved functional capacity followed by rapid decline and death [Lynn and Adamson, 2003]. This makes identifying individuals in the final stage of their disease easier compared to COPD. The 90-day mortality of patients with inoperable non-small cell lung cancer who present with respiratory failure approaches 100% [Medarov and Challa, 2011].

The final year of life of lung cancer patients is quite similar to that of patients with chronic lung disease. The prevalence of dyspnea in chronic lung disease is higher—94% vs. 78% and anorexia is more common in lung cancer—76% vs. 67%. The rate of cough, nausea, low mood and insomnia is similar [Edmonds *et al.*, 2001]. The high rate of severe symptoms has a large impact on the quality of life of those patients. Palliative care is an extremely valuable tool to address discomfort and distress in this patient population (*Table 1*).

A detailed discussion of dyspnea, pain and cough can be found elsewhere in this book. As the same general treatment principles apply to the management of those ever-troublesome symptoms in lung cancer, herein these issues will not be addressed in much detail.

Muskuloskeletal and nervous system complications

The localized and proliferative nature of lung cancer sets it apart from other, mostly diffuse, lung conditions. Local or metastatic pain can complicate the course of the disease, which is not as common in other lung disorders. As any cancer pain, pain from lung cancer can be severe and debilitating. Opiates are frequently needed in advanced cases. External beam radiation is often applied with palliative intent to treat symptoms of locally spreading malignant tumor (airway obstruction, pain) or metastatic lesions (bone, brain). On average, about ³/₄ of bone metastatic lesions respond well to radiation therapy with the exception of squamous cell cancer, whose response rate is less than 50% [Murai et al., 1989]. Higher fractionated doses have the most predictable and lasting response but a single large fraction can be helpful in providing quick pain relief, especially in patients with short survival expectancy and small extremity lesions [Kvale et al., 2003]. The application of the latter is limited by the higher rate of local adverse effects. Adding steroids to radiation therapy may benefit some patients, especially those with high levels of

Symptom/complication	Treatment	Remarks
Bone metastases	Pain medications, external beam radiation, steroids, bisphosphonates, calcitonin, systemic radionuclides, internal fixation, endoprosthesis, arthroplasty, chemotherapy	Squamous cell carcinoma has the lowest response rate to radiation. Steroids may be beneficial if high osteolytic activity is present. Bisphosphonates are effective, low-toxicity adjunctive agents
Spinal cord compression	External beam radiation, surgical stabilization, high dose steroids, chemotherapy	Early intervention in ambulatory patients is effective in preserving mobility
Brain metastasis	Surgical resection of solitary lesions, external beam radiation, stereotactic radiosurgery, chemotherapy, steroids	Palliative treatment of brain metastasis may help slow disease progression and prolong survival
Superior vena cava syndrome	Caval stents, external beam radiation, chemotherapy	If technically feasible, caval stents provide best results.
Anorexia	Megestrol, medroxyprogesterone, olanzapine, cannabinoids, cyproheptadine	Treatment not always necessary
Malignant pleural effusion	Thoracentesis, pleurodesis, pleural catheters, chemotherapy	Outpatient placement of tunneled catheters is an effective long-term solution
Airway obstruction/ hemoptysis	Laser, electrocautery, argon plasma coagulation, cryotherapy, balloon dilatation, metallic and silicone stents, high-dose radiation brachytherapy, photodynamic therapy, bronchial artery embolization, lobectomy	Mortality of lung cancer-related massive hemoptysis is 60%

urine hydroxyproline excretion indicating high osteolytic activity [Teshima et al., 1996]. Bisphosphonates are well tolerated and can be effective for pain management. More importantly, they can be used as an adjunctive treatment added to radiation therapy. The combination is more effective than either modality alone with minimal or no additional toxicity [Bloomfield, 1998; Shucai et al., 1999]. The response rate of this regimen exceeds 90%. Although not widely used for this purpose, calcitonin has been found by some to be effective in alleviating pain related to bone metastases [Schiraldi et al., 1987]. Other data suggest that the role of calcitonin as an adjunctive agent in the treatment of intractable pain is extremely limited [Tsavaris et al., 2006]. Administration of bone-targeted enteral or parenteral radionuclides (most commonly Strontium⁸⁹, Samarium¹⁵³ or Phosphorus³²) has shown a variable response rate but can be a useful addition when medical therapy is not sufficient and external radiation is not feasible [Lee et al., 1996; Bauman et al., 2005; Hillegonds et al., 2007]. Prophylactic internal fixation of impending pathological fractures should be considered in ambulatory patients [Ryan et al, 1976]. The following criteria have been proposed for preventive fixation-persisting or increasing local pain despite the completion of radiation therapy, permeative involvement,

est that Spinal cord compression is a disabling complication of metastatic bronchogenic carcinoma. Ambulatory patients have a very good chance to preserve their mobility if promptly treated [Turner *et al.*, 1993]. Radiation is considered first-line therapy. Surgical intervention with laminectomy, debulking and/or stabilization should be considered in the case of spinal instability, progressive neurologic deterioration from hony collapse and

neurologic deterioration from bony collapse and compression, intractable pain or failure of conservative means of treatment [Jenis *et al.*, 1999]. High doses of dexamethasone (96 mg/day) have been shown to favorably affect outcome in metastatic cord compression related to solid tumors [Sorensen *et al.*, 1994]. Lower doses are probably not effective [Loblaw and Laperriere, 1998].

a solitary well-defined lytic lesion greater than 2.5 cm, a

solitary well-defined lytic lesion circumferentially involving

more than 50% of the cortex and metastatic involvement

of the proximal femur associated with a fracture of the

lesser trochanter [Haentjens et al., 1993]. Endoprosthesis

or total arthroplasty may be needed for intracapsular

or very proximal lesions [Fourneau and Broos, 1998].

Transcutaneous injection of ethanol can be attempted in

terminally ill patients with intractable pain not responding

to other treatment modalities [Gangi et al., 1994].

Part II
End stage pulmonary disease



Figure 1 PleurX[®] tunneled catheter. (Courtesy of CareFusion Corporation).

About one third of patients with non-small cell lung cancer develop brain metastasis—an ominous sign indicating poor short-term prognosis. An aggressive approach with surgical resection, stereotactic radiosurgery, radiation and/ or chemotherapy can provide some control over the disease progression and meaningful survival benefit [Kelly and Bunn, 1998; Burt *et al.*, 1992]. Steroids are effective but their benefit is temporary [Coia *et al.*, 1992]. Steroids are recommended for concurrent use with radiation therapy but their application should be limited to 1 month due to the high rate of adverse effects beyond the first 3-4 weeks [Weissman *et al.*, 1987].

Superior vena cava (SVC) syndrome

SVC syndrome is a complication of chest malignancies caused by occlusion of SVC by external compression. The affected patients develop swelling of the face and upper extremities often associated with dyspnea. SVC syndrome requires urgent management. Traditionally external radiation has been the modality of choice for lung cancer and other malignancies expected to respond to radiation. More recently, caval stents have been added to the palliative clinician's armamentarium [Hague and Tippett, 2010]. A Cochrane review suggested that stents might be the most effective treatment in SVC syndrome [Rowell and Gleeson, 2001]. Chemotherapy, usually in addition to radiation, can be helpful for SVC syndrome in small cell lung cancer, lymphoma and other chemosensitive tumors.

Anorexia

Anorexia is common in end-stage lung disease—both malignant and non-malignant. The degree to which poor

appetite and weight loss impact the patient's quality of life is variable. Some patients are not particularly distressed by these symptoms. For others, anorexia and weight loss are a constant reminder of having an incurable disease [Davis, 2012]. Symptomatic treatment with megestrol [McQuellon *et al.*, 2002], olanzapine [Navari and Brenner, 2010], medroxyprogesterone, cyproheptadine or cannabinoids can be offered to those patients. Cannabinoids are also effective antiemetic agents [Ben Amar, 2006]. Nausea is common and can be extremely troubling to patients receiving chemotherapy. It should be aggressively treated. Appetite stimulants and nutritional support unfortunately do not improve lean body mass significantly as cachexia is caused by upregulated catabolic pathways and not just by poor oral intake [Tisdale, 2001].

Malignant pleural effusions

Malignant pleural effusions are common in lung cancer and can complicate other malignancies. Lung carcinoma is the number one cause of malignant effusions [Johnston, 1985]. Management of symptomatic pleural collections is an important aspect of the palliative care of these patients. Thoracentesis is helpful in the acute treatment of large symptomatic effusions. Recurrence is common and often rapid. Indwelling tunneled and nontunneled pleural catheters as well as pleurodesis can be considered in those cases. Tunneled indwelling catheters are an effective way to manage malignant effusions and feature a low complication rate (Figure 1). The procedure can be done in an outpatient setting. Symptomatic improvement is seen in more than 95% of the cases [Van Meter et al., 2011]. Spontaneous pleurodesis is common. For these reasons, tunneled catheters are becoming the treatment of choice for recurrent malignant effusions and are clearly superior to other options in patients with trapped lung [Chee and Tremblay, 2011].

Airway obstruction and hemoptysis

Airway compromise resulting in obstruction or hemoptysis may require invasive palliative measures. The choice of intervention depends on the urgency of the situation, lesion anatomy and desired outcome. In the case of intraluminal obstruction, debulking procedures can be performed using laser, electrocautery, argon plasma coagulation or cryotherapy. Balloon dilatation can be applied to short negotiable airway stenosis, frequently supplemented by stent deployment or performed prior to brachytherapy [Hautmann *et al.*, 2001]. Airway stents help maintain patency after debulking or dilatation. Uncovered metallic stents are relatively easy to place and do not require rigid bronchoscopy. They may be a good choice for external compression or emergent procedures but their long-term efficacy is limited due to tumor ingrowth and overgrowth when used for intraluminal lesions [Miyazawa *et al.*, 2000]. Silicon stents may be more appropriate for more lasting results but those do require rigid bronchoscopy and are more prone to migration [Dumon Tremblay, 1990].

High-dose radiation brachytherapy (HDR) is used to deliver internal radiation directly to tumors located in the large airways in order to promptly resolve obstruction or control bleeding [Gaspar, 1998]. It can be used as standalone treatment or as an adjunctive modality following external radiation, stent placement or debulking procedures. Brachytherapy does not eradicate the tumor lesions and rarely prolongs survival but it can be an extremely effective palliative measure, especially combined with external radiation. The palliation rate for hemoptysis exceeds 95% and HDR improves dyspnea and chest pain in 80-90% of the cases [Anacak *et al.*, 2001].

Photodynamic therapy uses light to inflict tissue injury to targeted malignant lesions after the application of light sensitizers, usually polyhematoporphyrins. It is a useful palliative measure to treat inoperable airway lesions with a high rate of successful resolution of endobronchial obstruction [Moghissi *et al.*, 1999]. The bronchoscopic illumination is performed 1-3 days after the administration of the photosensitizer. For this reason, photodynamic therapy is not suitable for emergent treatment. Lesions with a surface area exceeding 3 cm² are generally considered poor candidates for photodynamic therapy [Edell and Cortese, 1987].

Hemoptysis can be palliated with bronchial artery embolization. If endobronchial intervention or embolization are not feasible or are unsuccessful, palliative lobectomy or pneumonectomy is occasionally done in patients who are otherwise considered unsuitable candidates for curative surgery [Naef and de Gruneck, 1974]. Mortality of massive hemoptysis (blood loss \geq 200 mL/24 h) in lung cancer is 60% despite any intervention-much higher than in other etiologies [Corey and Hla, 1987].

Chemotherapy

The palliative application of chemotherapy is common in lung cancer. Platinum-based regimens have traditionally

been the treatment of choice for nonsmall cell lung cancer. Pemetrexed, a taxane (docetaxel), gemcitabine or a vinca alkaloid (vinorelbine) is generally added to the regimen. Vascular endothelial or epidermal growth factor (EGF) inhibitors may have a role in selected cases. Poor performance status patients are usually not considered good candidates for full chemotherapy. The rate of adverse reactions is high and survival is poor in those patients [Sweeney et al., 2001]. They can be palliated with a single EGF receptor inhibitor if a sensitive mutation has been identified in the tumor. This regimen can improve the patient's functional status. Gefitinib-a commonly used EGF receptor inhibitor-used as monotherapy has shown a response rate of 70%, a disease control rate as high as 90% and median survival of 18 months in patients with poor functional status, who are not suitable candidates for full chemotherapy [Inoue et al., 2009].

Small cell lung cancer (SCLC) is an aggressive malignancy that progresses rapidly and metastasizes early. Chemotherapy is the treatment of choice as SCLC is rarely curable by surgery [Agra et al., 2003]. Radiation therapy is added to the regimen for disease limited to the same hemithorax (limited stage SCLC). SCLC is very chemo- and radiosensitive with a high initial response rate. The most commonly used chemotherapy regimen is a combination of a platinum-based agent and etoposide. Quick relapse is however the rule and only 10-15% of patients with limited stage disease achieve survival beyond 5 years [Gaspar et al., 2005]. Therefore, at the onset of the treatment regimen, chemo- and radiotherapy are considered both curative-intent and palliative. This is an example that the separation of restorative and palliative therapy is often artificial and symptom control can be pursued along with curative efforts.

It has long been recognized that early palliative care in metastatic non-small cell lung cancer results in significant improvements in quality of life and mood. Patients receiving timely palliative therapy live longer and require less aggressive care at the end of life [Temel *et al.*, 2010]. Early multidisciplinary symptom management is highly recommended for patients diagnosed with lung cancer.

Other lung diseases

The general principles outlined previously about the management of advanced COPD and lung cancer are applicable in other forms of end-stage lung disease and respiratory failure. The disease specific treatment is tailored to the particular disease. Bronchodilators are often used even if the underlying respiratory condition is restrictive and does not affect primarily the airways (e.g., idiopathic pulmonary fibrosis, other interstitial lung diseases). There is little evidence or sound theoretical consideration to justify the use of bronchodilators in the absence of obstruction but it is hard to condemn this practice when faced with a severely symptomatic patient and limited treatment options.

In like manner, oxygen use is acceptable in dyspneic nonhypoxemic patients if it provides subjective relief.

Although most research has been done in COPD, there is clear evidence that pulmonary rehabilitation is no less beneficial in other respiratory conditions [Foster and Thomas, 1990]. Individuals with advanced interstitial lung disease, especially idiopathic pulmonary fibrosis, have generally a shorter disease trajectory compared to COPD. Nevertheless, pulmonary rehabilitation clearly improves dyspnea, fatigue, functional capacity and overall quality of life in this population [Jastrzebski *et al.*, 2006]. However, the benefits are rarely sustained 6 months later if the program is discontinued [Holland *et al.*, 2008].

Withdrawal of mechanical ventilation

In the intensive care setting, the transition from curative care to end-of-life palliative care is often made in mechanically ventilated patients. This step is frequently a difficult one and may involve withdrawal of mechanical ventilation, which can cause a great deal of distress not only to the patient but also to the family and the involved health care professionals. Terminal extubation has been viewed by some as a drastic measure with consequential ethical and legal implications. It has been argued that withdrawing essential life support is not different than "killing" the patient or euthanasia. When the parents of Karen Ann Quinlan, a 21-year-old girl in a persistent vegetative state following a cardiac arrest, asked for her daughter to be removed from the ventilator in 1975, they met with a lot of resistance. The hospital refused to discontinue mechanical ventilation, which led to a legal battle and intense debates. Since then, the courts in the US have clearly rejected the view that withdrawal of life support was "killing" the patient and reaffirmed the patients and their surrogate decision makers' right to refuse any and all treatment [Quinlan J, 1977]. Today, there is a broad consensus that it is appropriate to withdraw life-sustaining care including mechanical ventilation in certain situations and especially upon a specific request by the patient

[Prendergast and Puntillo, 2002]. The principle of patient autonomy allows patients and their surrogates to forego or actively discontinue any undesired treatment. It is less clear what the right approach is when the patient lacks decision capacity and there is no surrogate decision maker. Accepted practices vary by locale and jurisdiction. Considering the serious consequences of the decision to withdraw life-sustaining support, it is recommended to solicit a broader discussion involving other health care professionals, e.g., an ethics committee [Truog et al., 2001]. Similar approach is recommended when there is a disagreement among health care providers and/or family members regarding treatment goals and plan of care. As a competent patient has always the ultimate decision power, it is advisable to lighten or temporarily discontinue sedation if possible, so the patient can participate in the decision-making.

The question of whether it is acceptable to withdraw life-support has been covered extensively in the literature [Prendergast and Puntillo, 2002]. There is much less consensus on what the best way to do that is and especially how to discontinue ventilatory support. Patient comfort and family's expectations should guide the clinician. Both extubation and gradual weaning of oxygen or ventilatory support are acceptable. Proponents of the latter argue that complete mechanical ventilation withdrawal may result in severe distress and dyspnea. Keeping the endotracheal tube in place may be beneficial for patients who have excessive airway secretions. The argument against slow weaning is that it prolongs the dying process, thus possibly increasing patient's suffering and the family's grief experience [Truog et al., 2001]. There are no good data comparing various methods of life support withdrawal. The clinicians should work with the patient and the family to determine the optimal approach based on their own comfort level and the patient's individual needs. Organ and tissue donation may need to be discussed prior to withdrawal. Both the family and the clinical staff should be prepared for the possibility of delayed death even if the patient appears to be heavily dependent on the respirator. Unexpected prolonged survival after terminal extubation may lead to emotional exhaustion and frustration in the family. Doubts about the appropriateness of the decision to withdraw life-sustaining care may arise. In order to prevent this, it is advisable to counsel the patient's family about the unpredictability of the death process. As mechanical ventilation withdrawal has the greatest potential to cause distress, all other essential treatment should be generally withdrawn first. For example, discontinuing pressor treatment in a patient

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in shock may lead to a relatively peaceful death without the need to embark on more drastic measures such as extubation. Pacemakers can be turned off. Implantable cardioverter-defibrillators deserve special mention. Those should always be turned off in anticipation of death. Electrical shocks from those devices can be extremely distressing and painful. Defibrillating a dving patient in the setting of terminal care is not justified. Conventionally, the defibrillator and antitachycardia pacing ("overpacing") function can be deactivated noninvasively by placing a magnet over the device [Wilkoff et al., 2008]. When in doubt, a consultation with a specialist or the manufacturer should be sought. Paralytic agents should be discontinued as they have no palliative value and may actually worsen distress. Withdrawal of life support should be done when neuromuscular function is restored unless that will cause an unacceptable delay and suffering to the patient. Great care should be taken in those cases to ensure comfort as signs of even severe distress may not be apparent. Eliminating fluid and enteral intake is advised in order to avoid aspiration, pulmonary edema and excessive secretions resulting in "death rattle". Anticholinergic agents such as atropine and scopolamine can be administered to diminish respiratory and oral secretions and have been found to be quite effective in the management of "death rattle" [Wildiers and Menten, 2002]. The patients need to be premedicated with opiates and often sedatives. Aggressive dyspnea management is needed after discontinuation or weaning of life support. Opiates are always required to ensure comfort if the patient was ventilator dependent. Benzodiazepines and neuroleptics should be liberally used for treatment of anxiety and terminal delirium. Hastening death by aggressive use of opiates and sedatives used to ensure comfort in the dying patient is acceptable under the principle of the "double effect" [Quill et al., 1997]. This principle states that an action may be morally justified even if it has foreseeable but unintended undesired consequences. Therefore, administering high doses of an opiate to provide pain control and comfort is not considered euthanasia even if the risk of causing death is high. In view of the ultimate goal to provide comfort, sedation should not be limited out of fear of hemodynamic compromise. The family members should be given a choice to be present for the process of life support withdrawal. Spending the final moments of life with the family may be comforting to the dying patient. Being present is often important spiritually and emotionally to the family too. Witnessing the last breath of their loved one may serve as closure and facilitate the bereavement process.

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Introduction

Pain can be defined as an unpleasant sensory and emotional experience of actual or potential tissue damage or an experience expressed in such terms. Both excitatory and inhibitory physiologic and pathologic mechanisms are involved in its generation and maintenance. Recent research has uncovered important pathophysiological mechanisms that are underlying different clinically relevant pain disorders. This chapter will briefly describe types of pain, pain pathways, peripheral and central mechanisms that are involved in pain. A better understanding of pain, particularly the translation of pathophysiological mechanisms into sensory signs, will lead to a more effective and specific mechanism-based treatment approach.

Types of pain

Pain is a major symptom of many different diseases and a subjective result of nociception. Nociception is the encoding and processing of noxious stimuli in the nervous system that can be measured with electrophysiological techniques [Greene, 2010].

Pain may be classified in various ways: physiologically, it contains nociceptive and neuropathic pain; by etiology, it contains malignant and nonmalignant pain; temporally, it contains acute and chronic pain [Katz and Rothenberg, 2005]. Acute pain often lasts less than three months [Barkin and Barkin, 2001], and is often associated with an identifiable injury or trauma. Thus, it responds to relatively simple analgesic therapy, and it will be resolved as the area of injury heals or is treated. Acute physiological nociceptive pain is elicited when a noxious stimulus is applied to normal tissue. Because withdrawal reflexes are usually elicited, this pain would protect tissue from being further damaged. When the tissue is inflamed or injured, pathophysiologic nociceptive pain will occur, which is one of the most frequent reasons why patients seek medical care. This kind of pain may appear as spontaneous pain, hyperalgesia, and/or allodynia [Schaible and Richter, 2004].

Chronic pain lasts longer than three months and exceeds the typical recovery time for the initial injury. It may or may not be explained by low levels of identified underlying pathology [Greene, 2010]. It is often accompanied by neuroendocrine dysregulation, fatigue, increased irritability, depression, social withdrawal, emotional stress, loss of libido, disturbed sleep patterns and weight loss [Chapman and Gavrin, 1999]. Although injury may elicit chronic pain, factors remote from its cause may perpetuate it. Environmental and affective factors can also exacerbate and perpetuate chronic pain. Interestingly, the causal relationship between nociception and pain may not be clear in many chronic pain states and certain pain states may not reflect tissue damage.

Chronic pain

Chronic pain may also be categorized by its character. It can be nociceptive, neuropathic, or both. It may be caused by cancer, inflammation, or a variety of non-life-threatening conditions such as arthritis, fibromyalgia, and neuropathy [Katz and Rothenberg, 2005]. Chronic pain may result from a chronic disease and then actually result from persistent nociceptive processes.

Cancer pain

Most chronic cancer-related pains are caused directly by the tumor. Bone metastases and compression of neural structures are the two most common causes [Twycross and Harcourt, 1996]. Bone metastases could potentially cause pain by many mechanisms, including endosteal or periosteal nociceptor activation or tumor growth into adjacent soft tissue and nerves [Mercadante, 1997]. In fact, there is no homogenous entity of "cancer pain"; pain in cancer, which is often tied up with concomitant psychosocial upheaval and existential anxiety, can be inflected by a multitude of emotional, psychological and spiritual factors [Maxwell, 2012]. To many cancer sufferers, their pain has a "sinister meaning" over and above its inherent unpleasantness as a sensory experience [Maxwell, 2012]. Chronic cancer pain rarely involves medicolegal or disability issues and is distinct from acute physiological pain. It has a significant effect on every aspect of a person's life, including daily physical activities, mood, social relationships, sleep patterns, cognition and existential beliefs (whether the person's life has meaning, purpose or value in relation to mortality) [Katz and Rothenberg, 2005]. The patients with cancer may become withdrawn and unable to focus if the pain is not managed well.

Neuropathic pain

Neuropathic pain is thought to arise from abnormal physiology of the peripheral or central nervous systems and may be unrelated to ongoing tissue damage or inflammation [Dworkin and Backonja, 2003]. There are numerous causes of nervous system injury, including exposure to toxins, infection, viruses, metabolic disease, nutritional deficiencies, ischemia, trauma (surgical and nonsurgical), and stroke [Pasero, 2004]. Some patients with neuropathic pain may have severe pain without obvious clinical signs of nerve injury, whereas others may have significant nerve injury without pain. In addition, neuropathic pain may be precipitated by a relatively minor physical insult, and the severity of pain may be much greater than the extent of damage might suggest. Although the mechanism underlying neuropathic pain is not completely understood, it is considered to be complex, multifactoral, and could evolve over time. Normally, peripheral and central sensitization phenomena would dissipate as tissue heals and inflammation subsides. However, neuropathic pain may be elicited when changes in primary afferent function persist after disease or injury of the nervous system [Dworkin and Backonja, 2003].

Inflammation pain

Chronic inflammation is a feature of a large number of painful chronic degenerative diseases, such as arthritis, low back pain, and inflammatory bowel disease [Sommer and Birklein, 2011]. Unfortunately, it may be the single greatest cause of pain, which is the result of activation and sensitization of primary afferent nerve fibers. Inflammation pain is experienced predominantly when the inflamed site is mechanically stimulated by being moved or touched. The stimulation-induced pain is thought to be referred to as inflammatory hyperalgesia. Inflammatory hyperalgesia has been shown to be produced by inflammatory mediators released from circulating leucocytes and platelets, vascular endothelial cells, immune cells resident in tissue and sensory and sympathetic nerve fibers. Since the first mediator bradykinin was reported in 1953 [Armstrong and Dry, 1953], researchers have identified a number of inflammatory mediators which can produce hyperalgesia, including prostaglandins, leukotriene, serotonin, adenosine, histamine, interleukin-1, interleukin-8 and nerve growth factor (NGF).

Pathways for pain

Pain is a sensation that evokes an emotional response and involves a complex interaction between the periphery, the spinal cord, the brainstem and higher cortical centers.

Nociceptors

Nociceptive afferents do not have specialized receptors; they use free nerve endings and most are polymodal [Purves *et al.*, 2001]. They respond to more than one kind of stimulus, such as chemical, thermal or mechanical stimuli. Free nerve endings are found in all parts of the body except the interior of the bones and the brain itself. A δ fibers mediate the "fast" pain, whereas C-fibers signal the "slow" pain. Not all A δ and C fibers are nociceptors. Some respond to low threshold stimuli such as sensual touching or brushing the skin. Many C fibers are thermoreceptors, and respond to warm or cold, providing homeostatic responses via emotional tagging of sensations. Additionally, there is a population of "silent" nociceptors that reside in most tissues and are normally insensitive to mechanical and thermal stimuli. They become active under pathological conditions such as inflammation and nerve injury.

There are several differences between cutaneous and muscle or visceral nociceptors [Bessou and Perl, 1969; Snider and McMahon, 1998; Djouhri and Lawson, 2004]. The first is that cutaneous sensation is well localized and the pain is usually constant. Visceral and muscle pain is poorly localized, due to the lower innervation densities of these tissues, and is often periodic. Secondly, visceral afferents are insensitive to direct trauma but very sensitive to distension. Lastly, as most visceral organs have very few low threshold myelinated fibers and comprise mostly of Aδ and C fibers, their stimulus response properties differ from cutaneous and muscle afferents, which have specialized receptors to detect innocuous stimuli. Visceral afferents encode a stimulus response in an intensity dependent manner, the more painful the stimulus the greater the number of action potentials and frequency of discharge.

Cutaneous pain pathways

Cutaneous nociceptor afferents terminate mainly in laminae I, II and V of the spinal cord dorsal horn and synapse on second order neurons that carry the signal to either the brainstem or the thalamus. It is only when the nociceptive signal reaches the brainstem that it is translated into a conscious sensory perception. Three ascending pathways are concerned with pain transmission: the spinothalamic tract (STT), the spinoreticular tract (SRT) and the spinoparabrachial tract (SPBT). Each appears to be concerned with a particular aspect of pain processing. Simplistically, the sensory discriminative aspect is signaled by the STT, and the homeostatic and affective qualities of pain are signaled by the SRT and SPBT [Fields et al., 1974; Foreman et al., 1984; Bester et al., 1997]. Therefore, fast and slow pain travel by different pathways to different areas of the brain. The fast pathway connects directly to the thalamus, which then relays the information to the primary sensorimotor cortices for analysis and response. Its function is to act as a warning system by signaling the exact location and severity of the injury and the duration of the pain. Fast pain predominantly arises from STT neurons in the laminae IV-V of the spinal cord. Slow pain is mediated by C-fibers and signals the emotional aspects of pain. It reaches the thalamus indirectly via connections with the brainstem reticular formation. The slow pain axons innervate the non-specific intrathalaminar nuclei of the thalamus, and the autonomic centres of the reticular formation in the brainstem. Slow pain may remind the brain that pain has occurred, that protective attention to the injury site is required and that normal activity may need to be restricted while healing occurs [Schott, 2001].

The projections to the reticular formation underlie the arousal effects of the painful stimuli via activation of the ascending reticular activating system that projects to all areas of the brain. Activation of the reticular formation stimulates noradrenergic neurons in the locus coeruleus, and thus decreases the pain transmission by activating the descending pain modulating system [Jones, 2008].

Thalamocortical axons transmit the information from the thalamus to the cortex. There is no one specific cortical region that can be designated as "pain cortex". Rather, functional brain-imaging studies have revealed several regions that are active when a pain stimulus is sensed and these are associated with different functional components of pain [Casey *et al.*, 2003; Bosshard *et al.*, 2010]. "Where and how much it hurts" involves the somatosensory cortex whereas "I do not like it or stop it" are associated with the limbic regions, such as cingulate cortex or insula. Parts of the prefrontal motor cortex are also involved in cognitive evaluative process.

Visceral and muscular pain pathways

Considering that muscle and visceral pain evoke distinct sensations, it would be logical to expect to find cells in the spinal cord that respond only to muscle or visceral stimulation. Interestingly, no such cells exist in the spinal cord. All cells that have either a visceral or muscle receptive field also have a separate cutaneous receptive field. This means that convergence occurs within the spinal cord.

The central terminals of visceral and muscle nociceptors terminate in laminae I and V but also laminae II, unlike skin nociceptor afferents. In lamina I, these fibers converse onto projection neurons of the STT and SPBT, which then project to the brainstem and thalamus and from there to the somatosensory cortex [Navarro *et al.*, 2007; Saadé and Jabbur, 2008]. Visceral afferents also terminate on SPT neurons and onto cells that project to the dorsal column

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nuclei and recent research suggests that this latter pathway is exclusively involved in visceral pain, whereas the STT and SRT visceral pathways are more concerned with autonomic reflex functions than visceral pain [Newman, 1974]. Lesions of the dorsal columns effectively relieve chronic visceral pain and have led to new clinical treatments for managing visceral cancer pain.

Spinal dorsal born loco circuits for pain modulation

The initial integration of noxious information occurs in the superficial dorsal horn of the spinal cord (SDH), which is very important for understanding pain sensation and developing effective analgesic strategies [Wu *et al.*, 2010].

Peripheral nociceptors transmit noxious information to spinal neurons that further project afferents through ascending tracts, such as the STT, and neurons located in the SDH (including laminae I and II). These secondary and third order axons then synapse with sensory relay nuclei in the thalamus and then onto the cerebral cortex. SDH neurons (including projection neurons and interneurons) receive nociceptive information conveyed by the thinly myelinated (A δ) and unmyelinated (C) primary afferent fibers (PAFs) [Kumazawa and Perl, 1978; Sugiura et al., 1986]. Additionally, SDH neurons and PAFs receive dense descending inputs, including serotonergic and noradrenergic components mainly originating from the raphe magnus and locus ceruleus in the brain stem respectively [Kwiat and Basbaum, 1992]. The sole noxious output of SDH projection neurons to the higher brain structures are likely modulated by complicated interneuronal interactions within the SDH. Thus the integration of nociceptive transmission within the SDH is very important for understanding pain sensation and developing effective analgesic strategies. The platform for such complicated integrations is the circuits formed by pools of neurons that are highly plastic under conditions of inflammatory or neuropathic pain.

Descending pain control pathways

The idea of descending control systems dates back to the 1970s and 1980s when its original version was that structures in the brain stem send impulses that "descend" and thus inhibit the nociceptive transmission in SDH [Fields and Basbaum, 1999; Fields *et al.*, 1983]. A simplified descending inhibitory system was depicted as the following: The PAG projects to the rostral ventromedial medulla (RVM), which includes the serotonin-rich nucleus raphe magnus (NRM)

as well as the nucleus reticularis gigantocellularis pars alpha and the nucleus paragigantocellularis lateralis [Fields *et al.*, 1991]. Serotonergic [Zhang *et al.*, 2006] and some GABAergic or glycinergic [Antal *et al.*, 1996; Kato *et al.*, 2006] neurons in RVM then project along DLF to terminate in SDH, where they inhibit nociceptive transmission. Besides RVM, locus coeruleus and subcoeruleus nucleus are important supraspinal descending inhibitory structures which contain the majority of noradrenergic neurons with projections to SDH [Millan, 2002]. These supraspinal structures together form the descending control system of the spinal nociceptive transmission.

Complicated circuits can be formed between those key elements within SDH, thus facilitating or inhibiting nociceptive transmission. These circuits can be delineated according to different criteria. However, they are not hardwired since they are capable of dynamic change under different pain states. Furthermore, depending on the membrane properties (e.g., different receptor types on the membrane), the same classic neurotransmitter can function inhibitorily or excitatorily.

Peripheral mechanisms of pain

At the peripheral level, a "pain" signal is initiated when physicochemical stimuli of high intensity or a particular quality are detected by a subpopulation of sensory neurons termed nociceptors. Traditionally, nociceptors are noncapsulated nerve endings of thin myelinated (Aδ-type) and nonmyelinated (C-type) fibers in the tissue, which can sense the actual or potential tissue damage and convert the energy into a changed membrane potential that is sufficient to generate an action potential, a cognizable "language" of nervous system. Most of the nociceptors respond to mechanical, chemical and/or cold stimuli and thus are polymodal. During the pathophysiological process, however, the nociceptor per se also undergoes functional or structural changes in response to the tissue damage. These changes may amplify the effect of initial stimulus to make pain either a powerful defense system for individual safety (nociceptive pain) or even a diseased condition torturing patients (chronic pain). Due to the limited space, we will focus on reviewing the main peripheral mechanisms of pain, which have been proved to be effective targets for clinical therapy.

Peripheral sensitization

During tissue injury or inflammation, polymodal

nociceptors undergo decreased excitation thresholds, increased response to suprathreshold stimuli, such that even light or normally innocuous stimuli can activate the receptors. Such phenomenon is referred to as peripheral sensitization or nociceptor sensitization [Ringkamp and Meyer, 2009]. As a consequence, noxious stimuli applied to the injured tissue area evoke more severe pain (primary hyperalgesia) than in the non-sensitized state and innocuous stimuli such as mechanical and cold stimuli also cause pain (allodynia). Thus, peripheral sensitization is a neuronal mechanism correlating with behavioral changes, i.e., hyperalgesia and allodynia. In addition to triggering the increased sensitivity of nociceptor to stimuli, inflammation also causes the recruitment of so-called "silent nociceptors". Silent nociceptors are A- or C-fibers that are unexcitable or hard to excite with a high mechanical threshold under healthy conditions. During inflammation, however, these fibers are sensitized and become susceptible to applied stimuli [Michaelis et al., 1996].

Nociceptor sensitization is initiated by the action of numerous inflammatory mediators released upon tissue injury from surrounding cells such as mast cells, keratinocytes, macrophages and immune cells [Schaible and Richter, 2004]. Important among these inflammatory mediators or cytokines are bradykinin, serotonin, histamine, prostagladin, adenosine, interleukins, tumor necrosis factor alpha as well as neurotrophins like NGF [Schaible et al., 2011]. A mixture of these substances forms the "sensitizing soup" and modulates the sensitivity of nociceptors to thermal, mechanical or chemical stimuli. Primary afferent neurons express receptors for all these substances (however not all receptors are expressed in each nociceptor). The binding of specific ligands to these receptors leads to either the activation of nociceptors directly or indirectly via second messenger cascades which in turn influence the functional state or the expression of ion channels in the cell membrane [Ringkamp and Meyer, 2009]. Through such exogenous processes, the excitability of primary afferent neurons can be greatly enhanced with lowered threshold and increased action potential frequency by suprathreshold stimulation. Nerve cells are highly innervating cells at any time; in addition to passive alteration by micro-milieu substances, they are able to release neuropeptides from their peripheral terminals. The typical examples are calcitoningene related peptide (CGRP) and substance P (SP). CGRP causes vasodilation and SP induces protein extravasation, both effects being deteriorating inflammatory processes [Aubdool and Brain, 2011].

Ectopic discharge

As mentioned above, sensory discharges originate from nerve endings in somatic and visceral tissues where the receptor potential is transduced into action potential. When injury occurs to peripheral nerves, however, other cellular compartments such as the proximal parts of injury and the dorsal root ganglia (DRG) cell bodies turn to generate action potential, an electrophysiological phenomenon referred to as ectopic discharge (ectopia) [Devor, 2009]. A feature of ectopic discharge is its mechanosensitivity, e.g., gentle and instantaneous touch of the injured nerves or spinal roots generates intense and outlasting discharges, which causes the sensation reminiscent of the stabbing or shock like sensation in patients with neuropathic pain. Thus, it is currently regarded that ectopic discharges of differential afferent fibers likely underlie the clinical manifestations called burning pain (C-fiber), dysesthesias (Aδ-fiber) or paresthesias (Aδ-fiber) resulting from nerve injury [Pasero, 2004]. Interestingly, a growing body of evidence suggests that the intact nerve neighboring injured axons may also develop ectopic activities [Shim et al., 2005].

Ectopia, which is characterized by tonic, burstic or irregular firing pattern, results from secondary changes that develop in hours and days following nerve injury [Devor, 2009]. The cellular mechanisms of ectopic impulse generation is not simply a decreased spike threshold but rather complex alterations in DRG neurons involving gene transcription, protein trafficking and ion channel kinetics.

One plausible example for these changes in DRG neurons is altered expression and location of Na⁺ channels. After nerve injury, Na_v1.3 and Na_v2 increased while Na_v1.1, 1.2, 1.6, 1.7, 1.8, 1.9 decreased in primary afferent neurons [Devor, 2006]. The distribution of Na⁺ channels also tends to accumulate in neuroma endbulbs and sprouts, rather than in the sensory nerve endings and intra-segmental parts of the node of Ranvier. The kinetics of Na⁺ channels are also modulated by proinflammatoy cytokines and other downstream mediators such as protein kinases (PKA and PKC) [Devor, 2006]. In addition to Na⁺ channels, N-type Ca²⁺ channels are also found to decrease in expression in DRG neurons [Devor, 2009]. All these quantitative and qualitative changes of channel proteins contribute to the altered electrophysiological phenotype of injured nociceptive neurons. In support of this, some clinically effective analgesics such as local anesthetic lidocaine and anticonvulsant gabapentin actually act as modulators of Na⁺ and Ca²⁺ channels, respectively [Beydoun and Backonja, 2003].

Sympathetically maintained pain

Spinal nerve comprises four types of nerve fibers, i.e., somatic afferent and efferent, and visceral afferent and efferent (sympathetic or parasympathetic) fibers. Normally, the sympathetic nervous system does not activate somatic primary afferents, while in the nerve-injured conditions, such cross-talk might occur. The responsiveness of afferent neurons to sympathetic transmitters (noradrenaline and adrenaline) is likely to contribute to causalgia, the burning pain in patients with injury in the main nerve of a limb [Bossut and Perl, 1995; Xie et al., 1995; Nickel et al., 2012]. This is evidenced by the effectiveness of systemic injection of phentolamine, the α -adrenoceptor blocker, in alleviating the pain [Ali et al., 2000]. Such pain depending on the activity of sympathetic neurons is termed sympathetically maintained pain (SMP). SMP is a symptom characterized by spontaneous pain and/or pain evoked by mechanical or thermal stimuli and may be present in the complex regional pain syndrome (CRPS) type I and type II [Drummond, 2010].

The mechanisms for SMP are not well understood despite long exhaustive efforts of researchers over tens of years. Several experimental models are, however, suggestive and influential. Following nerve section or ligation, electrical stimulation of lesioned or intact sympathetic supply excites unmyelinated and myelinated afferent fibers. This coupling is chemical and may occur via noradrenaline acting on the α 2-adrenoceptors, as the ephaptic coupling between sympathetic fibers and afferent fibers has not been experimentally validated so far [Chen et al., 1996]. In addition to this chemical coupling mechanism, aberrant structural changes can also occur between sympathetic and afferent neurons. Under healthy conditions, most sympathetic postganglionic fibers project distally to peripheral target cells via gray rami and a small quantity of fibers project proximally and usually target along blood vessels. After nerve injury, however, many proximally projecting perivascular catecholamine-containing axons start to sprout in the DRG and even form "baskets" along the cell bodies of injured nerve fibers [McLachlan et al., 1993]. The mechanisms underlying this collateral sprouting of postganglionic sympathetic fibers is partially due to the neurotrophic signals and their receptors enriched along the afferent cells with lesioned axons [Deng et al., 2000; Drummond, 2010]. Whether such pathological changes in structure are related to pain behavior in patients after peripheral nerve lesions is still uncertain and further investigations are expected.

Central mechanisms of pain

Although peripheral mechanisms play an important role in the induction and transmission of nociceptive information, it alone cannot explain all the characteristics of pathological pain. Pathological nociceptive inputs also induce central sensitization.

Central sensitization

The spinal cord is a pivotal gateway where the primary central sensory neurons exist and peripheral noxious inputs are transmitted. In chronic pain states, modification and plasticity of local neural circuits in the spinal dorsal horn (SDH) were induced. As a result, ongoing noxious information to the brain is amplified and prolonged, a phenomenon which we call central sensitization. Central sensitization is the abnormal hyperexcitability of nociceptive related neurons in the SDH following intense peripheral noxious stimuli, tissue injury or nerve damage [Zimmermann, 2001; Ji and Kohno, 2003; Fornasari, 2012]. Nociceptive information is transmitted from peripheral sites to the SDH via unmyelinated (type C) and myelinated (type A δ) fibers. Usually, central sensitization disappears when the peripheral input is reduced. However, in some serious pathological pain, central sensitization can be isolated from the peripheral nociceptive transmission. At this time, the central sensitizition exists even when the peripheral stimulation and inputs disappear. Processes that are known to contribute to hyperexcitability of dorsal horn neurons include: changes in neurotransmitters and tachykinins and in their receptors [Fundytus, 2001; Zimmermann, 2001; Harden, 2005; Seybold, 2009], aberrant remodeling of peripheral afferent fibers and the synaptic dendrites in the SDH [Tan and Chang, 2011; Tan and Waxman, 2012], and the loss of inhibitory GABAergic inputs [Bridges et al., 2001; Drew and Siddall, 2004].

Central mechanisms on the spinal cord

Neurotransmitters and tachykinins are released from the central prominence of the nociceptive neurons in the DRG. Glutamate is the main transmitter in the DRG neurons [Fundytus, 2001]. Tachykinins include SP and neurokinin and neurotension [Basbaum, 1999; Beydoun and Backojna, 2003]. In addition, different kinds of receptors are also involved in the induction and maintenance of central sensitization. There are three kinds of glutamate receptors in the SDH: the ionotropic N-methyl-D-aspartate (NMDA)

receptor, non-NMDA receptors, and metabotropic glutamate receptors. When glutamate binds to non-NMDA receptors, the receptors are opened and sodium influx depolarizes the neurons. However, under normal conditions or during weak stimulation, the channels of NMDA receptors are closed because of the presence of magnesium. When pathological pain occurs, the magnesium ion is removed by the tonic nociceptive stimulation. At this time, the increased glutamate releasing can activate the NMDA receptor in the SDH, which causes large amounts of calcium flow into the neuron [Siddall and Cousins, 1997; Gordon and Love, 2004]. Calcium ions induce second-messenger cascades that increase neuronal excitability. Thus, the NMDA receptors and their downstream molecules play an important role in nociceptive information transmission, central sensitization induction and maintenance as well as the chronic pain deterioration. Laboratorially and clinically, administration of the NMDA receptor antagonist can prevent central sensitization and inhibit pain responses of animals or patients [O'Connor and Dworkin, 2009]. After central sensitizition occurs, the neuronal excitability and sensitivity is increased and the response to nociceptive stimuli is exaggerated. This phenomenon is called "wind up" [Davies and Lodge, 1987; Herrero and Laird, 2000].

Neuropeptides also play critical roles in the induction and maintenance of central sensitization. SP and CGRP released from the central terminals of nociceptive neurons in the DRG can bind to receptors expressed on the neurons of SDH and contribute to the persistent hyperalgesia. CGRP can facilitate glutamate release through the activation of CGRP receptors on terminals of primary afferent neurons [Seybold, 2009]. Additionally, SP activates neurokinin receptors which couple to phospholipase C and several kinds of intracellular messengers. After binding to receptors, SP's downstream effects include depolarizing the membrane and facilitating the function of α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid receptor (AMPA) and NMDA receptors [Sevbold, 2009]. In addition, both CGRP and SP can activate transcription factors and then increase the expression of related genes that contribute to long-term changes in the excitability of SDH neurons and maintain hyperalgesia. The changes abovementioned finally induce the plasticity of the SDH which is another important factor of central sensitization.

With augmented noxious inputs and prolonged activation of pain pathways, neural plasticity is occurs and remodeling of synapses in the SDH is induced. Type A-beta fibers, which originally transmit peripheral proprioceptive information, can release SP and are involved in the nociceptive inputs transmission under the pathological pain [Gracely, 1999]. More than 70% excitatory synapses are located on the dendritic spine in the CNS, specifically on pyramidal cells and neurons in the SDH. Dendritic spines can receive highly convergant inputs from different origination [Yuste and Majewska, 2001], and then regulate synaptic transmission [Bourne and Harris, 2007]. After disease and injury, such as the pathological pain discussed here, the dendritic spine morphology can change. Mushroom shape dendritic spines are increased, which indicates the increased synaptic efficacy. New dendritic spines grow from the dendrites of neurons, which can provide more postsynaptic binding sites [Yuste and Majewska, 2001]. All the changes of dendritic spines contribute to the hyperexcitibility and central sensitization of spinal neurons.

The third mechanism underlying the central sensitization is the disinhibitatory action of GABAergic input in the SDH [Drew and Siddall, 2004]. The reduction of GABA release from the presynaptic terminals occurs during pathological pain, which finally induces a functional loss of GABAergic inhibition to excitatory neurons in the SDH [Cao and Yang, 2011].

Central mechanisms on supraspinal level

Recently, using an integrative research approaches in animal models, genetically manipulated mice or human patients, accumulated evidences have consistently suggested that chronic pain is due to long-term plastic changes along sensory pathways. Plastic changes not only take place in peripheral nociceptors and SDH but also in cortical areas and subcortical areas that are involved in the processing of painful information. The region of the brain activated by noxious stimuli is termed the "pain matrix", and is comprised of the primary/secondary somatosensory cortex, insular cortex, prefrontal cortex (PFC), anterior cingulate cortex (ACC), thalamus, limbic system, basal ganglia and brainstem. Neuroimaging studies reveal neuronal activity in these regions during pathological pain [Hirano, 2012]. The ACC, PFC, insular and amygdala are pain-related structures with a close morphological and functional interconnection. It is reported that synaptic plasticity occurs in these cortical or subcortical areas, such as in the ACC and amygdala [Han and Neugebauer, 2005; Zhao and Toyoda, 2005]. In addition, neuronal activities in the ACC and IC are believed to be important for pain perception and

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unpleasantness. Cortical manipulations can modulate pain behavior and pain-related memory traces. Thus, treating chronic pain requires an understanding of plastic changes in somatosensory pathways.

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Overview of pain in palliative medicine

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Introduction

The International Association for the Study of Pain has defined pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" [Merskey and Bogduk, 1994]. As such, pain is one of the most common complaints for which a patient seeks help from clinicians. Currently, 1.5 billion people worldwide suffer from chronic pain. In patients with advanced cancer, pain is the primary symptom affecting 80% to 90% of patients [Portenoy and Lesage, 1999]. Pain is both common and costly. The annual cost in lost productive time due to pain in the United States alone is estimated to be \$61.2 billion [Stewart et al., 2003]. In palliative medicine, pain can be severely debilitating and devastating.

Palliative care is an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual [WHO, 2002]. This definition reflects the complexity of palliative care and emphasizes the current goal of palliative care, which is to provide early, effective symptom management to patients with serious illnesses, regardless of whether the disease is curative or not.

Unfortunately, palliative care is often mistaken for being synonymous with hospice care. Palliative care is aimed at improving symptoms and quality of life and can be implemented and integrated at any point in the disease trajectory of a serious illness. Prognosis does not preclude palliative care in contrast to hospice care. Hospice care is a particular type of palliative care that focuses on end of life care typically for persons in the last six months of life.

The significance of pain as a symptom in palliative care/hospice care

Advanced disease is typical in patients who enter palliative or hospice care. For these patients, pain is intense, frequent, and debilitating. For instance, pain affects 70% to 90% of patients with advanced cancer [Portenoy and Lesage, 1999]. However, it is undertreated in the majority of those cases, especially among minorities [Fisch et al., 2012]. It is important to recognize that pain is seldom an isolated problem. Patients with advanced illness typically suffer from multiple concurrent symptoms, which include depression, anxiety, delirium, dyspnea, and fatigue [Dalal et al., 2006]. With disease progression, the loss of autonomy can form an agonizing downward spiral of functional deterioration influencing emotional deterioration. These factors compound the severity of pain, further perpetuating this spiral. Given the devastating impact of pain, a thorough assessment is warranted.

Assessing pain

In order to formulate an effective therapeutic strategy, the different dimensions of pain need to be assessed, including the etiology of pain, the quality and intensity of pain, how pain affects daily activities and function, and barriers to pain management. An astute clinician must differentiate between

Edmonton Sympton Numerical Scale Regional Palliative C	m As Care F	sessr ^o rogra	ment Im	Syste	m:							
Please circle the	num	ber th	nat be	est de	escril	oes:	_					
No pain	0	1	2	3	4	5	6	7	8	9	10	Worst possible pain
Not tired	0	1	2	3	4	5	6	7	8	9	10	Worst possible tiredness
Not nauseated	0	1	2	3	4	5	6	7	8	9	10	Worst possible nausea
Not depressed	0	1	2	3	4	5	6	7	8	9	10	Worst possible depression
Not anxious	0	1	2	3	4	5	6	7	8	9	10	Worst possible anxiety
Not drowsy	0	1	2	3	4	5	6	7	8	9	10	Worst possible drowsiness
Best appetite	0	1	2	3	4	5	6	7	8	9	10	Worst possible appetite
Best feeling of wellbeing	0	1	2	3	4	5	6	7	8	9	10	Worst possible feeling of wellbeing
No shortness of breath	0	1	2	3	4	5	6	7	8	9	10	Worst possible shortness of breath
Other problem	0	1	2	3	4	5	6	7	8	9	10	
Patient's Name Date		÷		Time	ə							omplete by (check one)] Patient] Caregiver

Figure 1 Edmonton symptom assessment scale (ESAS). (Reproduced, with permission, from Kantarjian H. The MD Anderson Manual of Medical Oncology. New York, NY: McGraw Hill, 2011.).

the different causes and types of pain using history and physical and other available tools, including nonverbal cues and body language, radiologic imaging, and various pain scales. Pain is a complex and subjective syndrome. There are many tools to measure pain, including visual analog scales, verbal digital scales, numerical rating scales, or more complex pain questionnaires [Bruera *et al.*, 1991]. Other tools include the Brief Pain Inventory, Wisconsin Brief Pain questionnaire, the Wong-Baker Faces Scale, and the Edmonton Symptom Assessment System (*Figure 1*).

Causes and types of pain

Pain can either be acute or chronic. Acute pain occurs after trauma via nociceptive activation at the site of tissue damage and typically lasts for hours to days while the injured tissue heals. Chronic pain exceeds the expected time frame for healing and is typically perpetuated by factors other than the cause of pain.

Causes of pain

Pain in palliative care patients can be attributed to one or several causes (*Table 1*).

Types of pain

Types of pain can be separated into two categories by pathophysiology: nociceptive pain and neuropathic pain.

Nociceptive pain

- (I) Somatic: somatic pain is often well localized, usually to skin, bone, muscle, or other soft tissue. It is usually associated with tenderness or swelling and can be described as sharp, gnawing, aching.
 - (II) Visceral: visceral pain is vague and not well localized

Table 1 Causes of pain in palliative care patients
Disease related
Neuropathy secondary to uncontrolled diabetes mellitus
Tumor infiltration and nerve impingement
Treatment related
Post-surgical pain syndromes (e.g., following amputation, mastectomy, thoracotomy)
Post radiation pain (e.g., mucositis, esophagitis)
Post chemotherapy pain (e.g., chemotherapy-induced painful peripheral neuropathy, myalgia, and arthralgia)
Pre-existing pain
Chronic and or pre-existing pain (e.g., fibromyalgia, low back pain, post-herpetic neuralgia, osteoarthritis)
Psychosocial pain
Spiritual pain (e.g., pain deep within the soul)
Total pain (e.g., the suffering that encompasses all of a person's physical, psychological, social, spiritual, and practical struggles)

but may be referred to a distant structure. Visceral pain is caused by activation of pain receptors in the chest, abdomen, or pelvic areas via stretching, ischemia, inflammation, or invasion of an organ. Visceral pain is often described as deep, squeezing, aching, dull, or sickening.

Neuropathic pain

Neuropathic pain is caused by damage or disease affecting any part of the nervous system, central or peripheral. Neuropathic pain has two components: an epicritic or sharp, lancinating component and a protopathic or chronic burning component. As such, neuropathic pain is often described as burning, tingling, electrical, pinching, stabbing, sharp, shooting, or pins and needles.

Spiritual pain and total pain

Dame Cicely Saunders created the concept, "total pain" to describe the all-encompassing nature of pain within a "whole-person" framework.

Managing pain

Pharmacological and non-pharmacological treatment options

Given the complexity of pain as a syndrome, no one treatment may effectively treat pain. The delicate balance of achieving relief yet minimizing side effects must be successfully met. Careful patient selection and a thorough assessment of pain should precede the decision to initiate a trial of opioids and/or non-opioid analgesics.

Opioids including methadone and non-opioids for pain management and addressing their side effects

Opioids are commonly used in the treatment of cancer pain as recommended by the World Health Organization analgesic ladder for cancer pain [WHO, 1990]. Opioids have been shown to be slightly more effective in relieving pain and improving function in patients with various forms of chronic non-cancer pain as compared to placebo in a meta-analysis of 41 randomized trials [Furlan et al., 2006]. Guidelines such as those put forth by the World Health Organization (WHO), the National Comprehensive Cancer Network (NCCN), and American Cancer Society (ACS) exist as a systematic approach to decipher pain and to guide treatment tailored to the individual patient and pain syndrome. Please refer to Figure 2 for the WHO model. The most commonly used short-acting opioids are hydrocodone, morphine, oxycodone, hydromorphone, and fentanyl. Fentanyl is unique in that is semisynthetic and its rapid onset and relatively short duration of action make it a good choice for control of acute pain and breakthrough pain. Methadone is a completely synthetic opioid agonist and N-methyl-D-aspartate (NMDA) antagonist with unique pharmacodynamics and pharmacokinetic properties that make it a potent weapon against pain unrelieved by other potent opioids.

Much controversy exists over the use of opioids, as it is not without risk. Side effects of opioids can include hyperalgesia, constipation, nausea and vomiting, somnolence, and opioidinduced neurotoxicity such as myoclonus, delirium, and hallucinations. Even more controversy surrounds the use of methadone given the possibility of prolonged QTc intervals;

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Figure 2 World Health Organization (WHO) three-step ladder oral analgesic program for managing cancer pain. (Reproduced, with permission, from Kantarjian H. The MD Anderson Manual of Medical Oncology. New York, NY: McGraw Hill, 2011.).

however, there is limited evidence regarding the efficacy or safety between methadone and placebo, other opioids, or other analgesics. In fact, some studies have shown no prolongation of QTc interval in patients taking methadone in the palliative care setting [Reddy *et al.*, 2004; 2010]. As such, caution must be used in choosing to use methadone, carefully weighing risks and benefits of the use of methadone in the palliative care setting.

Nonopioids including acetaminophen, nonsteroidal anti-inflammatory medicines, and adjuvant therapies such as anticonvulsants, antidepressants, local and topical anesthetics, and corticosteroids have also been effective in pain relief. Nonopioids can be the primary treatment for mild pain or as an adjuvant therapy to opioid therapy for moderate to severe pain [WHO, 1990].

Interventional procedures

Various types of peripheral nerve/plexus blocks such as

intercostal nerve block, celiac plexus, hypogastric, ganglion impar block, or other interventional procedures such as vertebral augmentation, spinal cord stimulation, intrathecal drug delivery system, and radiofrequency ablation have been shown to be helpful. Neurosurgical procedures can offer yet another form of pain relief, including rhizotomy, cordotomy, myelotomy, and motor cortex stimulation [Giller 2003]. Additionally, physical therapy in patients with musculoskeletal pain can enhance exercise tolerance and aid in rehabilitation and possibly restore function.

Alternative/complementary medicine

Complementary and alternative medicine measures should be considered for symptom management as per patients' preferences or when there are limited treatment options. Complementary and alternative measures for pain management include music therapy, massage therapy, healing touch, Reiki, acupuncture, and herbal remedies. Music therapy has been shown to reduce pain scores in hospitalized palliative care patients [Gutgsell *et al.*, 2013]. The mind and body play an important role in pain management. In chronic pain, depression, anxiety, fear, and stress can amplify pain sensation. Techniques such as biofeedback, cognitive behavioral therapy, meditation, and relaxation techniques offer a mind-body approach to the control of pain [Astin, 2004].

Supportive care

A significant barrier to palliative care is its name, as some clinicians find the name more distressing in that the name may reduce hope in patients and their families. Current research supports that using the term 'supportive care' may alleviate this barrier [Fadul *et al.*, 2009]. Supportive care may better align with and depict the goal of treating total pain regardless of disease trajectory.

Advanced care planning (in regard to pain management)

Advance care planning has been shown to improve endof-life-care [Davison, 2006]. Advance care planning is a process involving discussion, decision making, and documentation of a patient's wishes once his or her health deteriorates and once he or she understands the disease trajectory and treatment options [Health & Aging, 2012]. Advance care planning often focuses on the documentation

Table 2 Pain assessment in palliative care patients
Characterize the different dimensions of the pain via a
thorough history and physical
Intensity
Temporal features: onset, course, daily fluctuation, and breakthrough pains
Location and radiation
Quality
Alleviating or aggravating factors
Characterize the of pain
Cause
Inferred pathophysiology
Characterize the effect of the pain on quality-of-life domains
Effect on function
Effect on mood, coping, and related aspects of
psychological wellbeing
Effect on role functioning and social and familial
relationships
Effect on sleep, mood, vitality, and sexual function
Clarify the extent of disease, planned treatment, and
prognosis
Clarify the nature and quality of previous testing and past treatments
Elucidate medical comorbidities
Elucidate psychiatric comorbidities
Substance use history
Depression and anxiety disorders
Personality disorders
Identify other needs for palliative care interventions
Other symptoms
Distress related to psychosocial or spiritual concerns
Caregiver burden and concrete needs
Distress related to financial concerns
Problems in communication, care coordination, and goal setting
Adapted from Portenoy, 2011.

of decisions regarding life-sustaining medical treatments in advance directives. Advance directive is but one component of advance care planning. As such, currently, there is limited research available in regard to pain management discussions, decisions, and preferences in advance care planning.

Patients are more likely to receive symptom-directed care when they understand they are terminally ill [Mack *et al.*, 2010]. Comfort measures and pain management should be extensively discussed with patients and their surrogate decision makers in conjunction with discussion of advance directives, especially if the wish is to pursue palliative treatment via nonaggressive measures and focus on quality of life and minimizing suffering.

Role of multidisciplinary team

As pain is a complex syndrome, a multidisciplinary approach is vital to therapy. Distress caused by pain, both physical and spiritual, can only be addressed through a multidisciplinary approach that focuses on depression, anxiety, spirituality, and faith. This approach opens discussion for not only more thorough advance care planning but also a more thorough assessment of pain and suffering. The multidisciplinary team includes members such as a counselor, psychologist, social worker, chaplain, physical therapist, occupational therapist, and pharmacist.

Summary

Pain is a complex issue, confounded by physiologic and psychosocial aspects, which is further compounded when patients face life-threatening illnesses and require palliative care. A thorough assessment of pain and the patient's medical and psychosocial history is crucial in order to successfully achieve relief (*Table 2*).

Pain is only one of the many symptoms but yet an ever-so pervasive one that palliative care patients face. Disturbingly, studies have reported that adequate pain control is unsatisfactory in a portion of the population [Deandrea *et al.*, 2008; van den Beuken-van Everdingen *et al.*, 2007].

Physician and philosopher Albert Schweitzer once said, "We must all die. But if I can save him from days of torture, that is what I feel is my great and ever new privilege. Pain is a more terrible lord of mankind than even death itself." As clinicians of pain medicine and palliative care, we should strive to uphold this duty and privilege of relieving a patient's pain.

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Breakthrough pain

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Introduction

Cancer pain is a serious public health issue, with prevalence rates of upwards of 70-90% in patients with advanced oncologic disease [Foley, 2004]. Breakthrough pain (BTP) is present in the majority of patients with cancer pain and may be higher in patients with certain types of cancers as well as certain characteristics and degrees of metastatic disease. BTP was present in 75% of cases of cancer-induced bone pain (CIBP) [Laird *et al.*, 2011].

BTP: definition, prevalence and characteristics

The first definition of cancer BTP published in a peerreviewed journal was presented by Portenoy and Hagen in 1989 [Portenoy and Hagen, 1989]: "BTP is a transitory increase in pain to greater than moderate intensity which occurs on a baseline pain of moderate intensity or less". Baseline pain was defined as that reported by the patient as the average pain intensity experienced for 12 or more hours during the 24 h prior to the interview [Portenoy and Hagen, 1990]. In their 1990 paper, the same authors presented the above-mentioned definition as a study definition, in addition to the following definition [Portenoy and Hagen, 1990]: "BTP is a transitory exacerbation of pain that occurs on a background of otherwise stable pain in a patient receiving chronic opioid therapy". This and other definitions essentially abolished the need for a particular intensity for baseline or BTP in order to be considered BTP.

The Scientific Committee of the Association for Palliative Medicine of Great Britain and Northern Ireland in 2008 proposed a new definition; "*BTP is a transient exacerbation of pain that occurs spontaneously or in relation to a specific predictable or unpredictable trigger, despite relatively stable and adequately controlled background pain*" [Davies *et al.*, 2009; Zeppetella, 2008], and a definition was put forth as part of the development of the Alberta BTP Assessment Tool [Hagen *et al.*, 2007; Hagen *et al.*, 2008]: "*BTP is a* transitory exacerbation of pain experienced by the patient who has relatively stable and adequately controlled baseline pain."

BTP experienced by most patients can be categorized as one of three subtypes: *incident*, idiopathic or spontaneous, and end of dose (*Table 1*) [Bennett *et al.*, 2005; Abrahm, 2005]. The incident subtype is the most common, accounting for about half of BTP episodes. Incident BTP can be predictable and directly related to musculoskeletal movements, such as coughing or turning over in bed [Portenoy and Hagen, 1990].

BTP has been reported in 40-80% of cancer patients, depending on the setting and the definition used to identify it [Davies, 2006; Portenoy *et al.*, 2004], but although there is significant variability among studies (*Table 2*), BTP is present in roughly two-thirds of cancer or hospice/palliative care patients. Portenoy and Hagen, using a questionnaire with pain intensity described on a verbal scale, showed a 64% prevalence of BTP in inpatients referred to a U.S. hospital pain service [Portenoy and Hagen, 1990]. In a study on cancer pain in U.S. veterans, 70% were found to have BTP [Hwang *et al.*, 2003]. A large, prospective, multicenter survey of pain specialists in 24 countries found that 65% of 1,095 cancer patients had BTP [Caraceni *et al.*, 2004].

Caraceni and colleagues attempted to assess the prevalence and clinical characteristics of breakthrough/ episodic pain (BP-EP) in a cross-sectional multicenter prevalence study of 240 unselected consecutive Italian patients with cancer-related chronic pain, based on clinical diagnosis and on the use of an assessment tool, the Questionnaire for Intense Episodic Pain (QUDEI) [Caraceni *et al.*, 2012a]. The QUDEI, a screening and assessment tool based on patient interview, diagnosed the presence of BP-EP in patients regularly taking analgesics for the previous three days and who had at least one pain flare in the previous 24 hours [Caraceni *et al.*, 2012a]. The estimated prevalence of BP-EP was 73% [95% confidence interval (CI), 67%, 79%] when the diagnosis was made

	Prevalence of t	oreakthrough pa	in subtypes (%)
Study	Spontaneous	Incident pain	End-of-dose	Comments
	pain (a)	(b)	failure (c)	
Portenoy & Hagen [1990]	27	43	18	12% of pain reports were 'mixed' in nature (incident and end-of-dose failure). Incident pain precipitants: movement 22%; coughing 12%; sitting 4%; touch 2%
Fine & Busch [1998]	No data	~50	No data	No further details in paper
Portenoy <i>et al.</i> [1999]	38	49	13	Incident pain precipitants: movement 27.8%; defecation 5.7%; urination 3.8%; coughing 3.7%; sitting 3.7%; breathing 1.9%; eating/drinking 1.9%
Zeppetella et al. [2000]	59	24	17	No further details in paper
Gómez-Batiste e <i>t al.</i> [2002]	32	52	15	Incident pain precipitants: movement 38%; eating/drinking 3%; defecation 2%; coughing 2%
Hwang <i>et al.</i> [2003]	17	64	19	Data based on initial assessment of patient Incident precipitants: movement 44%; coughing 4%; eating/drinking 4%; defection 2%; sitting 2%
(a) Indianathic: Not indu	read by a readi	ly identifiable (auco: laste la	proof than incident subtype: (b) Incident prodictable:

Table 1 Prevalence of breakthrough pain subtypes in studies applying standard criteria for breakthrough pain [adapted from Davies, 2006]

(a) Indiopathic: Not induced by a readily identifiable cause; lasts longer then incident subtype; (b) Incident, predictable: Consistent temporal relationship with a precipitating factor; Incident, unpredictable: Inconsistent temporal relationship with precipitating factor; (c) End of dose: Presents prior to a scheduled dose of an around-the-clock analgesic; onset is more gradual and duration is longer than either incident or idiopathic subtypes [Bennett *et al.*, 2005].

by physicians and 66% (95% CI, 60%, 72%) when the QUDEI was applied (86% agreement). When only patients with baseline pain less than or equal to six were included in the analysis, the above prevalences decreased to 67% and 60%, respectively [Caraceni *et al.*, 2012a].

Portenoy and colleagues extended published "inpatient" observations about the association between BTP and adverse effects on mood and function to populations undergoing routine treatment in the community setting and provide evidence that these associations are greater in those with noncancer pain [Portenoy *et al.*, 2010a].

Patients with BTP had greater interference on aspects of life (mood, relationships, sleep, activity, walking ability, work, enjoyment of life) than those with no BTP (P<0.01). Almost half of BTP episodes were rapid in onset (<5 min) and short in duration (<15 min) (ROBTP). Forty-four per cent of patients with BTP had pain that was unpredictable [Laird *et al.*, 2011]. Studies have shown that up to 45% of patients with CIBP report poor pain control [Meuser *et al.*, 2001; de Wit *et al.*, 2001].

Clinically meaningful BTP may impact or interfere with multiple aspects of life including activities of daily living which may adversely affect patient's quality of life. Webber *et al.* performed a qualitative study which illustrated the true impact of BTP on activities of daily living [Webber *et al.*, 2011]. Many of the participants had needed to make changes to their lifestyle, and in some cases, the changes in lifestyle were profound (e.g., giving up working). Such lifestyle changes have implications not only for the patient but also for the patient's family and the wider society. However, other participants had needed to make lesser changes to their lifestyle, which may reflect differences in BTP experience and/or BTP management. It was evident that lifestyle changes were associated with feelings of 'loss of role' and contributed to psychological distress associated with BTP [Webber *et al.*, 2011].

Zeng and colleagues assessed the levels of interference caused by pain after treatment with conventional radiotherapy using the Brief Pain Inventory (BPI). Patients experiencing lower body pain resulting from bone metastases seem to have greater levels of functional interference than those with upper body pain [Zeng *et al.*, 2011].

Clinical feature of BTP

Breakthrough pain is not a single condition, but a spectrum of very different conditions. The clinical features vary from individual to individual, and may vary within an individual

Table 2 Prevale	ence of BTP in studies applying star	idard criteria for	BIP [adapted from Davies, 2006]
Study	Population	Prevalence of BTP (%)	Comments
Portenoy &	Hospital inpatients	63	Criteria for BTP outlined in this study. 90 patients assessed;
Hagen [1990]	(pain-team referrals)-USA N=90		63 patients reported controlled background; 41 patients reported BTP
Fine & Busch	Palliative care patients	86	Only patients with pain eligible
[1998]	(home setting)-USA N=22		22 patients assessed; 22 patients reported background pain; 19 patients reported BTP
Portenoy et al.	Hospital inpatients-USA N=178	51	Only patients on regular opioid analgesics eligible
[1999]			178 patients assessed; 164 patients reported controlled background pain; 84 patients reported BTP
Zeppetella <i>et al.</i> [2000]	Hospice inpatients-UK N=414	89	381 patients assessed (33 patients not assessable); 245 patients reported background pain; 218 patients reported BTP
Fortner	Cancer patients	63	Telephone survey of cancer patients
<i>et al.</i> [2002]	(home setting)-USA N=1,000		1,000 patients assessed; 256 patients reported regular analgesic usage; 160 patients report BTP
Gómez-Batiste et al. [2002]	Palliative care patients (various settings)-Spain N=407	41	397 patients assessed (10 patients not assessable); 163 patients report BTP
Fortner <i>et al.</i> [2003]	Cancer patients (outpatient setting)-USA N=373	23	Non-specific data relating to the patients' pain scores/pain medications were used to diagnose presence of BTP
			373 patients assessed; 144 patients reported background pain;
			33 patients were deemed to have BTP
Hwang	VA hospital patients	70	Only patients with pain eligible
et al. [2003]	(in/outpatient setting)-USA N=74		74 patients assessed; 74 patients reported background pain;
			52 patients reported BTP. After a week of treatment,
			BTP prevalence decreased from 70% to 36%
	1 1 1/4 1 1/4 1		

BTP, breakthrough pain; VA, veterans affairs.

[Portenoy, 1997; Davies et al. 2008]. Nevertheless, despite variability, BTP is usually reported to be frequent in occurrence, acute in onset, short in duration, and moderateto-severe in intensity (Table 3). The clinical features of the BTP are often related to the clinical features of the background pain [Portenoy et al., 1999].

Gómez-Batiste and colleagues evaluated the prevalence of BTP among oncology patients managed by palliative care teams in Catalonia, Spain, and to characterize the frequency, intensity, and treatment of BTP episodes [Gómez-Batiste et al., 2002]. BTP can also be categorized into 2 major subpopulations: those patients with rapid onset BTP (ROBTP) [usually less than 5 minutes] and those patients with gradual onset BTP (GOBTP) [usually more than 15 minutes]. Additionally, ROBTP tends to be unpredictable and have a relatively short duration (less than 20 minutes); whereas GOBTP tends to be more predictable and have a longer duration (more than 30 minutes).

A total of 244 episodes of BTP were reported by the 163 patients experiencing BTP on the index day, for an average of 1.5 episodes per patient per day. Of the 244 BTP episodes, 60% were of rapid onset (as described by the patient) and 39% were of gradual onset. The mean (SD) duration of the BTP episodes was 33.8 (32.0) minutes, and the mean (SD) intensity of the BTP episodes was 7.3 (2.0). Slightly over half of the BTP episodes were incident pain (52%), and the most frequent trigger was mobilization (74% of incident pain episodes). The next most common triggers of incident pain, although considerably less frequent than mobilization, were ingestion (5%), defecation (4%), and coughing (3%) [Gómez-Batiste et al., 2002].

The characteristics of BTP were evaluated according

Table 3 Characte	eristics of BTP in studies	applying standard criteri	a for diagnosis [adapted from	Skinner, 2000j
Study	Duration BTP (min)	Onset of BTP	Intensity of BTP	Comments
Portenoy & Hagen [1990]	Median duration-30 (range, 1-240)	Rapid onset-43% Gradual onset-57%	Severe/excruciating-100%	Only patients with severe or excruciating pain were classified as having BTP
Fine & Busch [1998]	Median duration-52 (range <1-240)		Mean intensity-7/10 (range, 3/10-10/10)	
Portenoy <i>et al.</i> [1999]		Median time to peak intensity-3 min (range 1 sec to 30 min)	Severe/excruciating-100%	Only patients with severe or excruciating pain were classified as having BTP
Zappetella et al. [2000]	73% episodes-≤30	Rapid onset-49% Gradual onset-51%	Slight-16% Moderate-46% Severe-36% Excruciating-2%	
Gómez-Batiste et al. [2002]	Mean duration-33.8 (range, 1-180)	Rapid onset-60% Gradual onset-39% (Not recorded-1%)	Median intensity-8/10 (range, 2/10-10/10)	
Hwang <i>et al.</i> [2003]	Median duration-15 (range, 1-120)	Rapid onset-62% Gradual onset-38%	Severe/excruciating-194%	Only patients with severe or excruciating pain were classified as having BTP
BTP, breakthroug	gh pain.			

Table 3 Characteristics of BTP in studies applying standard criteria for diagnosis [adapted from Skinner, 2006]

to the type of BTP, that is, spontaneous, incident, or endof-dose failure. The type of BTP significantly influenced the onset of BTP, with approximately 76% of incident BTP episodes being unexpected or paroxysmal in onset, compared with 52% of spontaneous BTP episodes and 24% of end-of-dose episodes (P<0.0001). The type of BTP was significantly related to the duration of BTP episodes. BTP episodes of the incident type were significantly shorter than BTP episodes of the spontaneous or end-of-dose failure types, 26.7 vs. 43.9 and 36.4 minutes, respectively (P<0.0001) [Gómez-Batiste *et al.*, 2002].

The mean (SD) (minutes) duration of BTP episodes overall, was 33.8%; with 31% being less than or equal to 15 minutes, 33% being greater than 15 but less than or equal to 30 minutes, 23% being greater than 30 minutes but less than or equal to 60 minutes, 5% being greater than 60 minutes but less than or equal to 120 minutes and 2% being greater than 120 minutes (*Figure 1*) [Gómez-Batiste *et al.*, 2002].

The circadian variation of BTP was assessed in two different series (group 1, n=47; group 2, n=76) of advanced cancer patients suffering from severe chronic pain and undergoing analgesic treatment with major opioids [Saini *et al.*, 2012]. BTP episodes showed a circadian pattern, with an acrophase occurring at 10:00 a.m. (P<0.001) in all

patients. When the two series of patients were considered separately, an acrophase was similarly observed, with 60% of BTP episodes recorded between 10:00 a.m. and 6:00 p.m. The circadian rhythm of BTP was maintained after stratifying the patients according to whether they had bone metastases or visceral metastases. BTP episodes negatively correlated with quality of life [Saini *et al.*, 2012].

Assessment of BTP

The assessment of BTP is vitally important in efforts to fully appreciate how BTP affects a specific individual patient's life/lifestyle, as well as to be able to follow the patient longitudinally over time and how they are responding to therapy. Davies and colleagues identified multiple factors of an optimal BTP assessment tool [Davies *et al.*, 2009] (*Table 4*).

Haugen and colleagues performed a systematic review of the assessment and classification of cancer BTP [Haugen *et al.*, 2010]. A systematic search of the peer-reviewed literature was performed using five major databases. Of 375 titles and abstracts initially identified, 51 articles were examined in detail. Analysis of these publications indicates a range of overlapping but distinct definitions have been used







Figure 2 BTP, breakthrough pain.

to characterize BTP; 42 of the included papers presented one or more ways of classifying BTP; and while ten tools to assess patients' experience of BTP were identified, only two have been partially validated [Haugen *et al.*, 2010].

Portenoy *et al.* developed a diagnostic algorithm for BTP, which necessitated the presence of controlled background pain [Portenoy *et al.*, 1999]. Recently, Davies *et al.* adapted

Table 4 Features of an optimal breakthrough pain assessment

Based on the review findings, an optimal BTP assessment tool should include the following domains:

- Number of different BTPs
- Relation to background pain (the same or different)
- Intensity
- Temporal factors: frequency, onset, duration, course, relationship to fixed analgesic dose
- Localization (bodymap)
- Pain quality
- Treatment-related factors: exacerbating and relieving factors including precipitating events and predictability, treatment, response to treatment (time to meaningful relief), treatment satisfaction
- Interference with activities of daily living and quality of life

Portenoy's original diagnostic algorithm for BTP; the updated algorithm utilizes stricter criteria for controlled background pain than the original algorithm (Figure 2) [Davies et al., 2009]. On the basis of the above, the term BTP should not be used to describe episodes of pain that occur during the initiation and/or titration of opioid analgesics, since the patient clearly does not have controlled background pain in this situation [Davies et al., 2009]. Such episodes of pain should be termed either a "background pain flare", or simply an "exacerbation of background pain" [Davies et al., 2009]. Similarly, the term BTP should not be used to describe episodes of pain that occur shortly before the administration of the next dose of opioid analgesics ("end of dose failure"), since the patient again does not have controlled background pain in this situation [Davies et al., 2009]. It should be noted, however, that end-of-dose failure is regarded as a subtype of BTP by some experts in the field.

Hagen and colleagues developed a BTP assessment tool for research purposes and then gathered validity evidence for this BTP assessment tool, using a Delphi process involving an expert panel review [Hagen *et al.*, 2008]. Two expert panels were formed: a national panel (within Canada; n=16) and an international panel (including experts from North America, UK, Europe, the Middle East, Australia, and New Zealand; n=22). The overall level of agreement with the tool, averaged over the four evaluated aspects of all items, was 80% among national panelists and 88% among international panelists. The validity evidence gathered in this study suggests the Alberta Breakthrough Pain Assessment Tool is conceptually grounded and is

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Ia	ble 5 Association for palliative medicine of great Britain and Ireland recommendations [adapted from APM reco	mmendations, 2012]
	Recommendation	Grade of
		recommendation
1	Patients with pain should be assessed for the presence of BTP	D
2	Patients with BTP should have this pain specifically assessed	D
3	The management of BTP should be individualized	D
4	Consideration should be given to treatment of the underlying cause of the pain	D
5	Consideration should be given to avoidance/treatment of the precipitating factors of the pain	D
6	Consideration should be given to modification of the background analgesic regimen/"around the clock	D
	medication"	
7	Opioids are the "rescue medication" of choice in the management of BTP episodes	D
8	The dose of opioid "rescue medication" should be determined by individual titration	В
9	Non-pharmacological methods may be useful in the management of BTP episodes	D
10	Non-opioid analgesics may be useful in the management of BTP episodes	D
11	Interventional techniques may be useful in the management of BTP	D
12	Patients with BTP should have this pain specifically re-assessed	D

understandable by patients and clinicians.

Treatment of BTP

Mercadante and colleagues attempting to find a meaningful cut-off pain intensity for BTP changes in advanced cancer patients, studied a consecutive sample of fifty-two patients who were receiving oral morphine equivalents equal to or more than 60 mg daily, and were prescribed rapid onset opioids for the management of episodes of breakthrough cancer pain [Mercadante *et al.*, 2013]. The meaningful pain intensity for asking for a BTP medication was 7.1; 77% of patients had a pain intensity of 7-8 on a numerical scale of 0-10. The meaningful pain intensity for adequate analgesia after a BTP medication was 3.5. Similarly, 77% of patients had a pain intensity of 3-4 [Mercadante *et al.*, 2013].

Generally, opioid monotherapy has been utilized to combat BTP in practice as well as in the literature. There are no studies on the use of multiple analgesics co-administered for the treatment of BTP. However, it is conceivable that in the future "combination therapy", attempting to take advantage of synergistic effects, may be beneficial. Baba and Gomwo reported a young patient with lung cancer suffering from sudden exacerbation of symptomatic sciatica, whose pain was markedly reduced within 30 minutes by taking immediate release oxycodone 5 mg and pregabalin 75 mg simultaneously [Baba and Gomwo, 2012].

In order to simplify the pharmacologic approaches to

the treatment of BTP, two major types of BTP in palliative medicine will be considered: rapid onset BTP (ROBTP) and gradual onset BTP (GOBTP). ROBTP generally comes on and reaches a peak intensity which is usually severe within five minutes and tends to be unpredictable. The optimal pharmacologic approach to the treatment of ROBTP appears to be the use of opioids and in particular rapid onset opioids. Nonopioid agents do not currently have any nonparenteral/nonspinal formulation with a quick enough onset; although intranasal and other routes are under development for a variety of nonopioid agents (e.g., ketamine, dexmedetomidine). Traditional immediate release oral opioids [e.g., morphine sulfate immediate release (MSIR), oxycodone immediate release (OxyIR)] may be reasonable agents for a trial to treat gradual onset BTP (GOBTP).

Recommendations for opioids for BTP

In 2009, a task group of the Association for Palliative Medicine of Great Britain and Ireland published recommendations on the management of breakthrough cancer pain [Davies *et al.*, 2009]. On the basis of a review of the literature, the task group was unable to make recommendations about any individual interventions, but was able to make a series of twelve recommendations about certain generic strategies (*Table 5*). The evidence was graded according to the Scottish Intercollegiate Guidelines Network grading system for recommendations in evidence-based guidelines [Harbour and Miller, 2001]. It should be noted that most of the recommendations were based on limited evidence (i.e., grade of recommendation-D) [Harbour and Miller, 2001]. Thus, most of the recommendations were based on non-analytical studies or so-called "expert opinion".

In February 2012, the European Association for Palliative Care (EAPC) published updated recommendations on the use of opioid analgesics in the treatment of cancer pain [Caraceni *et al.*, 2012b]. These recommendations included a section on opioids for BTP, which was derived from the related review of the medical literature [Zeppetella, 2011]. The following text is taken from the EAPC web version of the recommendations [3-EAPC]:

They decided to limit the characteristics of BTP to transitory exacerbations of pain that occur on a background of stable pain otherwise adequately controlled by aroundthe-clock opioid therapy [Davies et al., 2009; Haugen et al., 2010]. The Cochrane review by Zeppetella and Ribeiro [Zeppetella and Ribeiro, 2006] was updated [Zeppetella, 2011] and a further update was undertaken to include articles published up to June, 2010. Nine studies were available as RCTs involving new formulations of transmucosal oral and intranasal fentanyl. None of the patients enrolled were opioid-naïve, they had already been exposed to variable doses of systemic opioids at doses equivalent to at least 60 mg of oral morphine daily. These studies demonstrated that the oral transmucosal and intranasal preparations were associated with better BTP outcomes than was placebo, and that oral transmucosal fentanyl was more effective than immediaterelease oral morphine. Unblinded comparisons have shown that intravenous morphine is superior to oral transmucosal fentanyl in the first 15 min but this difference is no longer evident at 30 min after administration [Mercadante et al., 2007], and that intranasal fentanyl provides a faster onset of analgesia than the oral transmucosal preparation.

"No simple relation could be demonstrated in the RCTs between the effective doses of oral transmucosal, buccal tablet, and intranasl fentanyl and the 24 h dose of opioid, but an association was evident in two open-label studies [Mercadante *et al.*, 2007; Mercadante *et al.*, 2009] and has been reported in an observational cohort study [Mercadante *et al.*, 2010]. Experienced clinicians often start treatment with doses higher than the lowest recommended for patients who are already on high doses of opioids."

"Most of these studies reported multiple adverse events, including expected opioid-related side-effects such as sedation and dizziness, as potential limitations of titration to an effective dose of transmucosal, buccal tablet, and intranasal fentanyl. The local mucosal tolerability was good, but some cases of local ulcer have been reported and data on long-term use are limited [Weinstein *et al.*, 2009]. Intravenous opioid titration and bolus administration have been also used for improving control of BTP [Radbruch *et al.*, 2011; Mercadante *et al.*, 2008]."

"The data permit a strong recommendation that pain exacerbations resulting from uncontrolled background pain should be treated with additional doses of immediate-release oral opioids, and that an appropriate titration of around-theclock opioid therapy should always precede the recourse to potent rescue opioid analgesics. BTP (e.g., incident pain) can be effectively managed with oral, immediate-release opioids or with buccal or intranasal fentanyl preparations. In some cases the buccal or intranasal fentanyl preparations are preferable to immediate-release oral opioids because of more-rapid onset of action and shorter duration of effect. Additionally, the data permit a weak recommendation that immediate-release formulations of opioids with short half-lives should be used to treat pre-emptively predictable episodes of BTP in the 20-30 min preceding the provoking maneuver/trigger".

The SIGN guidelines state that both morphine sulfate immediate release and oral transmucosal fentanyl citrate are effective in reducing breakthrough cancer pain [Cormie *et al.*, 2008]. But little evidence (and certainly not grade B evidence) supports the unlicensed use of oral morphine. Its pharmacodynamic profile also does not mirror the temporal characteristics of most episodes of breakthrough cancer pain (e.g., ROBTP). These are acute in onset, short in duration, and moderate to severe in intensity—for example, 64% of episodes last <30 minutes and 87% <60 minutes [Gomez *et al.*, 2002]. Thus, morphine's slow onset of action (onset of analgesia, 20-30 minutes; peak analgesia, 60-90 minutes) results in delayed and ineffective analgesia and its prolonged duration of effect (3-6 h) has ongoing adverse effects [Bailey and Farley, 2006].

In contrast, evidence (at least grade B) supports the licensed use of oral transmucosal fentanyl citrate (OTFC) for BTP episodes from cancer pain [Zeppetella and Ribeiro, 2006]. Its pharmacodynamic profile better mirrors the temporal characteristics of most episodes of breakthrough cancer pain (e.g., ROBTP). A Cochrane review found that OTFC lozenges produced lower pain intensity scores and higher pain relief scores than both placebo and oral morphine [Zeppetella and Ribeiro, 2006]. The Cochrane review also found no relation between the dose of fentanyl required to control BTP and the dose of opioid required to control background cancer pain, thus, there exists enough evidence to definitely state that oral transmucosal fentanyl should be titrated to "match" the

Breakthrough pain

Table 6 Rapid onset opioids [Smith, 2012a]
Oral transmucosal fentanyl citrate (OTFC) [Atiq®]
Fentanyl buccal tablet (FBT) [Fentora®]
Fentanyl buccal soluble film (FBSF) [Onsolis®]
Sublingual fentanyl (SLF) [Abstral [®]]
Fentanyl pectin nasal spray (FPNS) [Lazanda $^{\circ}$][PecFent $^{\circ}$ -in
Europe]
Fentanyl sublingual spray (FSS) [Subsys®]
Intranasal fentanyl spray (INFS) [Instanyl [®]]

level of the ROBTP and not merely "calculated" as 15% or as the background or maintenance opioid.

Treatments of BTP

Opioids

Immediate release oral morphine has, at best, an onset of action of about 30 min [Bailey and Farley, 2006]. This means that in patients with rapid-onset, short duration BTP (ROBTP), immediate release morphine will probably be ineffective. Jandhyala and colleagues reviewed the literature and used in a mixed-treatment meta-analysis to indirectly compared fentanyl preparations, morphine, and placebo for the treatment of breakthrough cancer pain [Jandhvala et al., 2013]. Their analysis incorporated five relevant studies which revealed that the fentanyl preparations provide superior pain relief than placebo in the first 30 minutes after dosing [fentanyl buccal tablet (FBT) provided 83% probability of superior pain relief, orally disintegrating table (ODT) 66%, and OTFC 73% than placebol, however, oral morphine only performed a little better than placebo (56% probability). This mixed-treatment analysis suggest that FBT, ODT, and OTFC might provide more efficacious treatment options than otal morphine for breakthrough caner pain [Jandhyala et al., 2013]. Titration of opioids to doses that control episodes of BTP may result in unacceptable opioid side-effects [Portenoy et al., 1999]. The optimal opioid formulation available to treat rapid onset BTP (ROBTP) appears to be rapid onset opioids (ROOs) (Table 6).

Fentanyl has a high lipophilicity (octanol: water partition coefficient >700), which allow it to cross quickly between plasma and central nervous target sites (transfer half-life of 4.7-6.6 min) [Lötsch *et al.*, 2013]. It undergoes first-pass metabolism via cytochrome P450 3A (bioavailability ~30% after rapid swallowing), which can be circumvented by non-intravenous formulations (bioavailability 50-90% for oral

transmucosal or intranasal formulations). Oral transmucosal and intranasal routes provide fast delivery [time to reach maximum fentanyl plasma concentrations 20 min (range, 20-180 min) and 12 min (range, 12-21 min), respectively] suitable for rapid onset of analgesia in acute pain conditions with time to onset of analgesia of 5 or 2 min, respectively. Intranasal formulations partly bypass the blood-brain barrier and deliver a fraction of the dose directly to relevant brain target sites,

a fraction of the dose directly to relevant brain target sites, providing ultra-fast analgesia for BTP [Lötsch *et al.*, 2013]. The rapid onset opioids [suboptimally termed transmucisal immediate-release fentanyl (TIRF) medicines by the US FDA] currently available, are all formulations of fentanyl but differ somewhat in their various characteristics (*Table 7*).

Oral transmucosal fentanyl citrate (OTFC)

OTFC (Actiq[®]) is a sweetened lozenge containing fentanyl citrate that is attached to a stick to help the patient sweep the medication across the buccal mucosa (lining of the cheek). Administration of the lozenge takes approximately 15 min [Actiq, 2009.] OTFC was approved in the USA in 1998 for BTP in adults with cancer who are receiving, and are tolerant of, opioid analgesics for underlying chronic cancer pain. OTFC was approved in Europe for the same indication in 2002. OTFC is available in six dose strengths—200, 400, 600, 800, 1,200, and 1,600 µg lozenges. The oral mucosal route of delivery offers some advantages. The oral mucosa is highly permeable, 20 times more than skin; and highly vascularized.

Pharmacokinetics

When the OTFC lozenge is administered as directed, 25% of the total dose of fentanyl is absorbed by the buccal mucosa and becomes systemically available. Approximately 75% of the OTFC dose is swallowed and is then absorbed from the gastrointestinal tract where two-thirds is eliminated via first-pass metabolism [Streisand *et al.*, 1991]. The bioavailability of OTFC is therefore approximately 50% of the total dose, split evenly between transmucosal and (slower) gastrointestinal absorption [Streisand *et al.*, 1991].

Clinical efficacy vs. placebo

The efficacy of OTFC has been compared against placebo in a multicenter, double-blind, randomized study of opioidtolerant patients with cancer and BTP [Farrar *et al.*, 1998]. Compared with BTP episodes in patients administered placebo, PID scores for episodes in those treated with OTFC were significantly greater from 15 min to 1 h after

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Agent Available strengths Dral transmucosal 200, 400, entanyl citrate 600, 800, 1,200, Actiq, 2011] 1,600 µg Pentanyl buccal 100, 200, 300, 400, entanyl buccal Fentora, 2011] 600, 800 µg, 600, 800 µg, fentora, 2011]	Absolute bioavailability 50% compared to intravenous fentanyl 65% 71%	Fraction absorbed transmucosally 25% though buccal mucosa	T _{max} 20-40 min (range,	C _{max} 0.39-2.51 na/mL	AUC _{0-int} ª 102 ng·min/mL for	T _{1/2} 193–386 min for
Dral transmucosal 200, 400, entanyl citrate 600, 800, ACTIQ [®]) 1,200, Actiq, 2011] 1,600 µg Fentanyl buccal 100, 200, ablets (FENTORA [®]) 300, 400, Fentora, 2011] 600, 800 µg,	50% compared to intravenous fentanyl 65% 71%	25% though buccal mucosa	20-40 min (range,	0.39-2.51 na/mL	102 ng·min/mL for	193-386 min for
entanyl citrate 600, 800, ACTIQ [®]) 1,200, Actiq. 2011] 1,600 µg ⁼ entanyl buccal 100, 200, ablets (FENTORA [®]) 300, 400, Fentora, 2011] 600, 800 µg, ⁼ entanyl buccal 200, 400,	65% 71%	buccal mucosa				
ACTIQ [®]) 1,200, Actiq, 2011] 1,600 µg ⁼ entanyl buccal 100, 200, ablets (FENTORA [®]) 300, 400, Fentora, 2011] 600, 800 µg, ⁼ entanyl buccal 200, 400,	65%		20-480 min) for	for doses from	200 to 1,026 ng·min/mL	doses from
Actiq, 2011] 1,600 µg ⁼ entanyl buccal 100, 200, ablets (FENTORA®) 300, 400, Fentora, 2011] 600, 800 µg, ⁼ entanyl buccal 200, 400, ⁼ entanyl buccal 200, 800 рд,	65%		doses from	200 to 1,600 µg	for 1600 µg (AUC ₀₋₁₄₄₀)	200 to 1,600 µg
-entanyl buccal 100, 200, ablets (FENTORA [®]) 300, 400, Fentora, 2011] 600, 800 μg, -entanyl buccal 200, 400,	65%		200 to 1,600 µg			(mean)
ablets (FENTORA [®]) 300, 400, Fentora, 2011] 600, 800 µg, ⁻ entanyl buccal 200, 400, solicible film 600 800 800	71%	48% though	35-45 min (range,	0.25-1.59 ng/mL	0.98-9.05 ng·h/mL	2.63-11.70 h for
Fentora , 2011] 600, 800 μg, -entanyl buccal 200, 400, soluble film 600 800	71%	buccal mucosa	20-181 min) for	for doses from	for doses from	doses from
Tentanyl buccal 200, 400,	71%		doses from 100 to 800 µg	100 to 800 µg	100 to 800 µg	100 to 800 µg
soluble film ROD ROD		51% though	60 min (range,	0.38-2.19 ng/mL	3.46-20.43 ng·h/mL	~14 h (terminal
		buccal mucosa	45-240 min) for	for doses from	for doses from 200 µg	half life)
Onsolis") [Onsolis, 1,200 µg 2009]			800 µg dose	200 to 1,200 μg	to 1,200 µg	
Sublingual fentanyl 100, 200,	54%	N/A	30-60 min (range,	0.187-1.42 ng/mL	0.974-8.95 ng·h/mL	5.02-10.1 h for
ablet (ABSTRAL [®]) 300, 400,			16-240 min) for	for doses from	for doses from	doses from
Abstral, 2011] 600, 800 µg,			doses from	100 to 800 µg	100 to 800 µg	100 to 800 µg
			1 nn to 8nn hg			
Sublingual fentanyl 100, 200,	76%	N/A	0.69,1.25 h (range,	0.20-1.61 ng/mL	1.25-10.38 ng·h/mL	5.25-11.99 h for
spray (SUBSYS™) 400, 600,			0.08-4.00 min) for	for doses from	for doses from	doses from
Subsys, 2012] 800			doses from 100 to	100 to 800 µg	100 to 800 µg	100 to 800 µg
			800 µg			
ntranasal fentanyl 50, 100,	89%	Not relevant	12-15 min for	0.35-1.2 ng/mL	N/A	Elimination
spray (Instanyl [®]) 200 µg			doses from 50 to	for doses from		half-life 3-4 h
Entanyi, 2011] Entanyi nontin 100 400 un	NIZA	NIA	200 µg 0 32 0 35 h for	361 5 28/1 0 ma/ml	0160 E 17 070 nd.h/ml	15 OA O h for
				331.3-2044.0 pg/111L	2400.3-17,272 pg.17111L	10-24.3 11 101
າasal spray (enabling	PI states that		doses from 100 to	for doses from	for doses from	doses from
Lazanda [®]) dosing at	bioavailability is 20%		800 hg	100 to 800 µg	100 to 800 µg	100 to 800 µg
Lazanda, 2011] 100, 200, 40	0, higher than oral					
and 800 µg)	transmucosal					
	fentanyl citrate					

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information; $T_{1/2}$, half-life; T_{max} , time taken to reach C_{max} .^aUnless otherwise stated; ^bparameters based on arterial sampling.

administration (P<0.0001) [Farrar *et al.*, 1998]. Significant differences between OTFC and placebo were also evident in terms of global performance (mean scores 1.98 and 1.19 for OTFC and placebo, respectively; P<0.0001) and use of rescue medications (supplementary medication taken in addition to the initial dose of opioid for BTP; 15% *vs.* 34% of episodes, respectively; P<0.0001). In a placebo-controlled, randomized, double-blind study, the most common treatment-emergent adverse events were dizziness (17% of patients), nausea (14%), somnolence (8%), constipation (5%), asthenia (5%), confusion (4%), vomiting (3%), and pruritus (3%) [Farrar *et al.*, 1998]. Hallucinations and confusion relating to the use of OTFC have also been reported in clinical studies of this formulation [Coluzzi *et al.*, 2001].

Fentanyl buccal tablet (FBT)

The FBT Fentora® was approved in the USA in 2006 for BTP in adults with cancer pain who are receiving and are tolerant of opioid analgesics for underlying chronic cancer pain. FBT is available in doses of 100, 200, 400, 600, and 800 µg buccal tabs. FBT uses OraVescent[®] delivery technology to alter the pH of the oral environment in order to assist with dissolution and maximize absorption of fentanyl. Dissolution takes 14-25 min with FBT and does not require active participation from the patient [Fentora, 2011]. The OraVescent[®] system produces an effervescence reaction that releases carbon dioxide to produce carbonic acid in the buccal cavity. The resultant decrease in pH optimizes tablet dissolution. FBT then releases sodium carbonate to increase the pH in order to increase permeation of fentanyl through the buccal mucosa [Durfee et al., 2006; Pather et al., 2001]. The buccal pH changes orchestrated by this effervescence reaction result in a greater proportion of fentanyl being absorbed transmucosally instead of being swallowed and absorbed by the slower gastrointestinal route. Furthermore, because 50% of the fentanyl in FBT is absorbed transmucosally [Darwish et al., 2007], cytochrome P450 metabolism is bypassed to a greater extent than with traditional short-acting opioids and OTFC, so a greater proportion of fentanyl enters the systemic circulation [Darwish et al., 2006].

Pharmacokinetics

After FBT administration, fentanyl was rapidly absorbed in a dose-dependent fashion, with T_{max} ranging from 20 minutes to 4 hours postdose. Mean AUC (0- ∞) was 1.49 ng·hour/mL, and mean C_{max} was 0.237 ng/mL. However, plasma fentanyl concentration reached 80% of C_{max} within 25 minutes and was maintained through 2 hours after administration [Darwish and Xie, 2012].

In a study of 39 healthy volunteers that evaluated the single-dose pharmacokinetics of FBT (270-1,300 µg), mean $t_{1/2}$ values ranged from 6.6 to 13.2 h [Darwish *et al.*, 2006]. A lower dose of FBT (1,080 µg) provided comparable systemic exposure to that of a higher dose of OTFC (1,600 µg) [Darwish *et al.*, 2006].

Clinical efficacy vs. placebo

FBT has been shown to confer statistically and clinically significant improvements in the treatment of BTP in patients with cancer and noncancer pain in five placebocontrolled studies [Farrar *et al.*, 2010; Portenoy *et al.*, 2006; Portenoy *et al.*, 2007; Simpson *et al.*, 2007; Slatkin *et al.*, 2007]. In brief, compared with placebo, FBT demonstrated significant reductions in SPID₆₀ and PID from 10 min, significant increases in pain relief from 10 min, lower rates of rescue medication use, significantly greater medication performance assessment scores, and moderate and substantial clinically relevant improvements in pain intensity from 5 and 15 min, respectively [Farrar *et al.*, 2010; Portenoy *et al.*, 2006; Portenoy *et al.*, 2007; Slatkin *et al.*, 2007].

Fentanyl buccal soluble film (FBSF)

The fentanyl buccal soluble film (FBSF) Onsolis[™] utilizes BioErodible MucoAdhesive (BEMA[™]) technology (BioDelivery Sciences International). It was approved in the USA in 2009 for BTP in adults with cancer who are receiving and who are tolerant of opioid analgesics for chronic cancer pain. FBSF is available in doses of 200, 400, 600, 800, and 1,200 µg per film.

FBSF presents fentanyl in a layer that adheres to the inside of the patient's cheek; an outer layer isolates the fentanyl-containing layer from saliva. In this way, the FBSF minimizes the quantity of fentanyl that is swallowed in the saliva and which is consequently lost during first-pass metabolism [Vasisht *et al.*, 2010].

Pharmacokinetics

The absolute bioavailability of fentanyl from FBSF was reported to be 71%, with approximately 51% of the administered dose being absorbed through the buccal mucosa [Vasisht *et al.*, 2010]. FBSF demonstrated low intraindividual pharmacokinetic variability (coefficient of variation 7-10%) in a study of 24 healthy subjects, indicating that it would be expected to have consistent effects within a single individual in clinical practice [Davies *et al.*, 2011].

Clinical efficacy vs. placebo

The efficacy of FBSF has been assessed in a multicenter, randomized, placebo-controlled, multiple crossover study of 80 opioid-tolerant adult patients with cancer who experienced BTP. Patients were eligible to enter the doubleblind crossover period if they were successfully titrated within a 2-week period to an FBSF dose (200-1,200 µg) that provided suitable pain relief. Compared with placebo, FBSF significantly reduced pain intensity, as measured by the SPID at 30 min (SPID₃₀; 38.1 vs. 47.9, respectively; P=0.004) [Rauck et al., 2010]. A statistically significant (P<0.05) improvement with FBSF over placebo was reported for the SPID from 15 min and persisted to the last time point assessed in this study (60 min; P<0.001) [Rauck et al., 2010]. PID over time was statistically significantly greater for FBSF vs. placebo from 30 min until the final assessment (P<0.01). The percentage of BTP episodes with a 33% [64.3% for FBSF vs. 48.2% for placebo (P<0.001)] or 50% [46.3% for FBSF vs. 34.0 for placebo (P<0.005)] decrease in pain scores 60 minutes after administration was significantly greater with FBSF than with placebo [Rauck et al., 2010].

Sublingual fentanyl (SLF)

SLF (Abstral[®]) was approved in the USA for opioidtolerant adults with cancer in 2011. The sublingual mucosa is highly vascularized and has good permeability, allowing rapid absorption of fentanyl [Lennernäs *et al.*, 2010]. SLF is a tablet comprising water-soluble carrier particles that are coated with fentanyl and a mucoadhesive agent to hold the tablet under the tongue. SLF is available in doses of 100, 200, 300, 400, 600, and to 800 µg sublingual tabs. The median dose used in a Phase III study of 60 patients with cancer and BTP was 600 µg (mean, 550.8 µg) and a median of three doses were taken each day [Rauck *et al.*, 2009].

Pharmacokinetics

Total fentanyl exposure with SLF was proportional to the administered dose (dose range, 100-400 µg) in a pharmacokinetics analysis of 11 patients with cancer [Lennernäs *et al.*, 2005]. Systemic exposure and absorption increased in a linear fashion with the doses assessed, and dose proportionality was also reported for the C_{max} of SLF (100 µg 0.24 ng/mL, 200 µg 0.41 ng/mL, and 400 µg 0.91 ng/mL). T_{max} ranged from 40 to 60 minutes for the 100 and 400 µg doses, respectively [Lennernäs *et al.*, 2005].

Clinical efficacy vs. placebo

In a small crossover study of 27 adult patients with locally advanced cancer and BTP, patients received placebo and SLF 100, 200, or 400 µg for one BTP episode in a random order separated by a washout period of 1 day [Lennernäs et al., 2010]. This study did not use a preliminary titration phase to find the dose with optimum efficacy and minimal adverse events for each patient. SLF 400 µg was associated with the greatest improvements in PID when compared with placebo and the other doses assessed. SLF 400 µg demonstrated an improvement of 8.57 mm (on a 100 mm VAS) compared with placebo over the treatment period (P<0.0001) and also gave a clinically (>20 mm) and statistically significant improvement in PID at an earlier time point (15 min; P=0.005) compared with the other doses [Lennernäs et al., 2010]. Use of rescue medication was significantly less common with SLF 400 µg compared with placebo (5 vs. 15 patients, respectively; P=0.001).

Fentanyl pectin nasal spray (FPNS)

The fentanyl pectin nasal spray (FPNS), Lazanda[®] (US trade name), in the US in 2011 for BTP in adults with cancer who are receiving and who are tolerant of opioid analgesics for chronic cancer pain. The addition of pectin in FPNS promotes the formation of a gel on contact with calcium cations on the nasal mucosa, prolonging the residence time of fentanyl at the mucosa and giving a rounded pharmacokinetic profile compared with the sharp profile of non-gelling sprays [Fisher et al., 2010; Watts and Smith, 2009]. This pectinbased drug delivery system is referred to as PecSys [Watts and Smith, 2009]. The high, early C_{max} of the non-gelling sprays is reported to be indicative of a wide coefficient of variation and less predictable efficacy and tolerability [Fisher et al., 2010]. Furthermore, FPNS has demonstrated a slower decline in plasma fentanyl levels compared with non-gelling nasal sprays, suggesting that FPNS provides comparably extended analgesia vs. non-gelling intranasal formulations [Fisher et al., 2010].

Pharmacokinetics

In a study of healthy volunteers, T_{max} for FPNS was approximately 20 minutes and the C_{max} was 337 pg/mL, with a t¹/₂ mean ranging from 15-24.9 hours (depending on dose) [Fisher *et al.*, 2010].



Figure 3 Two different types of breakthrough pains (BTPs) and their "matching" opioid treatment.

Clinical efficacy vs. placebo

In a randomized, placebo-controlled study of 83 opioidtolerant patients with cancer and BTP, clinically relevant reductions of ≥ 2 points in absolute pain intensity (measured on an 11-point numeric scale) were observed within 10 min in 33% of BTP episodes treated with FPNS vs. 25% of patients given placebo (P<0.05). Clinically meaningful improvements in pain relief were also recorded at 10 min with FPNS (33% vs. 24% for placebo; P<0.01) [Taylor et al., 2010]. Rescue medication use was required within 60 min in 9% of BTP episodes treated with FPNS compared with 20% of episodes treated with placebo (P<0.001) [Taylor et al., 2010]. A number of additional endpoints were assessed in this study of FPNS and published in a separate paper [Portenoy et al., 2010b]. FPNS demonstrated significantly greater mean SPID₃₀ scores compared with placebo (6.57 vs. 4.45; P<0.0001) [Portenoy et al., 2010b]. Compared with placebo, a significantly greater proportion of patients treated with FPNS reported onset of analgesia (≥1 point-reduction in pain intensity score) from 10 min (38.4% vs. 56.2%; P<0.01). Furthermore, the reduction in pain intensity became clinically meaningful (≥2 point-reduction) for 49% of FPNStreated patients at 15 min and 63% at 30 min [Portenoy et al., 2010b]. Clinically meaningful pain relief was reported by a significantly higher proportion of patients receiving FPNS vs. placebo from 10 min (32.9 vs. 24.5; P=0.01). Rescue medication within 60 min was required during 9.4% of BTP episodes treated with FPNS compared with 20.0% of episodes treated with placebo (P<0.001) [Portenoy et al., 2010b].

Opioids

A "Triple opioid therapy (TOT) approach" to using opioid

analgesics has been proposed to treat painful osseous metastases, BTP episodes in patients who are experiencing both rapid onset BTP (ROBTP) and gradual onset BTP (GOBTP) [Smith, 2012b]. A triple opioid therapy approach utilizes three different opioid formulations [a controlled release opioid, an immediate release opioid, and a rapid onset opioid (ROO)] and attempts to match the pharmacokinetic properties of the opioid formulation with the temporal characteristics of the pain. Enteral or transdermal extended release (ER) or controlled release (CR) opioids are employed for "maintenance" therapy to control the baseline or background constant pain. The patient receiving TOT then evaluates BTP episodes; (I) if a BTP episode seems relatively predictable and gradually intensifies over a half-hour or more [Gradual Onset BTP (GOBTP)] then it may be treated early with an immediate release (IR) opioid formulation, however, (II) if a BTP episode is unpredictable and/or the intensity suddenly increases rapidly [Rapid Onset Breakthrough Pain (ROBTP)], then it should be treated with a rapid-onset opioid (Figure 3) [Smith, 2012b].

Summary

Breakthrough pain is experienced in about two thirds of patients with cancer and may significantly detract from a patient's quality of life. Although a spectrum exists it appears that there are two major types of BTP; rapid onset BTP and gradual onset BTP. Optimally, the type of analgesic chosen to treat BTP should "match" the temporal and other characteristics of the BTP.

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Part III

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Introduction

Pain is "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage" [Vervest and Schimmel, 1988]. Nearly 2/3 of individuals with advanced cancer (over half receiving anticancer therapy and one third of cancer survivors) have pain either from cancer or as sequelae of treatment [van den Beuken-van Everdingen, 2012; van den Beuken-van Everdingen *et al.*, 2007a; van den Beuken-van Everdingen *et al.*, 2007b]. Of those with pain, half to two thirds have severe pain and the same proportion will have transient flares of pain [Plante and VanItallie, 2010; Haugen *et al.*, 2010]. Despite World Health Organization guidelines, cancer pain is significantly undertreated [Apolone *et al.*, 2009].

Cancer pain can be classified temporally as acute, chronic and breakthrough pain (BTP). And intermittent acute pain may arise from a complication of cancer such as a fracture, bowel perforation, cancer progression, or as an acute complications from treatment such as mucositis [Plante and VanItallie, 2010]. BTP (or transient flares of pain) peaks in severity within minutes and is most commonly associated with bone metastases. These flares of pain are classified as spontaneous or incident (pain related to activity). Incident pain is either volitional or non-volitional [Plante and VanItallie, 2010]. Most cancer patients experience two or more distinct pains [Portenoy, 1989; Twycross and Fairfield, 1982]. Bone metastases are most commonly associated with cancer pain. Of patients with bone metastases, 60-80% experience pain [Plante and VanItallie, 2010]. Other causes for pain include infiltration of nerves by tumor resulting in plexopathies or mononeuropathies and obstruction to the lumen of hollow visceral. Pain is also prevalent among

the elderly. Over the 40% of nursing home residents have pain recorded in their Minimum Data Set Assessment. Pain severity in the elderly is moderate, present daily and occasionally excruciating [Teno *et al.*, 2001].

Assessment of pain

Pain severity is gauged through categorically descriptive scales (none, mild, moderate, severe) or numerical scales (NRS) (0= no pain, 10= severe pain) or by a visual analog scale (consisting of a 10 cm line with anchors of no pain at one end and severe pain at the other end). Categorical scales and NRS are the easiest of scales for patients to use. NRS severity is divided into mild (less than 4) moderate (5 and 6) and severe (7 or greater) [Farrar et al., 2000; Farrar et al., 2001; Farrar et al., 2010]. A 33% reduction in pain severity by NRS is considered clinically meaningful analgesia. Using a percentage reduction in pain severity by NRS is nonlinear and more likely to reflect clinical relevance than a standard 2 point reduction [Farrar et al., 2010]. A 33% reduction in pain severity by NRS is equivalent to one categorical change from severe to moderate, moderate to mild or mild to none. A 33% induction in pain severity by NRS is equivalent to a 3-point decrease in the Brief Pain Inventory score. A 50% reduction in pain intensity by NRS is equivalent to a 2-category reduction in pain severity and a 5-point reduction in pain score using the Brief Pain Inventory [Farrar et al., 2010; Hoffman et al., 2010].

Pain is a multidomain experience influenced by and influencing the meaning of pain perceived by patients. Pain severity is influenced by mood, anxiety and the spiritual state of patients. Mood, anxiety and spirituality should be addressed through nonpharmacologic modalities such as 164

acupuncture, biofeedback, distraction, hypnosis, imagery, massage, meditation, religious counseling and rituals and cognitive behavioral therapy if opioids are to be truly effective [Plante and VanItallie, 2010].

Pain should be assessed as to location, quality, radiation, referred pattern, palliative and exacerbating factors and associated symptoms. Cancer pain has been further classified into discrete syndromes based on these pain characteristics [Portenoy, 1992; Caraceni and Portenoy, 1999].

Assessment of pain by nurses in the hospital is important for accurate opioid dosing strategies. However, some nurses may have problems separating background from BTP [Rustøen *et al.*, 2013]. Dependence on nurse assessments alone may lead to inappropriate opioid dosing strategies such as increasing the around-the-clock (ATC) opioid dose where rescue doses need to be adjusted and vice versa. Patient pain diaries are frequently used to adjust opioid doses and schedules. Diaries are important since there are differences between patient 7-day recall and daily diaries pointing out out the necessity of having diaries completed as outpatients [Schneider *et al.*, 2012].

Opioid choices

The European Union Seventh Framework Project explored consensus of palliative specialists about drugs to manage symptoms at the end of life. Common symptoms recognized by consensus were dyspnea, nausea, vomiting, delirium, pain and respiratory tract secretions. Four essential drug classes were agreed upon as essential to managing symptoms commonly occurring in the dying; morphine (opioid), midazolam (or alternative benzodiazepine), haloperidol (or a neuroleptic) and an antimuscarinic drug [Lindqvist *et al.*, 2013].

The European Society for Medical Oncology clinical practice guidelines were recently published [Ripamonti *et al.*, 2012]. Recommendations are that codeine, tramadol and dihydrocodeine are appropriate for mild-to-moderate pain and morphine, methadone, oxycodone, hydromorphone, fentanyl, alfentanil, buprenorphine, diacetylmorphine, levorphanol and oxymorphone are drugs of choice for moderate to severe pain. Similar recommendations have been made by the European Association of Palliative Care (EAPC) [Caraceni *et al.*, 2012].

Opioid receptor

Three opioid receptors, mu, delta and kappa, are G protein

coupled receptors which modify neuron signaling through second messengers such as cyclic AMP, phospholipase C, various protein kinases (A and C), ion channels (potassium rectifying channels and calcium channels) and mitogen activating protein kinase (MAPKs) [Christie, 2008]. Activated opioid receptors inhibit calcium channels and adenylyl cyclase presynaptically which prevents neurotransmitter release (substance P, calcitonin gene related protein and glutamate) from presynaptic neurons. Opioids also hyperpolarize secondary afferent neuron membranes by stimulating rectifying potassium channels [Kondo et al., 2005; Collin et al., 1993; Rusin and Moises, 1995]. Receptors are coupled into homo or heterodimers, which alter signaling [George et al., 2000]. The formation of dimers is specific to regions within the CNS. Dimers have different G protein interactions, and conformations which, once bound by an opioid, will result in different receptor trafficking patterns and downstream signaling relative to monomers [Milan-Lobo and Whistler, 2011]. Multiple mu receptor subtypes are formed by way of post-translational splicing of mRNA involving exon 4 and 1 [Majumdar et al., 2011; Xu et al., 2009; Xu et al., 2011; Pasternak and Pan, 2000]. Each opioid may interact with a unique group of mu receptor subtypes. Analgesic tolerance develops through phosphorylation of opioid receptors and downregulation of expression. Analgesic tolerance is associated with superactivation of adenylyl cyclase, up-regulation of N-methyl-D-aspartate (NMDA) receptors and GABAergic neurotransmission [Sivam and Ho, 1985; Contet et al., 2008; Desantana et al., 2008; Ma and Pan, 2006; Bespalov et al., 2001]. Mu receptors form a multitude of conformations, opioid ligand stabilize mu receptors in a particular conformation which influences activation of G proteins and beta arrestin interactions, kinase activation and receptor trafficking [Kenakin, 2011]. Receptors are not "on" and "off" and opioids are not "partial" or "full" agonists [Vaidehi and Kenakin, 2010]. Certain pathways (such as the beta arrestin pathway) are responsible for particular adverse effects such as respiratory depression and constipation [Raehal et al., 2005]. Certain pathways (such as the beta arrestin pathway) are increased by inflammation [Hernandez et al., 2009]. The clinical relevance is that functional selectivity is likely to be the mechanism behind the benefits to opioid rotation and analgesic non-cross tolerance between opioids. Rotating opioids may change the receptor conformation which in turn changes downstream signaling. An important point to know is that opioid receptor affinity plays little role in functional selectivity and does not correlate with

activation of the receptor (intrinsic efficacy). For instance, buprenorphine has a high affinity for receptors but low intrinsic efficacy, therefore a unique set of G proteins are activated [Davis, 2005]. Buprenorphine, despite its "partial agonist" label, has analgesic potency equivalent to fentanyl [Mercadante *et al.*, 2007]. Opioid ligands are not only agonists but also antagonists (which block receptor activation by agonists but not basal receptor signaling) or inverse agonists (which block both agonist activation of the receptor and basal receptor signaling) [Wang *et al.*, 2004].

Variability in opioid responses among individuals

Genetic differences between individuals play a large role in the variability of opioid requirements and opioid responsiveness. There is a greater diversity of opioid pharmacodynamics than pharmacokinetics between individuals [Morgan and Picker, 1996]. There are large differences in adverse effects, analgesic tolerance, respiratory depression and psychological dependence [Hanks and Forbes, 1997]. The degree to which mu receptors are expressed in animal models influences opioid efficacy [Tremblay and Hamet, 2010]. Expressions of various mu receptor subtypes and single nucleotide polymorphisms could explain in part the variability in morphine responses [Pasternak, 2010]. A particular mu receptor subtype involves the promoter site of the mu receptor (exon 11) and results in a 6 rather than 7 transmembrane receptor structure. This subtype uniquely forms dimers with the opioid receptor-like orphan receptor, ORL-1. Opioid agonists which bind this heterodimer have great analgesic potential, no respiratory depression at analgesic doses, reduced gastrointestinal side effects, and no withdrawal [Majumdar et al., 2011]. It may be that buprenorphine which targets ORL-1 and known to have reduced respiratory depression, constipation and is a potent analgesic binds to this heterodimer [Davis, 2012a].

Drug metabolizing enzymes, cytochromes and conjugases, as well as drug transporters, influence analgesic responses. Opioid clearance and/or activation as well as distribution is greatly influence by genetic variants of cytochromes, conjugases and transporters [Tremblay and Hamet, 2010]. Amplification of CYP 2D6 influences tramadol and codeine analgesia whereas up-regulation or inhibition of CYP 3A4 influences methadone, oxycodone, and fentanyl clearance [Tremblay and Hamet, 2010; Sindrup and Brosen, 1995; Kosarac *et al.*, 2009]. Inhibition of brain P-450 arachidonate epoxygenase blocks morphine antinociception in mice. This enzyme is an intrinsic part of the mu receptor transduction mechanism. Polymorphisms influence transduction pathways and morphine responsiveness [Conroy *et al.*, 2010].

Opioids in the management of pain

The World Health Organization Analgesic Stepladder provides recommendations for the use of opioids based on pain severity alone. The analgesic stepladder fails to provide the nuances necessary for effective dosing strategies [Walsh and Mohr, 2004]. Patient demographics, history of addiction, clinical context, type of pain, co-medications, past experience with opioids, organ function, temporal pain patterns and goals of treatment (analgesia with minimal opioid-related side effects and maximum function) must be taken into account when prescribing opioids. Individualization of therapy is necessary due to differences in opioid responses between individuals [Hanks and Forbes, 1997; Vellucci, 2012; Hanks, 1991].

Patient education and communication

Prior to prescribing an opioid, patients should be asked about concerns regarding addiction, analgesic tolerance and side effects. Individuals with advanced cancer may believe that prescribing an opioid is indicative of a shortened survival. Verbal and written information should be provided to address these questions [Swift, 2012; Bennett et al., 2012]. Patients and caregivers need to know when and why a strong opioid is to be used and how effective the opioid is likely to be. Goal orientation to pain control, minimal side effects and maximum function is important. Analgesia alone should not be the primary focus. Explanation of the treatment strategy for continuous pain and transient flares of pain is important in order to avoid opioid dosing errors. Patients are frequently given sustained-release and immediate release opioids and can easily confuse the two; using immediate release preparation for continuous pain and sustained-release for BTP. Patients should understand how, when and how often to take ATC and rescue opioids and how long pain relief should last. It is important that they understand that they should not increase doses or alter dosing schedules unless instructed by a physician to do so. Patients need to understand potential side effects and signs of toxicity and when and whom to call if they are experiencing side effects. Laxatives and stool softeners should be prescribed with the first opioid dose and patients should be instructed in proactively managing constipation

with additional or alternative laxatives, suppositories or enemas. Individuals need to be instructed in safe storage of opioids to avoid children inadvertently take them or having them diverted to the streets by someone in the house. They are not to share their medication. A pain diary helps in management by providing information about severity and temporal patterns of pain. Diaries empower patients to manage their pain. Follow-up should be established and information about whom to contact out of hours is important for continuity.

Patient perceived barriers to opioid therapy

Multiple patient related barriers exist which impede the proper use of opioids for moderate to severe pain. Patients worry about addiction and analgesic tolerance. They may want to "save opioids" until absolutely necessary [Bender et al., 2008; Reid et al., 2008; Hill, 1993; Zuccaro et al., 2012]. Patients have concerns about side effects and will reduce opioids and experience more pain in order to reduce opioid related symptoms such as constipation. Patients are reluctant to draw attention to their pain and would rather have physicians focus on their disease in the short time they have in consultation. There is a misperception that analgesia masks complications or progression of cancer or that a prescription of an opioid means that end of life is near. Patients are more likely to accept opioids if educated about side effects, particularly the transient nature of nausea and sedation, that occur with initial therapy. Prophylactic management of constipation with opioid therapy will improve patient compliance. Patients will be more at ease about taking opioids if they are told that the initial opioid doses are low, that changes will be incremental and based upon response and that opioids can be tapered and discontinued if necessary [Reid et al., 2008].

Opioid choices and cost-effectiveness

Opioid choices for severe and/or moderate pain include morphine, hydromorphone, oxycodone, fentanyl, methadone, oxymorphone and buprenorphine [Caraceni *et al.*, 2012]. Clinical context leads one to choose one opioid over another. Methadone is the least expensive but has complex pharmacokinetics and a large number of drug interactions. Methadone should be prescribed by physicians experienced with its use even though it is cost-effective. Patients who are prescribed an expensive opioid, at least in the United States, may not be able to afford the opioid if not covered by their insurance company or the co-pay is too expensive for their budget.

As an example of opioid pharmacoeconomics, multiple fentanyl pharmaceuticals have been developed for the purpose of managing BTP, but insurers are reluctant to have prescribers use them [Zeppetella and Ribeiro, 2002; Zeppetella and Ribeiro, 2006; Bulloch and Hutchison, 2013]. Intranasal and buccal fentanyl are superior to placebo in managing BTP [Vissers et al., 2010a]. By responder's analysis, intranasal fentanyl was better than oral immediate release morphine with a numbers needed to treat (NNT) that was between 14-18 at 10 minutes and 12-16 at 15 minutes after dosing [Fallon et al., 2011]. In a similar trial, buccal fentanyl tablets were superior to oral oxycodone immediate release with a NNT of 25 at 15 minutes and 11 at 30 minutes after dosing [Ashburn et al., 2011]. The cost differential comparing fentanyl to inexpensive immediate release opioids is greater than \$500,000 US. per year depending on the number of doses used per day [Davis, 2012b]. In light of the large cost differential and the marginal response difference between fentanyl and immediate release opioids, immediate release opioids (morphine and oxycodone) should be used first for BTP.

The economics of opioids in maintenance of analgesia

Transdermal opioids have better adherence, fewer gastrointestinal side effects and better patient acceptance than oral sustained-release opioids. How do transdermal opioids compare with oral sustained-release opioids when measuring quality-adjusted life days and incremental costeffectiveness? In a recent analysis, transdermal fentanyl compared to sustained release morphine cost 107,532 pounds sterling per quality adjusted life days at one month [Swift, 2012]. Therefore, it is recommended that sustained release morphine or oxycodone be preferred as maintenance therapy. Transdermal fentanyl or buprenorphine should be used in those where oral opioids are not suitable. On the other hand, transdermal opioids are less expensive than subcutaneous opioids delivered by a computer assisted delivery device (CADD) pump. There is little cost difference between transdermal buprenorphine and fentanyl. However, in the United States buprenorphine patch strengths are limited to moderate pain (5, 10 and 20 µg patches). Sublingual buprenorphine is an alternative for severe pain and is less expensive than transdermal opioids. (Of note, in the United States sublingual buprenorphine is licensed as an addiction

maintenance therapy rather than as an analgesic) [Davis, 2012b]. A 12 mcg per hour fentanyl patch is equivalent to 45 mg of daily oral morphine. A 20 mcg per hour buprenorphine patch is equivalent to 30 mg of oral morphine per day.

Dosing strategies

Starting doses, maintenance and titration strategies

Immediate release morphine, when compared to an equivalent dose of sustained release morphine, produces the same degree of pain relief [Arkinstall et al., 1989; Deschamps et al., 1992; Finn et al., 1993; Hanks et al., 1987; Klepstad et al., 2003; Knudsen et al., 1985; Walsh et al., 1992; Ventafridda et al., 1989]. There are no differences in toxicities between immediate and sustained release when assessed through multiple studies. Individual studies have suggested that there are lower rates of pruritus, dry mouth, tiredness, drowsiness, nausea, headache and constipation as well as improved sleep with sustained release morphine when compared to immediate release morphine [Klepstad et al., 2003; Ventafridda et al., 1989]. Others have reported increased toxicity with sustained release morphine and more alertness with immediate release morphine [Hanks et al., 1987]. Health related quality of life is not different between sustained release and immediate release morphine. In the same manner, there are no differences in pain relief between sustained release oxycodone and immediate release oxycodone [Kaplan et al., 1998; Parris et al., 1998; Salzman et al., 1999]. There are essentially no differences in side effects between sustained release and immediate release oxycodone. There are no randomized control trials which have compared immediate release morphine or oxycodone to transdermal fentanyl or buprenorphine as first line therapy. The quality of most studies is quite low but the multitude of studies comparing immediate and sustained release opioids are quite consistent.

Immediate release and sustained release oxycodone and morphine are equivalent when used to titrate to pain control and to maintain pain relief. There are minor cost differences between pharmaceuticals favoring immediate release opioids. However, patients may be less compliant with immediate release opioids since immediate release opioids need to be dosed every four hours. Initial doses of immediate release morphine are 5 mg every four hours, immediate release oxycodone 2.5-5 mg every four hours, sustained release morphine 15 mg every 12 hours and sustained release oxycodone 10 mg every 12 hours. Pain severity does not dictate the initial doses in opioid naïve individuals. Hydromorphone 1 mg every four hours may be substituted for immediate release oxycodone or morphine in those who are unable to take either one [Caraceni et al., 2012]. Opioids should be prescribed ATC if pain persists for greater than 50% of the day. Doses of ATC opioid should not be changed until reaching steady state which would be 20 hours for immediate release opioids and 48 hours for sustained-release opioids. Rescue opioid dose and frequency are the four hourly dose every 1-2 hours or 10-20% of the total daily opioid dose hourly [Bennett et al., 2012; Walsh, 2005; Hanks et al., 2001; Ripamonti, 2012]. There are no comparisons between immediate release or sustainedrelease opioids and transdermal fentanyl or buprenorphine for titration to pain control. In general, transdermal opioids should not be used until pain is controlled and not for titration [Bennett et al., 2012]. When titrating opioids, analgesia, side effects and function should be assessed and doses adjusted. Ideally the goal is to reduce pain severity to less than 4 on a NRS (0 to 10) and limit rescue doses except for incident pain to 4 or less, with the least number of side effects and improved sleep and activities of daily living.

For maintaining analgesia there is no difference between sustained release oxycodone and sustained release morphine. These sustained formulations are preferred over immediate release opioids for convenience and compliance. However, sustained release morphine may have more nausea and dry mouth [Caraceni *et al.*, 2011; Reid *et al.*, 2006].

Comparisons have been made between transdermal opioids and sustained-release opioids during maintenance of pain control. In cancer patients, treatment discontinuation is greater with sustained release morphine than transdermal fentanyl, mainly due to fewer side effects with fentanyl [Bekkering *et al.*, 2011]. Patients often prefer fentanyl over sustained release morphine because fentanyl is less constipating [Tassinari *et al.*, 2008]. Sustained release morphine is better than transdermal buprenorphine for treatment durations of less than one month but transdermal buprenorphine is superior to morphine for treatment durations greater than a month [Bekkering *et al.*, 2011]. More individuals discontinue sustained release morphine compared with transdermal buprenorphine for gastrointestinal side effects [Tassinari *et al.*, 2008].

Management of acute severe pain

Those in severe pain need urgent relief and should be admitted to the hospital. Opioid titration should be either via subcutaneous or intravenous routes to rapidly relieve

pain [Ripamonti, 2012]. Transdermal buprenorphine and fentanyl are inappropriate in these circumstances. Small doses of morphine, hydromorphone or fentanyl are given parenterally at frequent intervals until pain is controlled. We have used a bedside titration with 1 mg of morphine given IV each minute for ten minutes followed by a five minute respite. This is repeated ×2 or until pain is controlled. Patients are assessed for pain relief with each injection; titration is discontinued when there is a significant reduction in the NRS, usually to 6 from 10 [Walsh et al., 2004]. Others have used morphine at 2-10 minutes intervals until pain is controlled [Davis et al., 2004]. The key to success is frequent assessment and stopping when the patient perceives significant relief. Alternative opioids to morphine are hydromorphone 0.2 mg or fentanyl 20 mcg as a substitution for morphine 1 mg in titration. If subcutaneous morphine is used, we use morphine 2 mg or fentanyl 40 mcg or hydromorphone 0.4 mg every five minutes [Walsh et al., 2004]. The longer duration between doses in the subcutaneous route compared with intravenous opioids is due to the delay to maximum concentrations [Stuart-Harris et al., 2000]. Once pain relief is achieved, maintenance of analgesia requires utilizing the effective titrated doses parenterally every four hours or one fourth of the effective titrated dose given hourly as a continuous infusion. If the patient was on opioids before titration, the pre-titration opioid dose will need to be added. Naloxone should be available for respiratory depression, however this rarely occurs if titration is properly done and assessment is frequent [Davis et al., 2004].

Patient-controlled analgesia (PCA) by demand only has been used as a means to control acute pain [Davis *et al.*, 2004]. Time to pain relief is longer. There are several drawbacks to using PCA. Patients may not activate the PCA until severe pain recurs or they may fear that they will overdose themselves. In addition, patients may not be able to keep up the demand if frequent doses are required to maintain pain control.

Immediate release and sustained-release opioids have been used to treat acute pain. The same dose has been given frequently hourly to four hourly or a dose escalation strategy is used with dose increments depending on pain response [Davis *et al.*, 2004]. A recent large multiinstitutional study used oral immediate release morphine in outpatients who were either opioid naïve or had previously been on weak opioids [De Conno *et al.*, 2008]. The dosing strategy involved immediate release morphine 5 mg for those who were opioid naïve and 10 mg for those who had previously been on weak opioids. Doses were given every four hours with a double dose at night. Rescue doses were 5 and 10 mg for naïve and opioid tolerant individuals hourly as needed. Doses were adjusted daily based on the morphine use of the previous day. The primary outcome was the proportion of time in pain control defined as a 50% reduction in baseline pain severity. The proportion of time in pain control over five days was 75% using this strategy, and 45% achieved pain control for 90% of the time. Within the first 24 hours, pain control was achieved in 79%, with 50% of patients achieving pain control within eight hours. Pain severity by NRS dropped from 7.6 to 2.4 within three days and 1.7 after five days. Adverse effects were somnolence (24%), constipation (22%), vomiting (13%), nausea (10%) and confusion (7%).

Managing uncontrolled pain without dose related side effects

Opioid requirements vary greatly among patients. Patient demographics, disease characteristics and pain severity do not predicted the effective opioid dose [Scholz and Steinfath, 1996]. A cross-sectional survey of palliative care in Europe found that 90% of individuals require less than 300 mg of morphine daily [Hanks and Reid, 2005]. Each individual has their own unique minimally effective opioid dose. As a result individual titration to response will be necessary to control pain. If pain is poorly controlled, the ATC and rescue doses for non-incident pain are totaled and increased by 30-50% [Walsh et al., 2004]. If baseline pain is well-controlled but BTP poorly controlled (percentage pain relief less than 50%), then rescue doses are doubled. If there is a greater than 50% relief but still suboptimal duration of pain relief then doses are increased 50% [Walsh et al., 2004]. Initial rescue doses are the four hourly dose or 10-20% of the total daily opioid dose [Mercadante, 2011; Mercadante et al., 2010; Mercadante, 2009; Mercadante et al., 2004; Mercadante and Arcuri, 1998]. If oral immediate release opioids fail to relieve pain due to too rapid onset of BTP, then transmucosal, buccal or intranasal fentanyl should be used as a substitute [Davis, 2011].

Strategies to manage opioid side effects when pain is controlled

Nausea, vomiting, sedation, cognitive impairment, nightmares, visual and tactile hallucinations and myoclonus are opioid related side effects which may emerge during

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titration [Stone and Minton, 2011]. If side effects occur and pain is controlled then the opioid doses are reduced by 30%. Methylphenidate may be used for sedation and cognitive impairment but the evidence for benefit is weak [Stone and Minton, 2011]. Anecdotal evidence supports the use of gabapentin, dantrolene, phenytoin, carbamazepine, valproate, phenobarbital and benzodiazepines for myoclonus [Stone and Minton, 2011]. There is little evidence for antiemetics when managing opioid related nausea and vomiting [Laugsand et al., 2011]. A change in route or opioid is often required. Laxatives, enemas and methylnaltrexone are used for constipation [Licup and Baumrucker, 2011]. A recently developed pharmaceutical combination of sustained release oxycodone plus sustained-release naloxone in a 2-1 dose ratio reduces constipation relative to oxycodone alone [Mercadante and Giarratano, 2013].

Opioid dosing strategies when pain is poorly responsive and rate limiting side effects are experienced

In this subset of individuals pain is suboptimally controlled despite opioid titration and/or bothersome side effects appear during opioid titration. Twenty percent of individuals with cancer pain do not respond to the initial opioid [Hanks and Forbes, 1997]. These individuals have opioid poorly responsive pain. Yet the issue is not analgesia but rather adverse side effects which are limiting to opioid titration [Hanks and Forbes, 1997]. Several pain and patient characteristics contribute to poorly responsive pain (Table 1). Neuropathic pain generally requires higher opioid doses and/or adjuvant analgesics. The onset of and peak intensity of BTP frequently occurs before analgesia can take place with immediate release opioids [Zeppetella, 2011a; Zeppetella, 2011b; Bruera et al., 1989; Mercadante and Portenov, 2001a; Mercadante and Portenov, 2001b; Mercadante and Portenoy, 2001c]. Incident pain may be disproportionately severe relative to baseline pain and require higher opioid doses [Mercadante and Portenoy, 2001a; Mercadante and Portenoy, 2001b; Mercadante and Portenoy, 2001c; McQuay and Jadad, 1994]. Opioids induce pharmacodynamic tolerance and neuroplasticity, resulting in a pronociceptive response which, in rare circumstances leads to clinical opioid-induced hyperalgesia [Chu et al., 2008; Colvin and Fallon, 2010; Muñoz-Ramón and Galván Guijo, 2012]. Associated opioid tolerance occurs due to conditioning [Mercadante and Portenoy, 2001b; Mercadante and Portenoy, 2001c]. Tolerance to adverse effects such as sedation and nausea also develops and may improve the opioid therapeutic index over time. Tolerance generally does not appear to develop to constipation. The therapeutic window defined as the dose where toxicity occurs relative to the dose where analgesia is experienced may shift with time [Collin and Cesselin, 1991; Mao et al., 1995]. Disease progression not infrequently increases pain and opioid requirements thus increasing the risk of adverse effects. Psychological symptoms such as depression, delirium and/or anxiety reduce pain thresholds and narrow the opioid therapeutic index. The use of psychotropic drugs such as olanzapine in this particular situation may improve pain control [Khojainova et al., 2002]. Opioid metabolites may have a longer half-life than the parent drug and may accumulate resulting in delayed side effects [Mercadante and Portenoy, 2001b; Mercadante and Portenoy, 2001c]. Changing the route of administration may be important. Parenteral morphine has threefold less myoclonus compared to oral morphine and spinal opioids reduce adverse effects experienced by those on oral or systemic opioids [Samuelsson and Hedner, 1991; Vainio and Tigerstedt, 1988; Tiseo et al., 1995].

Four strategies are commonly used to manage cancer pain poorly responsive to opioids: (I) the addition of an adjuvant analgesic and reduction of the opioid dose by 30%; (II) opioid route conversion or rotation; (III) aggressive management of side effects and (IV) the use of nonpharmacologic interventions (neurolytic blocks, surgery, radiation, kyphoplasty, cognitive behavioral therapies). There are no trials which have compared approaches; choices are based on clinical context [Portenoy, 1999].

The use of adjuvant analgesics with opioids

The WHO analgesic stepladder recommends adjuvant analgesics for mild, moderate and severe pain. NSAIDs technically are not adjuvants but non-opioid analgesics. The advantages to NSAIDs with opioids include low cost, easy acquisition and benefits in multiple pain mechanisms even neuropathic pain [Dellemijn et al., 1994]. Disadvantages include increased toxicity particularly in the elderly, renal and gastrointestinal toxicity and contraindications in those with coagulopathies, thrombocytopenia, renal, cardiac or liver failure [McNicol et al., 2004]. Although NSAIDs are superior to placebo, there are marginal benefits to adding NSAIDs to opioids [McNicol et al., 2004]. These conclusions are based on poorly designed studies, population heterogeneity and a paucity of trials (most trials were of short duration, usually less than one week) [McNicol et al., 2004]. There are no studies of cyclooxygenase 2 inhibitors with opioids. There is no NSAID which is superior; choices are usually based on patient tolerance and physician experience [McNicol et al., 2004]. Combining NSAIDs with acetaminophen is superior to either alone [Wynn, 2012; Hyllested et al., 2002; Ong et al., 2010].

Gabapentin, pregabalin, tricyclic antidepressants (TCA) and selective norepinephrine and serotonin reuptake inhibitors (SNRI) treat neuropathic pain [Hayashida et al., 2008; Hayashida and Eisenach, 2008; Yang et al., 2012; Vadalouca et al., 2012]. There is analgesic synergy when a TCA and/or gabapentinoid are combined with an opioid to treat neuropathic pain [Christoph et al., 2011; Gatti et al., 2009; Gilron and Max, 2005; Gilron et al., 2005]. Because there are fewer side effects, better tolerance and fewer drug interactions with gabapentinoids, combinations of an opioid plus gabapentinoid are preferred. Analgesia occurs with lower doses of each compared with monotherapy. There is not an advantage of a gabapentinoid over duloxetine [Quilici et al., 2009]. Individuals who are not responding to gabapentin may be gain pain control by switching to pregabalin or to duloxetine or by adding duloxetine to gabapentin [Tanenberg et al., 2011; Devi et al., 2012; Saldana et al., 2012]. Combinations of lowdose TCA with gabapentin improve neuropathic pain [Gilron et al., 2009; Arai et al., 2010]. Several NSAIDs have been reported to produce synergistic analgesia in animal models of neuropathic pain [Ortega-Varela et al., 2004; Narai et al., 2012; Picazo et al., 2006]. Sodium channel blockers such as carbamazepine and lacosemide improve gabapentin antinociception in animal models [Chapman et al., 1998; McCleane, 2010]. Hence, multiple combinations of adjuvant analgesics and opioids may be considered to improve pain control. Strategies include switching adjuvants between those with complementary mechanisms of action or "adding-on" one to another. Either may be a reasonable approach when patients do not respond to a single adjuvant plus opioid combination [Smith et al., 2011; Chaparro et al., 2012]. The risk of utilizing combination adjuvants is increased drug interactions and side effects particularly with TCA and carbamazepine.

What about combining opioids at lower doses to improve analgesia and minimize side effects? The presence of multiple mu receptor subtypes, dimers and a large number of G proteins, as well as selective downstream signaling, are reasons for non-cross tolerance between opioids. Perhaps "partial rotations" are a consideration. It may be rational to believe that combining opioids amplify analgesic signals relative to a single opioid. Low doses of methadone are synergistic with morphine, morphine 6 glucuronide and codeine but not oxymorphone, oxycodone or the lipophilic opioids [Bolan et al., 2002]. Therefore, synergy is opioid ligand specific and perhaps species specific. Other combinations which have weak evidence for synergy include morphine and oxycodone, opioid receptor antagonists such as ultra low-dose naloxone or naltrexone with morphine, fentanyl prior to morphine and low-dose methadone plus morphine [Davis, 2012c; Fallon and Laird, 2011]. The downside to using opioid combinations include the complexity of dosing strategy, risks of dosing errors, reduced patient compliance and drug interactions, as well as increased treatment costs [Davis et al., 2005]. The present evidence does not support the use of drug combinations. The use of one opioid well rather than adding opioids at low to modest doses should be done for individuals with suboptimal pain control.

Route conversions

Changing routes of opioids may improve analgesia and reduce side effects. When switching from oral to parenteral (either IV or subcutaneous) the assumption is that oral bioavailability largely determines conversion ratios. This may not be accurate for some conversions, since active metabolites influence conversion ratios [Patanwala et al.,

2007]. Conversion ratios based on single dose studies are relatively inaccurate. Subcutaneous opioid doses approximate IV doses, but in certain circumstances it can be different [Moulin, 1991; Urguhart, 1988]. Opioid bioavailability differs clinically between individuals. Clinical situations alter opioid bioavailability and dose conversion ratios. Transdermal fentanyl absorption diminishes with cachexia and age [Heiskanen et al., 2009]. This is presumably due to loss of subcutaneous tissue. Conversion ratios from oral to parenteral morphine are 2-1 or 3-1 and from oral to parenteral hydromorphone 2-1, though some claim 5-1 (largely from single dose studies) [Davis and McPherson, 2010]. The conversion of oral to parenteral methadone is either 1-1 or 2-1 since oral bioavailability is 79 (±12)% [Patanwala et al., 2007; Gourlay et al., 1986]. Pragmatically, for safety reasons, the conversion from parenteral to oral should be 1-1 and from oral to parenteral 2-1 with dose adjustments based on response. Oxycodone bioavailability is subject to cachexia. Individuals with cachexia have increased serum levels and the metabolite noroxycodone levels are lower than in normal individuals. This is associated with reduced dose escalation but also greater CNS side effects in those with cachexia. This would obviously influence conversion ratios in those countries with parenteral oxycodone and influence equianalgesia with other opioids [Naito et al., 2012]. Transdermal to parenteral fentanyl or vice versa is usually 1-1 but there is great patient variability in subcutaneous absorption [Solassol et al., 2005a; Solassol et al., 2005b]. Half of patients require dose adjustments using a conversion ratio of 1-1.

Conversion to spinal opioids is dependent on patient specific factors such as pain severity, age, initial intravenous morphine dose, neuropathic pain and the use of spinal adjuvant analgesics such as bupivacaine. There is great variability in opioid conversion ratios between individuals [Du Pen and Williams, 1994]. The epidural to subcutaneous dose ratio for morphine is 1-3 with a range of 1-1 to 1-10 [Kalso *et al.*, 1996]. The oral to intrathecal morphine conversion ratio is 300-1 and IV to intrathecal ratio is 100-1 [Krames and Lanning, 1993; Krames, 1993; Gebhardt and Kinney, 2002]. However, because the evidence for conversion ratios is weak, a set conversion ratio between intraspinal and systemic opioids cannot be recommended [Moulin, 1991].

Opioid rotation

Opioid rotation reduces pain and improves side effects in

50-80% of individuals [Estfan *et al.*, 2005; Mercadante and Caraceni, 2011; Webster and Fine, 2012]. The main reason for rotation is poorly controlled pain in the face of limiting side effects. Other reasons for rotation include costs, patient compliance and limited insurance coverage [Estfan *et al.*, 2005].

Opioid rotation requires the use of an equianalgesic table. Equianalgesia is the dose that produces equivalent analgesia to a reference opioid, usually 10 mg of oral morphine [Mercadante and Caraceni, 2011]. There are a number of drawbacks to existing equianalgesic tables. Most tables were derived from non-cancer patients with adequate organ function who are experiencing acute pain and are opioid naïve [Mercadante and Caraceni, 2011]. This population is very dissimilar to opioid tolerant cancer patients with chronic pain, organ dysfunction and polypharmacy. Evidence which supports opioid rotation does not include high quality randomized studies. The tables do not take into account clinical context such as organ function, interfering or interacting medications, reasons for rotation and the patient's previous experience with an opioid [Webster and Fine, 2012]. Incomplete cross tolerance may not be the same for each individual which limits generalizability of conversion ratios [Webster and Fine, 2012]. Conversion ratios in tables are not consistent or consistently supported by research. The values are given as point estimates rather than confidence intervals which would be more appropriate due to the variability between individuals [Webster and Fine, 2012; Shaheen et al., 2009]. Methadone has a linear or asymptotic equianalgesic relationship to morphine and hydromorphone [Mercadante and Caraceni, 2011; Mercadante and Bruera, 2006; Weschules and Bain, 2008; Pollock et al., 2011]. Conversion for morphine to methadone at high doses of morphine is particularly inaccurate [Weschules and Bain, 2008]. Opioid rotations are difficult to understand for prescribers and are subject to dosing errors [Webster and Fine, 2012]. Equianalgesia between certain opioids is bidirectionally different. Therefore, opioid rotation should not be done in a rote fashion. Equianalgesic tables should be used as guides but adjustments will need to be made (Tables 2,3).

Opioid choices and dosing strategies in organ failure

Hepatic failure

Liver function influences opioid absorption, bioavailability, distribution and elimination. Parameters which are

Table 2 Basic principles to guide opioid rotation

Consider alternative strategies such as opioid dose reduction with the addition of an adjuvant analgesic or route conversion [Estfan et al., 2005]

Involve the patient in the decision-making process and educate them about the goals of rotation which are reduced pain, reduced side effects and improved function [Fine and Portenoy, 2009]

Individualize therapy based on patient demographics, past history with opioid analgesics, pain and reasons for rotation, co-medications, organ function, comorbidity, psychosocial factors and history of addiction [Fine and Portenoy, 2009]

If pain is rapidly changing, use immediate release rather than sustained-release or transdermal opioid preparations [Fine and Portenov, 2009]

Watch for withdrawal, which may be the manifested by dysphoria, fatigue and sleep disturbances during rotation [Shi *et al.*, 2007] Reduce equianalgesic doses by 25-50%, particularly if rotation is being done for side effects more than for poor pain control [Fine and Portenoy, 2009]. The exception is methadone which has a unique rotation strategy

After dose reduction, factor in pain severity, organ function, interacting drugs, age and psychosocial factors before adjusting doses up or down [Nalamachu, 2012]. Increase or decrease doses by 10-30% based on these factors [Fine and Portenoy, 2009]

Have a strategy to frequently assess responses and titrate the new opioid to optimize outcomes. Do not adjust the dose of the new ATC opioid until reaching steady state; instead adjust the rescue dose

Initial rescue doses should be 10-20% of the total daily opioid dose

Table 3 Equianalgesic opioid doses
Oral morphine to oral oxycodone: 1.5-1
Oral morphine to oral hydromorphone: 5-1
Parenteral morphine to parenteral hydromorphone: 5-1
Oral oxycodone to oral hydromorphone: 4-1
Oral morphine to transdermal fentanyl: 100-1
Oral morphine to transdermal buprenorphine: 75-1
Transdermal fentanyl to transdermal buprenorphine: 0.6-0.8
Transdermal fentanyl to methadone: 1-17
Oral morphine to oral methadone: 4-1 if current dose is less than and 90 mg/day of morphine, 8-1 if greater than 90 mg but less
than 300 mg of morphine /day, 12-1 if greater than 400 mg oral morphine/day

*[Mercadante and Caraceni, 2011; Mercadante and Bruera, 2006; Weschules and Bain, 2008; Vissers et al., 2010b].

important to pharmacokinetics include hepatic blood flow, first pass clearance, protein binding, biliary excretion, mixed function oxidases (CYP450 enzymes) and reductases (uridine glucuronosyl transferases or UGT) [Tegeder *et al.*, 1999; Davis, 2007]. The liver is situated between the upper gastrointestinal tract and systemic circulation and is the main regulator of systemic drug exposure. It is also the organ with the greatest concentration of drug metabolizing enzymes. The liver has a dual blood supply, the hepatic artery supplies 25% and the portal vein 75% of blood flow. The exchange between drug and hepatocytes occurs in modified capillaries (sinusoids) which are adversely influenced by cirrhosis, causing intrahepatic shunting [Morgan and McLean, 1995; Reichen, 1999].

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Cirrhosis causes capillarization of sinusoids and shunts blood away from hepatocytes. Drug binding proteins such as albumin and alpha-1 acid glycoprotein are reduced, resulting in increased drug distribution. Metabolizing enzymes, particularly the CYP450 family of enzymes, are reduced as liver function worsens. Conjugases (UGT) are relatively spared. Opioids with high extraction ratios (greater than 0.7) are highly dependent on hepatic blood flow and those with a low extraction ratio (less than 0.3) are dependent on protein binding and intrinsic clearance by drug metabolizing enzymes [Wilkinson, 1987; Rowland *et al.*, 1973]. Hepatic blood flow-dependent drugs, such as morphine, have greater bioavailability in liver disease due to shunting. Oral bioavailability will approximate parenteral

levels as liver disease worsens. There will be a greater area under the curve (AUC) of serum morphine concentration over time. Procedures that produce artificial shunting (TIPS procedures and portal caval shunting) dramatically increase morphine bioavailability [Chalasani et al., 2001]. Low hepatic extraction drugs with reduced protein binding have increased free drug fractions. Bilirubin competes with drug binding sites on albumin which results in increased free fraction of drugs which are largely bound to albumin. If total drug levels are used for pharmacokinetic studies, clearance will appear to be "well preserved" [Blaschke, 1977]. Hydrophilic drugs accumulate in ascites and edema increasing the volume of distribution and delaying drug clearance [Verbeeck, 2008]. Mixed function oxidases located in the smooth endoplasmic reticulum are vulnerable to hypoxia; activity diminishes with liver disease. Conjugases, on the other hand, do not require oxygen is frequently upregulated in liver disease. In addition extrahepatic UGT contributes to drug metabolism in liver failure [Morgan and McLean, 1991; George et al., 1995; Furlan et al., 1999a; Villeneuve and Pichette, 2004]. Certain cytochrome enzymes are more adversely influenced by liver disease (CYP 2C19 > CYP2D6, CYP1A2, CYP2E1 > CYP3A4/5). Renal function is lost in late stage hepatic failure, which further reduces opioid clearances. Creatinine as a measure of renal function is inaccurate due to reduced muscle mass and impaired metabolism of creatine to creatinine. True glomerular filtration rate (GFR) will be overestimated by a factor of 2 [Proulx et al., 2005]. In addition there are pharmacodynamic alterations independent of changes in drug clearance. GABAergic tone is increased, which increases neurotoxicity (sedation) with opioids and narrows the opioid therapeutic index. In addition, opioid receptors are up-regulated in the CNS in advanced liver disease [Bergasa et al., 2002; Abboucha and Butterworth, 2004; Ahboucha et al., 2004].

Prognostic scoring systems for liver disease such as the Child-Pugh classification (which uses bilirubin, albumin, prothrombin time, the presence of encephalopathy and ascites) and the MELD score (which uses bilirubin, creatinine, international normalized ratio or INR and underlying disease) lack sensitivity in quantifying drug clearance [Verbeeck, 2008].

Codeine is metabolized to morphine by CYP 2D6 but accounts for only 5% of the drug metabolism; 80% is conjugated to codeine 6-glucuronide. Analgesia is largely dependent on codeine 6-glucuronide [Vree *et al.*, 2000]. The parent drug, codeine, is a very weak agonist [Murtagh *et al.*, 2007]. Currently, there are no studies which have looked at altered metabolism or clearance of codeine in hepatic impairment. Glucuronidation is relatively spared until very advanced liver disease; therefore analgesia with codeine would be anticipated to be preserved. With the onset of renal failure codeine 6 glucuronide accumulates leading to opioid toxicity in the hepatorenal syndrome.

Tramadol analgesia is dependent on O-demethylation by CYP 2D6. CYP 2D6 is diminished in advanced liver disease, resulting in prolonged tramadol half-life by 2.6 fold and AUC by 3.2 fold Frye *et al.*, 2006; Stamer *et al.*, 2003]. Tramadol dose intervals should be extended in the face of liver disease.

Since Tapentadol is largely glucuronidated (55%), only 15% of the drug is dependent upon mixed function oxidases. Bioavailability is increased with liver disease. In moderate liver disease the AUC is increased 4.2 fold, however half-life is marginally increased 1.4 fold [Xu *et al.*, 2010]. Individuals with moderate liver disease should have single doses limited to 50 mg and no more than three doses per day.

Oxycodone metabolism and clearance is adversely influenced by liver disease. The AUC is increased by 90%, compared with individuals with normal liver function. The maximum concentration (Cmax) is increased by 40%. The half-life of immediate release oxycodone in advanced stages of liver disease is on average, 13.9 hours with wide individual variability (4.6-24.4 hours) [Kaiko, 1997; Tallgren *et al.*, 1997]. There is an increased risk of respiratory depression with oxycodone in advanced liver disease. Doses should be decreased and intervals extended. Sustained release oxycodone should be avoided.

Morphine elimination and clearance are relatively well preserved in mild to moderate liver disease (Child Pugh class A and B) [Patwardhan et al., 1981]. In advanced liver disease, half-life increases twofold and clearance is reduced by 37% [Hasselstrom et al., 1990; Mazoit et al., 1987; Kotb et al., 1997; Crotty et al., 1989]. Oral bioavailability increases and the AUC increases fourfold in advanced hepatocellular cancer and threefold in advance cancer with extensive liver metastases [Kotb et al., 2005]. Morphine doses should be reduced and the interval increased in advanced cirrhosis, hepatocellular carcinoma and advanced liver metastases with jaundice. Morphine and morphine 6 glucuronide accumulate with the development of the hepatorenal syndrome. Sustained release morphine should be avoided in advanced liver disease and in the hepatorenal syndrome [Bosilkovska et al., 2012].

Hydromorphone bioavailability increases with advanced liver disease. The AUC increases fourfold and Cmax fourfold in moderate liver disease. Hydromorphone half-life is relatively well preserved. Dose reduction with maintenance of drug interval is recommended in moderate liver disease. However, in advanced liver disease hydromorphone half-life is prolonged and the dosing interval will need to be increased [Bosilkovska *et al.*, 2012]. With the onset of the hepatorenal syndrome hydromorphone 3 glucuronide will accumulate leading to neurotoxicity [Babul *et al.*, 1995; Hagen *et al.*, 1995].

Buprenorphine has a high first past clearance. Sublingual bioavailability is 50%. It is metabolized to norbuprenorphine, a weak agonist by CYP 3A4. Both the parent drug and metabolite are rapidly glucuronidated [Elkader and Sproule, 2005; Kuhlman et al., 1996]. Elimination is mainly through feces (80-90%). Enterohepatic recirculation is responsible, in part, for the prolonged half-life of buprenorphine [Elkader and Sproule, 2005]. The pharmacokinetics of buprenorphine in liver failure has not been studied. It is commonly used in high risk populations who are on maintenance therapy for addiction. In advanced liver disease, bioavailability increases as CYP 3A4 diminishes, but this would have little clinical relevance. Anecdotal claims of buprenorphine hepatic toxicity are not substantiated by the experience in maintenance therapy [Bogenschutz et al., 2010; Herve et al., 2004]. Glucuronidation is rate limiting to buprenorphine clearance and is relatively spared in liver disease [Davis, 2005]. Therefore, the pharmacokinetics would be expected to be relatively unchanged in liver disease, though this requires confirmation [Bosilkovska et al., 2012].

Most phenylpiperidine opioids such as fentanyl, sufentanil, alfentanil (but not remifentanil) are metabolized through CYP 3A4 and are highly protein bound. All have high first pass hepatic extraction ratios [Bosilkovska et al., 2012; Labroo et al., 1997; Kharasch et al., 2004]. Shunting increases bioavailability. Transdermal fentanyl Cmax is increased 35% and AUC 73% in cirrhotic patients [Bosilkovska et al., 2012]. Fentanyl half-life is relatively spared. However, fentanyl half-life in single dose studies is dependent on redistribution which will be normal. Once steady state is achieved and muscle and fat stores are saturated, half-life will be prolonged due to reduced CYP 3A4 in advanced liver disease. Therefore, low doses should be used. Delayed opioid toxicity may be seen with transdermal fentanyl in liver failure. Clearance is further reduced once the hepatorenal syndrome develops and blood

urea nitrogen increases [Koehntop and Rodman, 1997]. Sufentanil has a 30% increase in half-life and marginal increase in volume of distribution in liver failure. There are no studies of prolonged infusions of sufentanil in advanced liver disease [Scholz *et al.*, 1996]. Alfentanil pharmacokinetics are dramatically altered in liver disease, and there is a 50% decrease in clearance and threefold increase in AUC [Ferrier *et al.*, 1985; Baririan *et al.*, 2007]. Remifentanil is hydrolyzed in blood, at its pharmacokinetics are unchanged in liver disease. However, individuals with cirrhosis are more sensitive to respiratory depression with remifentanil [Dershwitz *et al.*, 1996; Navapurkar *et al.*, 1998].

Opioids and renal failure

Creatinine has traditionally been used to gauge renal function. However, creatinine is influenced by gender, body weight, age, muscle mass, renal tubular secretion, hydration, hepatic function, catabolic state and certain drugs [Stevens and Levey, 2005]. Creatinine clearance may be falsely increased as GFR diminishes, since creatinine tubular secretion is increased as glomerular filtration fails. A substituted mathematical formula such as the Cockcroft-Gault equation should be used to derive estimated GFR [Cockcroft and Gault, 1976]. According to estimated GFR, there are 5° of renal dysfunction which can be used to adjust doses of renally excreted drugs [Murtagh et al., 2007]. Drugs and metabolite clearances are influenced by GFR, tubular secretion and tubular reabsorption. Therefore the estimated GFR is imperfect in predicting drug clearance, and the influence of GFR on drug clearance may significantly vary depending on the parent drug and metabolite.

Codeine is mainly metabolized to codeine 6 glucuronide which is an active metabolite. Moderate to severe renal failure reduces clearance of both [Murtagh *et al.*, 2007].

Tramadol and the active metabolite O-desmethyl tramadol half-life are prolonged twofold in renal failure. Dose reduction and extended intervals between doses are required with renal failure [Izzedine *et al.*, 2002].

The active metabolite of morphine, morphine 6 glucuronide, accumulates in renal failure resulting in sedation and neurotoxicity [Osborne *et al.*, 1993; Kurella *et al.*, 2003]. Morphine dose reductions have been recommended based upon GFR; 25% for GFR between 20 and 50 milliliters per minute, 50% for GFR between 10 and 20 mL per minute, and 75% for GFR less than 10 mL per minute. This has not been firmly established clinically and is largely expert opinion [Niscola *et al.*,

Table 4 Managing pain in the elderly

Use the least invasive route to administer opioids Use a sustained-release or a transdermal formulation

Do one thing at a time, introduce one drug at a time

Start low and go slow

Allow enough time to see the benefits, do not changing until steady state is reached and appropriate assessments are made.

Constantly monitor and adjust doses or change opioids if required. Delayed opioid toxicity is more likely in the elderly due to reduced organ function.

Be ready to switch opioids. Use a conservative approach to opioid rotation (50% reduction in equianalgesia) then adjust for clinical context

2010]. It is probably safer to avoid morphine in advanced renal failure [Mercadante and Arcuri, 2004]. Hemodialysis does clear morphine and morphine 6 glucuronide but peritoneal dialysis does not [Pauli-Magnus *et al.*, 1999]. Therefore, morphine can be cautiously used in individuals on hemodialysis with the understanding that pain may worsen post dialysis. Individuals on continuous abdominal peritoneal dialysis should not be treated with morphine.

Oxycodone and its active metabolite noroxycodone (through CYP 3A4) and oxymorphone (through CYP 2D6) accumulate in renal failure [Kirvela *et al.*, 1996]. Oxycodone should be avoided if GFR is less than 60 mL per minute [Niscola *et al.*, 2010].

Hydromorphone does not accumulate in renal failure and its primary metabolite, hydromorphone 3 glucuronide, though not analgesic, accumulates in renal failure. Hydromorphone 3 glucuronide presumably produces neurtoxicity [Smith, 2000]. Since hydromorphone is dialyzed, pain may recur after dialysis. The use of hydromorphone in renal failure is safer than morphine or oxycodone. However, it should be used with caution.

Methadone is metabolized in the liver by multiple cytochromes. However, it does not accumulate in renal failure nor is it removed by dialysis. Methadone is metabolized to an inactive metabolite which is excreted in feces [Furlan *et al.*, 1999b; Lugo *et al.*, 2005]. Methadone, which normally has unpredictable pharmacokinetics, is relatively safe to use in renal failure.

Fentanyl, sufentanil and alfentanil are relatively safe in renal failure. The lipophilic opioids are not removed by dialysis [Niscola *et al.*, 2010; King *et al.*, 2011].

Buprenorphine has the safest profiles for an opioid in the elderly patients and for those with renal impairment. Though buprenorphine 3 glucuronide may accumulate in renal failure, it may be a very weak analgesic. And although norbuprenorphine is responsible for respiratory depression, this adverse effect is blocked by buprenorphine [Hand *et al.*, 1990; Summerfield *et al.*, 1985; Ohtani *et al.*, 1997; Megarbane *et al.*, 2006]. Buprenorphine has a ceiling for respiratory depression but not analgesia [Dahan *et al.*, 2005]. Individuals with renal failure requiring dialysis and on transdermal buprenorphine do not accumulate buprenorphine or norbuprenorphine [Filitz *et al.*, 2006].

Opioids and the elderly

There are no well-designed randomized trials focused on the use of opioids in the elderly patient. The elderly have reduced renal and hepatic function, altered body composition and greater sensitivity to opioid side effects [Pergolizzi et al., 2008]. The elderly respond equally well to an opioid compared with younger individuals. This is true for transdermal fentanyl, morphine and sublingual buprenorphine [Menten et al., 2002; Kaiko, 1980; Nasar et al., 1986]. Transdermal opioids increase compliance and are suitable for those with swallowing difficulties. Buprenorphine is the only sublingual long-acting opioid tablet available which could also be used for those with dysphasia [Daitch et al., 2012; Schuh and Johanson, 1999]. Principles governing the use of opioids in the elderly are outlined in Table 4. This follows the recommendations by the American Geriatrics Society [Rose, 1998].

A consensus from an international expert panel recommended transdermal fentanyl or buprenorphine for moderate to severe pain and buprenorphine for neuropathic pain in the elderly [Pergolizzi *et al.*, 2008]. The panel recommended buprenorphine if there is hepatic or renal compromise. Buprenorphine was also recommended if there is a risk for respiratory depression. Because buprenorphine is not immunosuppressive, the panel recommended buprenorphine for individuals who are elderly and/or immunocompromised [Pergolizzi *et al.*, 2008].

Summary

The use of opioids in managing cancer pain requires an understanding of opioid pharmacology in order to take advantage of the differences between opioids. Thorough knowledge of opioids and clinical experience can make a clinician facile in managing pain. The evidence base for opioid choices, rotation and uses in multiple clinical situations is weak. Individual dose responses are highly variable. Opioid choices and titration are limited by intolerable side effects. Using basic principles and guidelines result in pain relief for most individuals.

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Opioid-related adverse effects

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Introduction

Traditionally, opioids have been considered to exert their analgesic effects through actions within the central nervous system. Successful pain management with opioids requires that analgesia be achieved without excessive adverse effects. On the other hand, evidence is accumulating that opioid effects and adverse effects may be initiated by activation of opioid receptors located outside the CNS. Successful opioid therapy requires that the benefits of analgesia outweigh treatment-related adverse events. Opioid side effects impair the quality of life, increase morbidity, and may cause a patient to discontinue therapy. Most adverse effects occur at initiation of opioid therapy or when a significant dose increase occurs.

Although many patients develop tolerance to adverse effects, for other effects, such as constipation, patients do not develop tolerance, possibly due to other concomitant factors. Whereas many side effects diminish or resolve with continued opioid use, some other effects such as immune and hormonal dysfunction are more apparent after longterm therapy. The aim of this chapter is to examine the principal mechanisms underlining opioid-related adverse effects and specific adjuvant drugs most commonly used able to counteract these symptoms.

General considerations

Opioid-related adverse effects may be grouped according to the organ system that is affected, for example neurologic, gastrointestinal, and so on [Harris, 2008]. Opioid effects may also be classified as either desirable or undesirable. Although the major use of opioids is to provide analgesia, they may also be used to achieve sedation, to suppress cough and dyspnoea, and as antidiarrheal agents, depending upon the clinical indications. Finally, many adverse effects may be dependent on cancer or cancer treatments and may aggravate opioid-related toxicity. Adverse effects vary in severity and incidence, and may be associated with any opioid.

Understanding the incidence, severity, and mechanisms of adverse effects related to opioid-therapy helps an optimal management with specific adjuvant drugs, which may in turn improve the therapeutic window of opioids [Mercadante and Portenoy, 2001]. Substantially, to address opioid-related adverse effects, four options have been proposed: reducing the doses of systemic opioids, managing adverse effects with symptomatic drugs, switching opioids and/or changing route of administration. With multiple classes of opioid receptors, selective drugs may be expected to exert their analgesic activity with markedly different adverse effects profiles.

Central adverse effects

Cognitive disturbances

Sedation and impaired psychomotor function are a dosedependent effect of opioids, and frequent at the beginning of treatment or when doses are increased [Kurita *et al.*, 2009]. Tolerance develops rapidly, but this effect may often prevent dose increases necessary to pain control. The specific contribution of opioids to the cognitive impairment associated with advanced cancer is often difficult to evaluate owing to the frequent presence of multisystem impairment, metabolic alterations, and the concurrent administration of other drugs, particularly during the last week of life [Lawlor, 2002]. For these reasons, it is not surprising that there is a paucity of data selectively evaluating the cognitive effects of opioids. Although the precise mechanism of opioid-induced

Table I Drugs and mechanisms for opioid-induced sedation					
Psychostimulants	Dose (mg)	Mechanism	Adverse effects		
Dextroamphetamine	5-10	Activation of reticular-activating system	Insomnia, agitation, weight loss		
Methylphenidate	5-10	Activation of reticular-activating system	Insomnia, agitation, weight loss		
Pemoline	18	Activation of reticular-activating system	Insomnia, agitation, weight loss		
Donezepil	5	Acetylcholinesterase inhibitor	Nausea		

sedation in unknown, it is likely that opioid administration leads to a decrease in central cholinergic activity [Slatkin and Rhiner, 2003].

The effect of opioids on driving performance has been much debated. Driving is a complex task requiring integration of many functions and often co-existing disease may alter this capacity. The common concept that chronic pain patients receiving stable doses of opioids are safe to drive cannot be generalized in cancer patients, but may be applicable only to a subset of individual situations [Mailis-Gagnon et al., 2012].

Recommendations on the management of opioid-induced central adverse effects are weak as they are based on poor quality evidence [Stone and Minton, 2011]. The use of psychostimulants has been advocated in the treatment of opioid-induced sedation. The rationale behind the use of psychostimulants is that they counteract the sedation and probably also the cognitive impairment associated with the upward titration of opioid (Table 1). Although psychostimulants have been proposed as a potential treatment for hypoactivehypoalert delirium, there is clearly concern regarding the potential for aggravation of perceptual disturbance, which is not an uncommon occurrence [Lawlor, 2002].

Dextroamphetamine blocks dopamine and norepinephrine reuptake from central presynaptic neurons and facilitates catecholamine release. Dextroamphetamine also has peripheral adrenergic effects. It is absorbed in the gastrointestinal tract and is partially metabolized in the liver. Owing to wide variability in an individual's response, the smallest dose should be started. The potential for drug interaction is relevant.

Methylphenidate possesses similar activity. Methylphenidate is well absorbed from the gastrointestinal tract and undergoes de-esterification. It is primarily excreted in the urine and secondarily in bile [Slatkin and Rhiner, 2003]. Methylphenidate blocks the uptake of dopamine, by binding to the dopamine transported in the presynaptic cell membrane, and uptake of serotonin and norepinephrine by binding to the specific transporter, although this effect seems to be weak. Similar to dextroamphetamine, dosing should be individualized and administration in divided doses is recommended. Drug

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interaction is of concern. Methylphenidate has been shown to have some efficacy in reversing opioid-induced sedation in different studies in doses of 10 mg in the AM and 5 mg at noon. The maximum recommended dose is 60 mg/day [Homsi et al., 2000; Sood et al., 2006].

Pemoline is structurally dissimilar to previous drugs but causes similar central effects. Compared to other psychostimulants, pemoline is more selective in inhibiting dopamine re-uptake. Pemoline is readily absorbed from the gastrointestinal tract and is partially metabolised in the liver and excreted in the urine as both unchanged drug and metabolites. No interaction with other drugs has been reported.

New stimulants modafinil and donezepil, often used for narcolepsy and Alzheimer disease respectively, have both shown some efficacy for treatment of opioid-induced sedation in pilot studies. They are not sympathicomimetics and do not induce psychoactive events, thus lowering their abuse potential. Donezepil, an oral acetylcholinesterase inhibitor, administered in doses of 5 mg, improved the level of sedation and fatigue in patients receiving more than 200 mg/day of oral morphine equivalents [Bruera et al., 2003]. The pharmacokinetics, pharmacodynamics, safety/tolerability profile and drug interaction properties of donepezil make it an easy and safe agent to use, although controlled studies should confirm early observation. The effects of modafinil may be mediated by inhibiting the release of γ -aminobutyric acid in the cerebral cortex. Modafinil is able to induce hyperlocomotor activity without stereotyped behaviour and does involve dopamine neurons minimally [Webster et al., 2003].

Sleep disorders in cursive

It is generally known that opioids may improve sleep quality in patients with pain. More recently, it has been shown that opioids may decrease the time spent in slow-wave and rapid eye movement (REM) sleep and increase non-REM stage 2 sleep without changing total sleep time [Onen et al., 2005]. Sleep-disordered breathing is increasingly reported in patients with chronic pain receiving opioids.

Opioid-related adverse effects

Obstructive and central sleep apnea syndromes occur more frequently than in general population [Webster *et al.*, 2008]. Although the exact mechanism by which opioids disrupt sleep is unclear, it is likely that they reduce REM sleep by modulating GABA-ergic signaling via inhibition of acetylcholine release in the medial pontine reticular formation [Benjamin *et al.*, 2008].

Hyperactive delirium in cursive

Sedation or alertness is only one component of cognitive dysfunction. The cognitive change in delirium can include memory impairment, sleep-wake cycle disturbance, disorientation, perceptual disturbances. While hypoactive is more common when initiating opioid therapy, the hyperactive type or agitated delirium prevail with chronic opioid use, representing one of neurotoxic effects which also include myoclonus, hyperalgesia, and allodynia. Significant associations between opioids and delirium have been found during hospitalization [Gaudreau *et al.*, 2007].

There is a paucity of randomized controlled trials regarding sedating agents. Haloperidol, a potent antidopaminergic neuroleptic with minimal anticholinergic effects, is considered the drug of choice for the symptomatic management of hallucinations or agitated delirium. Doses of 2 mg/day are commonly started to be titrated against the effects. When doses of 5-10 mg are ineffective, levomepromazine in doses of 25 mg/day is suggested, as second choice. Midazolam is a short-acting benzodiazepine commonly used for sedation of refractory symptoms, particularly when treatment of underlying causes is unlikely. The choice of a neuroleptic or hypnotic relies on the degree of symptom distress. Newer antipsychotic agents such as olanzepine with fewer extrapyramidal side effects could be of benefit [Lawlor, 2002].

Myoclonus

Myoclonus can be a manifestation of opioid-induced neurotoxicity. It is characterized by sudden, brief, shock-like involuntary movements caused by muscular contractions. The sequence of events is usually that of a nocturnal myoclonus preceding diurnal myoclonus, which in turn might precede convulsions. It appears to be dose-related in an unpredictable manner. It is possible that multiple etiologies might be interacting in order to produce the myoclonic activity. Different mechanisms have been proposed to explain the occurrence of a series of neuromuscular disturbances probably sharing final common pathways. A neuroexcitatory opioid metabolite accumulation has been proposed to have a relevant role in determining myoclonus in patients treated with chronic opioid therapy for cancer pain, especially in the presence of renal impairment [Mercadante, 1998].

A number of drugs have been used to treat myoclonus associated with opioids but the effectiveness reported is anecdotal. Benzodiazepines, such as clonazepam, diazepam and nitrazepam, and valproate, have been proposed to treat myoclonus induced by opioids [Stone and Minton, 2011]. This is consistent with studies that support a GABAergic mechanism of opioid toxicity. Clonazepam dramatically reduced myoclonus after lorazepam failed to control the contractions in a patient treated with high doses of opioids. A continuous infusion of midazolam may result useful because of the short half-life of the drug which allows for rapid titration to an effective dose [McNicol et al., 2003]. Myoclonic activity can be interrupted by drugs with muscle relaxant effects, such as dantrolene. It has antispasmodic properties with a specific inhibitory mechanism on the calcium release at the level of the sarcoplasmatic reticulum of the striated muscle. The muscle contraction activity responded at doses of 50-100 mg of dantrolene a day. Finally, gabapentin has been reported to be effective in a series of patients [Mercadante and Portenoy, 2001].

A possible therapeutic effect may be exerted by the botulinum toxin Type A by acting selectively on peripheral cholinergic nerve endings to inhibit the release of the neurotransmitter acetylcholine at the neuromuscular junction and producing a functional and reversible denervation. Its effects can be localized to targeted muscles to inject. So far experience is lacking. Baclofen, a GABAagonist that inhibits spinal reflexes, may be a potential alternative [Mercadante, 1998].

Tolerance and hyperalgesia

Beside their usual adverse effects, limitations for the use of opioids include the development of tolerance to analgesic effects, which leads to increased doses. Opioids are supposed to inhibit the nociceptive input that activates the central glutaminergic system. However, the prolonged opioid treatment not only results in a loss of opioid antinociceptive efficacy (known as tolerance) but also leads to activation of a pro-nociceptive system manifesting as a reduction of nociceptive threshold (sensitization) or opioidinduced hyperalgesia (OIH) [Fishban *et al.*, 2009].

Two main different processes contribute to tolerance. In the first, opioids elicit an opposing reaction within the same system of the primary action. This adaptive response involves the mechanisms of desensitization, internalization, downregulation and phosphorylation of opioids receptors or heterodymerization with other receptors. Moreover drug administration may recruit different neuronal circuits that oppose the primary drug effect, for example N-Nethyl-D-Aspartate (NMDA) receptors [Szabo et al., 2002]. The development of this second process may result in an opioid-induced increase of pain sensitivity, which could be interpreted as less analgesia. Clinical reports suggest that opioids, intended to abolish pain, can unexpectedly produce abnormally heightened pain sensations, which are characterized by a lowering of the pain threshold (hyperalgesia), and pain elicited by normally innocuous stimulation (allodynia). Such abnormal sensations have been described as being quantitatively different from normal pain sensation and differentially localized from the site of the original pain complaint. These conditions are difficult to identify and controversies exist about the real occurrence of this phenomenon in clinical setting. Thus, OIH is considered as a paradoxical response to an opioid, whereby instead of an antinociceptive effect occurring, there is an abnormal increase in pain perception [Chang et al., 2007]. The problem of hyperalgesia, tolerance, and nociception remains not clearly understood and quite difficult to interpret in the clinical setting of the cancer patients, where multiple factors are able to confound the picture.

Strategies for clinical management must be based on the current understanding of the complex mechanisms underlying these problems. In a clinical scenario, in a patient with worsening pain it will be reasonable first to escalate the dose of opioids. If the patients improve and remain stable, the cause of the pain is more likely to be tolerance. Preliminary data have suggested that an unsuccessful rapid opioid escalation could be followed by adding a second opioid at minimal doses, a sort of opioid semi-switching. This technique could maintain stable the dose of the first opioid [Mercadante et al., 2004]. The use of very low doses of methadone in conjunction with adjuvant haloperidol resulted in excellent pain control without dose escalation or OIH, for both cancer and noncancer diseases [Salpeter et al., 2013]. Anecdotal reports exist of patients treated with combinations, reducing the opioid first and then adding a low dose of methadone [Wallace et al., 2013].

There have been many case reports of cancer patients with high-dose OIH whose pain resolved after reduction in dose [Zylicz and Twycross, 2008]. A gradual decrease of the dose by 25% is usually suggested. The effect is unpredictable: the pain may increase, as effect of a decreased dose, or decrease, as effect of a reduced OIH, or patient may develop symptoms of abstinence.

Some types of pain may be poorly responsive to increasing doses of opioids and rational polypharmacy could be utilized when treating any patient with pain poorly responding to opioids. Anticonvulsants or antidepressants may provide further analgesia without increasing opioid doses, although starting these classes of drugs may be complicated in this context of toxicity. They should be better employed when an increase in opioid doses is less effective than expected. The use of these drugs could prevent further opioid dose escalation or reduce their doses [Chang *et al.*, 2007; Zylicz and Twycross, 2008; Vorobeychik *et al.*, 2008].

Ketamine may offer an interesting additional sparing opioid effect [Walker and Cousins, 1997; Mercadante et al., 2003a, 2003b]. Continuous low dose subcutaneous ketamine (1 mg/kg) has been used as an adjuvant to morphine therapy in advanced cancer patients, without inducing relevant adverse effects. However, although morphine doses were reduced while on ketamine infusion, discontinuation of ketamine infusion was followed by pain increase requiring restarting ketamine. This supports the additive analgesic effect of ketamine rather than a reversal of tolerance [Bell, 1999]. Higher doses of ketamine have been administered in patients with refractory cancer pain. Burst ketamine for 3-5 days in doses of 100 to 500 mg provided an overall response of 67% of patients. After cessation of ketamine, about 70% of patients maintained some pain relief, although no specific data were provided. Psychomimetic effects occurred, the incidence rising with increasing dose, in about 30% of patients [Jackson et al., 2001]. Ketamine was used to reverse the state of tolerance and/or hyperalgesia associated with prolonged use of opioids, rather than as a real analgesic, by using a burst of two days at doses of 100 mg/day, repeated monthly. The effects were evaluated during the intervals of ketamine bursts, excluding any possible direct analgesic effect, as commonly reported during its administration. It was possible to decrease the opioid dosage in time maintaining the same level of analgesia in a patient who did not show adverse effects [Mercadante et al., 2003a]. Unfortunately, the use of ketamine is associated with psychomimetic effects which render the use of this drug problematic and requires much expertise.

It may be possible to take advantage of the asymmetric tolerance between different opioid cross-sensitivity to different opioids. In this context, OIH may add a further element of confusion in choosing the initial conversion ratio, because it should be chosen the opioid dose before

developing OIH, rather than the dose achieved in a condition where increasing doses resulted in a worsening of the clinical condition. It is likely that patients receiving high doses of opioids may have a prevalent hyperalgesic component [Sjogren et al., 1993], so that the elimination of the first opioid "per se" implicates a consequent reduction of the state of hyperexcitation, to a level of "nociception" attributable to a meaningfully actual painful input, which requires doses even lower than expected with any prudent conversion ratio. In a switch from fentanyl to methadone, the final dose of the second opioid was exaggeratedly low (200:1), probably as a consequence of disappearance of OIH [Mercadante et al., 2003b]. In these circumstances, any attempt to calculate a dose fails. In fact, part of the dose of the first opioid should be subtracted for any kind of calculation, although the exact threshold is unknown and impossible to determine. In another example it has been reported only 1% of the equianalgesic dose of the prior opioid, which was parenteral morphine in doses of 21.6 gr/day [Hagen and Swanson, 1997]. Alternately, the anti-NMDA activity of methadone may play a significant role in such circumstances, producing an acute spinal barrage in a state of exaggerated trafficking of excitatory inputs [Mercadante and Arcuri, 2005]. Finally, interventional pain management can reduce the need for opioids. An anesthetic block could be able to interrupt this process at spinal cord level. The spinal administration of local anesthetics may reduce this process, as segmental analgesia may reverse the excitatory status at the spinal cord, while providing analgesia and reducing doses of the offending opioid. Local anesthetics were hypothetized to presumably block the intense state of spinal cord hyperexcitation induced by the critical situation of poor pain control, probably aggravated by opioids given in increasing doses [Mercadante and Arcuri, 2005].

Respiratory depression

Opioids are known to cause respiratory depression, particularly in overdoses and in opioid-naives. The incidence is very low, and mainly reported in opioid-naïvepatients, with spinal route, or patient-controlled analgesia with a background infusion [Dahan *et al.*, 2010]. Increased susceptibility to respiratory depression can also occur in the elderly, obese, neonates, those with cardiovascular disease or with conditions affecting consciousness [Yamanaka and Sadikot, 2012]. Opioids could also affect patients with sleep apnea. The clinical relevance of the development of opioidinduced central sleep apnea and ataxic breathing remains to be established [Walker *et al.*, 2007].

Respiratory depression is the only adverse effect that is potentially life threatening. This effect is largely mediated by mu-receptors in tandem with antinociceptive effects. The respiratory centre of the brain is located in the pons and medulla and provides the respiratory drive. These areas interface with each other and receive several inputs from peripheral nerves and baroreceptors. Both central and peripheral pathways provide feedback into these areas affecting respiration. Stimuli, such as pain, hypoxemia, and hypercarbia, increase respiration drive. This effect is blunted by stimulation of opioid receptors, while pain acts as the physiologic antagonist of opioid-induced depression. For this reason opioids are commonly used to reduce dyspnea in advanced cancer patients. Titration of opioid doses in patients with dyspnea, did not produce higher risks of respiratory depression and increases in carbon dioxide plasma concentration [Clemens et al., 2008].

Severe respiratory depression is considered at breathing rates of less than 8-10 breaths/min. Oxygen saturation is a simple measurement commonly used to monitor respiratory depression. However, oxygen saturation and breathing frequency are surrogates indicators of respiratory drive, while the hypercapnic response is the more direct measure.

Cases of respiratory depression published in literature predominantly involved morphine in cancer patients and methadone and fentanyl in non-cancer patients. Specific factors that contributed to respiratory depression were elevated opioid plasma levels due to renal impairment and sensory deafferentation or drug-interactions [Dahan *et al.*, 2013].

Discontinuation or opioid dose adjustments are the obvious precautions in the presence of respiratory depression. In more severe cases a precise dose titration of naloxone, preferably with a continuous infusion until chances for renarcotization have diminished, is commonly used to manage this worrying adverse effect.

Gastrointestinal adverse effects

Nausea and vomiting

Opioids are one of the most important causes of chronic nausea in cancer patients, particularly after initiation of therapy or increase in dose. This disappears spontaneously within 3-4 days, after tolerance develops. Opioids cause chronic nausea by a number of mechanisms, including stimulation of chemotrigger zone, gastroparesis, constipation,

Table 2 Sites of action of anti-emetics					
Vomiting center	Vestibular center	Gastrointestinal tract			
(5HT3, H1, Ach)*	(H1, Ach)*	(5HT3)*			
scopolamine	scopolamine	metoclopramide			
antihistamines	antihistamines	setrons			
setrons					
steroids	cannabinoids				
	Vomiting center (5HT3, H1, Ach)* scopolamine antihistamines setrons steroids	Vomiting center (5HT3, H1, Ach)*Vestibular center (H1, Ach)*scopolamine antihistaminesscopolamine antihistaminessetrons cannabinoids			

and by increasing the sensitivity of the vestibular center. The etiology of nausea and vomiting is often multifactorial and several mechanisms due to the illness, comorbidity, or concomitant drugs often play a role in facilitating the development of nausea and vomiting in patients receiving opioid therapy. Before treatment of opioid-induced nausea is initiated, reversible comorbidities should be assessed and emetogenic drugs should be tapered or discontinued.

Opioid-induced nausea and vomiting have been traditionally managed with antiemetics. In an etiologic approach, identification of neurotransmitters involved is of paramount importance to select the appropriate drug class. The chemoreceptor trigger zone is on the floor of the fourth ventricle, mostly outside the blood brain barrier and as a consequence vulnerable to metabolic and chemical substances. Receptors involved are acetylcholine, dopamine, serotonin, cannabinoid and opioids. In contrast, the vomiting center is within the blood brain barrier and contains acetylcholine, dopamine, GABA, and serotonin receptors. This center also receives afferent neural fibers from the chemoreceptor trigger zone, and the glossopharyngeal, splanchnic, and vagal nerves. Peripherally, within the gastrointestinal tract there are dopamine receptors and mechanoreceptors signalling distension through the vagus nerve [Gordon et al., 2014].

Opioids exert their emetogenic effects through multiple mechanisms, principally involving a direct stimulation of chemotrigger zone, inhibition of intestinal motility, and stimulation of the vestibular apparatus, while the role of cortex is unclear [Porreca and Ossipov, 2009]. Opioids activate their receptors and signal to the vomiting center primarily via D-dopamine receptors as well as via serotonin receptors present in the chemotrigger zone. Opioid-evoked emesis mediated via the chemotrigger zone decreases with repetitive opioid administration. Signalling to the vomiting center from gastrointestinal tract occurs via serotoninergic pathways. Opioid inhibition of intestinal motility can lead to distension of the gut, increased gastrointestinal emptying times, and constipation. The vestibular apparatus is stimulated directly by opioids. Sensory input to the vomiting center occurs via the histamine H1 and cholinergic pathways. Vomiting may be more common in ambulatory patients, due to rapid movement.

Antiemetics have been selected according to their putative triggering mechanism: delayed gastric emptying, stimulation of vestibular apparatus, and/or stimulation of the chemoreceptor trigger zone (Table 2). However, nausea if often multifactorial in advanced cancer patients. Antiemetics are often associated with a number of adverse effects such as sedation, confusion, and extrapyramidal symptoms and should be not used pre-emptively [McNicol et al., 2003]. No randomized controlled trials comparing different agents in the management of opioid-induced emesis exist. Dopamine D2 antagonists with a prokinetic effect like metoclopramide have been commonly used as first line agent. Drugs with central nervous system effects can also be useful because the vestibular center has a high concentration of muscarinic cholinergic and histamine H1receptors. However this group of drugs has the potential to cause sedation which can add to opioid toxicity in some patients. In case of refractory nausea and vomiting, instead of replacing one antiemetic agent with another, it could be of benefit to add drugs with another target mechanism, potentially resulting in a synergistic effect [Harris, 2008]. In a randomized prospective trial, tropisetron was more effective than chrorpromazine and desamethasone in the management of nausea and vomiting in advanced cancer patients receiving opioids [Mystakidou et al., 1998].

Constipation

Opioids invariably cause constipation when used in repeated doses to treat cancer pain. While other common unwanted effects, such as sedation, nausea, and vomiting, tend to

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improve with continued use and often resolve completely, opioid-induced constipation does not get better with repeated administration. It is likely that other factors can contribute to slow intestinal transit, such as immobility, concomitant medications, or disease-related factors. The importance of other factors for the development of constipation is demonstrated by the fact that approximately 50% of hospice patients not on opioids require regular oral laxatives [Mercadante, 2007].

Opioids cause constipation by binding to specific opioid receptors in the enteric and central nervous system. Opioid receptors have been identified on gut smooth muscle, suggesting that there is a local effect of opioid drugs, although central opioid effects cannot be excluded. Opioids affect the intestines by different mechanisms. Opioids augment the tone and non-propulsive motility of both the ileum and the colon, thereby increasing transit time. Opioids desiccate the intraluminal content, either reducing secretion and/or increasing intestinal fluid absorption, with an indirect mechanism, possibly by tryptaminergic neurons in the myenteric plexus. This results in the release of noradrenaline, which antagonizes the secretory mechanism of the enterocytes, regulated by α -2 adrenoreceptors. Opioids may also suppress the release of the vasointestinal peptide, an inhibitory neurotransmitter. Vasointestinal peptide is a potent colonic secretagogue and an important inhibitor of smooth muscle contraction. Moreover, the prolonged bowel transit on its own may facilitate the increased intestinal absorption of fluid and electrolytes. Opioid use may lead to fecal impaction, spurious diarrhea, and bowel pseudo-obstruction, causing abdominal pain, nausea and vomiting, and interference with drug administration and absorption.

Constipation may require modification of opioid therapy. Opioid switching is a strategy for maintaining or improving analgesic quality directed toward decreasing the effects of previous opiates on the gastrointestinal tract. Present research indicates that there is a relation between type of opioid and degree of constipation, i.e., treatment with transdermal fentanyl [Radbruck *et al.*, 2000] or methadone tends to cause less constipation compared to morphine or hydromorphone. Among opioids, there may be differences in the analgesia/constipation ratio [Mercadante, 2007].

Laxatives

Traditional treatment of opioid-induced bowel constipation includes the use of laxatives, although there are limited data on the efficacy and safety of laxatives in cancer patients [Larkin *et al.*, 2008]. No data exist to guide the clinician or patient in the optimal choice of laxatives, as there have been no adequate comparative studies of long-term management of opioid-induced constipation. One of the main limitations of such trials is the lack of reliable clinical assessment tools.

Traditional treatment of opioid-induced constipation includes the use of an agent with prevalent stimulant activity (senna, danthron, bisacodyl) and a stool softener (macrogol, docusate), with lactulose sharing both actions. The dose should be titrated until a bowel action is achieved. Softening laxative doses should prevail in patients presenting colic presumably due to stimulants. The longterm effectiveness and safety of such a regimen is unclear. Although there is no correlation between the dose of opioids and the dose of laxatives, an upward titration of laxatives in parallel to increasing doses of morphine has been observed). Approximate equivalents of laxatives and typical requirements of opioid therapy have been proposed, but there is clearly large individual patient variation. However, proportionally less laxative is required at a higher opioid dose. Bulking agents can precipitate intestinal obstruction through formation of a viscous mass in the bowel, particularly in patients who are unable to swallow large volumes of water [Mercadante, 2007].

Bulk-forming agents are high-fiber foods containing polysaccharides or cellulose derivatives resistant to bacterial breakdown. These agents increase stool bulk and correct its consistency by increasing the mass and the water content of the stool. Evidence of their effect may take 24 hours or more. Their effectiveness and feasibility in the advanced cancer patient are doubtful, as they require the patients to drink extra fluids to prevent viscous mass formation.

Emollient laxatives are surfactant substances not adsorbed in the gut, acting as a detergent and facilitating the mixture of water and fat. They also promote water and electrolyte secretion. Stimulant laxatives are the most commonly used drugs to treat constipation. They are represented by the anthraquinone derivatives, such as senna, cascara, and danthron, and the diphenylmethane derivatives, such as bisacodyl and phenolphthalein. This class of drugs acts at the level of the colon and distal ileum by directly stimulating the myenteric plexus. Senna is converted to an active form by colonic bacteria. As a consequence, its site of action is primarily the colon. Danthron and the polyphenolic agents, bisacodyl and sodium picosulfate, undergo glucuronidation and are secreted in the bile. The enterohepatic circulation may prolong their effect. An increase in myoelectric colonic activity has been observed after administration of oral senna. Bisacodyl stimulates the mucosal nerve plexus, producing contractions of the entire colon and decreasing water absorption in the small and large intestine. All of these drugs may cause severe cramping. The cathartic action occurs within 1-3 days. Starting doses proposed are 15 mg daily of senna, 50 mg daily of danthron, or 10 mg daily of bisacodyl. Bisacodyl suppositories promote colonic peristalsis with a short onset due to the rapid conversion to its active metabolite by rectal flora. Docusate alone or in combination with danthron is most commonly used at doses of 100-300 mg every eight hours. The effectiveness of docusate has been questioned.

Lubricant laxatives are represented by mineral oil. It may be useful in management of transient acute constipation or fecal impaction, but has a little role in the management of chronic constipation. It lubricates the stool surface. Coated feces may pass more easily and colonic absorption of water is decreased.

Hyperosmotic agents are not broken down or absorbed in the small bowel, drawing fluid into bowel lumen. Osmotic laxatives are divided into (magnesium) salts, saccharine, alcohols and macrogols. Lactulose increases fecal weight and frequency but may result in bloating, colic, and flatulence, as well as electrolyte imbalances at high doses. Moreover, it is expensive in comparison to other preparations. The latency of action is 1-2 days. Starting doses are 15-20 mL twice a day. Orally administered, macrogol is not metabolised and pH value and bowel flora remain unchanged. Macrogol hydrates hardened stools, increases stool volume, decreases the duration of colon passage and dilates the bowel wall that then triggers the defecation reflex. Even when given for some time, the effectiveness of macrogol will not decrease. Saline laxatives exert an osmotic effect, increasing the intraluminal volume. They also appear to directly stimulate peristalsis and increase water secretion. Magnesium, sulfate, phosphate, and citrate ions are the ingredients in saline laxatives. Saline laxatives usually produce results in a few hours. Their use may lead to electrolyte imbalances with accumulation of magnesium in patients with renal dysfunction or an excessive load of sodium in hypertensive patients. Moreover, their administration may result in an undesirable strong purgative effect. Administered rectally, they stimulate rectal peristalsis within 15 minutes. Glycerin can be used rectally as an osmotic and lubricant agent.

Opioid antagonists

Opioid-induced constipation can be severe and refractory to therapy with conventional laxatives. Naloxone is a competitive antagonist of opioid receptors inside and outside the central nervous system and, after systemic administration; it reverses both centrally and peripherally mediated opioid effects. This route of administration theoretically allows selective blocking of intestinal opioid receptors without blocking the desired opioid effects, as long as hepatic first-pass capacity is not exceeded. The low systemic bioavailability due to marked hepatic firstpass metabolism allows for the low plasma levels and high enteric wall concentration. However, analgesia may also be reversed and titration to a balance between reduced adverse effects and satisfactory analgesia results to be a complex approach.

Methylnaltrexone, the first peripheral opioid receptor antagonist has the potential to prevent or treat opioidinduced peripherally mediated side effects, such as constipation, without interfering with analgesia. Methylnaltrexone is an opioid antagonist that cannot penetrate the blood-brain barrier and has been shown to reverse morphine-induced delay of gastric emptying and intestinal transit time after intravenous infusion in volunteers. Several studies provided evidence that methylnaltrexone is efficacious in reversing opioidinduced increased gastrointestinal transit and constipation [McNicol et al., 2003]. In recent studies in cancer patients, subcutaneous methylnaltrexone rapidly induced laxation in patients with advanced illness and opioid-induced constipation, without affecting central analgesia or precipitate opioid withdrawal. Subcutaneous methylnaltrexone relieved opioid-induced constipation producing laxation in 1.26 hours at doses of 5 mg in patients with advanced illness and did not reduce analgesia or cause opioid withdrawal symptoms [Portenoy et al., 2008]. Subcutaneous methylnaltrexone at a dose of 0.15 mg/kg or placebo every other day for two weeks were administered in 133 patients who had received opioids for two or more weeks and who had received stable doses of opioids and laxatives for three or more days without relief of opioidinduced constipation. In the methylnaltrexone group, 48% of patients had laxation within four hours after the first study dose, as compared with 15% in the placebo group, and 52% had laxation without the use of a rescue laxative within four hours after two or more of the first four doses, as compared with 8% in the placebo group. The response rate remained consistent throughout the extension trial [Thomas et al., 2008].

Recent studies suggest that the formulation of prolonged-release oxycodone and naloxone in a ratio of

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2:1 may provide effective analgesia while preventing or reducing constipation, possibly due to the low absorption of sustained release naloxone. In constipated patients with high bowel function index, complete spontaneous bowel movement significantly increased with oxycodone-naloxone combination, and was associated with lower use of laxative in comparison with oxycodone group [Vondrackova et al., 2008]. In a randomized, double-blind, double dummy 12-week trial of 322 patients with chronic non-cancer pain, a significant improvement in bowel function index, less use of laxatives, and complete spontaneous bowel movements were reported with the combination in comparison with oxycodone alone, without compromising analgesia [Simpson et al., 2008]. In another randomized, double-blind, double-dummy, parallel-group multicenter study the impact of oxycodone-naloxone combination for patients with opioid-induced constipation having moderate-to-severe, non-malignant pain, was assessed. Improvements in bowel function were achieved without loss of analgesic efficacy as pain intensity scores were comparable between the groups and consistent for duration of the study [Löwenstein et al., 2009]. Only one study was performed in cancer patients, where 185 patients were assessed in a randomized, doubleblind, active controlled with an oxycodone, double-dummy, parallel-group study [Ahmedzai et al., 2012]. After four weeks mean bowel function index was significantly lower with oxycodone-naloxone combination and total laxative intake was 20% lower. As the studies in non-cancer pain are limited to a dose range of up to 80/40 mg, further research on higher doses would be recommended. Doses were extended up to 120/60 mg/day in cancer patients, without reporting loss of analgesia. However, in cancer patients it is often necessary to use high doses of opioids like oxycodone. These aspects should be assessed in future studies. New generations of opioid antagonists are going to be developed in the next future [Mercadante and Giarratano, 2013].

Other adverse effects

Pruritus

Pruritus is an occasional adverse effect of systemic opioid therapy. However, its incidence rises when the spinal route is employed. The mechanism underlying is still not understood, although given the high incidence with spinal administration, spinal opioid receptors may be involved. Opioids may cause histamine release from mast cells, which may account for the sensation of itch. Other proposed mechanisms include opioid-induced disinhibition of itch-specific neurons or activation of central 3 (5-HT3) subtype receptors [McNicol *et al.*, 2003; Ganesh and Maxwell, 2011].

Available data on the use of adjuvant drugs to treat opioid-induced pruritus in cancer patients are poor. Consequently, current recommendations are empiric and anecdotal. Opioid-induced pruritus is commonly treated with antihistamines. Diphenhydramine is employed with varying degrees of success, possibly due to its sedating effect which can be undesirable in patients who already suffering from opioid-induced sedation. Alternately a less sedating antihistamine such as hydroxyzine may be employed. D2-receptor antagonists such as droperidol have shown some efficacy [Kielleberg and Tramer, 2001]. Opioidantagonists may be helpful but they are unlikely to be used in patients receiving chronic opioid therapy [Kjelleberg and Tramer, 2001]. Limited evidence supports the use of 5-HT3 antagonists which may relieve pruritus through an inhibitory effect on the dorsal horn of the spinal cord [Ganesh and Maxwell, 2011; Bonnet et al., 2008].

Dry mouth

Xerostomia is defined as a subjective sensation of dryness of the mouth, usually associated with hyposalivation. Dry mouth is a very frequent, but rarely recognized symptom in advanced cancer patients. Clinical experience suggests that dry mouth is a common complaint of patients with cancer who are receiving morphine. A highly significant association was found between the use of morphine and dryness of the mouth and patients were four times likely to have dry mouth of any severity than patients taking weak opioids, non-opioids, or no analgesics. Xerostomia is also one of the most common complaints experienced by patients who have had radiotherapy of the oral cavity and neck region and is often multifactorial as other drugs; Anticholinergic, particularly, may produce a reduction of saliva.

Symptomatic relief can be offered by moistening agents and saliva substitutes. Effectiveness of sialogogue treatment requires residual salivary function. Various commercial products have been designed to moisten and lubricate the oral mucosa.

Mucin-based saliva substitutes have a neutral pH, an electrolyte composition similar to normal saliva, and contain fluoride, helpful to prevent dental caries. They are well-tolerated, have a rapid onset, but have a high cost and a relatively short effect, so that the major disadvantage of saliva substitutes is the temporary nature of the relief provided. Moistening agents, such as sugarless gum or candies, and frequent sips of liquids are common methods of relieving oral dryness. Unfortunately, these measures provide only temporary relief of dryness, especially for nocturnal dryness, and the frequent use may result inconvenient and embarrassing.

Pilocarpine is primarily a muscarinic agonist, showing some activity also on the beta-adrenergic receptors within the salivary glands, and saliva produced is similar in consistency to normal saliva. Because of its muscariniccholinergic properties it has a broad spectrum of pharmacological effects, including diaphoretic, miotic and central nervous system actions. It increases the secretion from the exocrine glands, including the sweat, salivary, lacrimal, gastric, pancreatic and intestinal glands. It also increases the tone and the motility of smooth muscles of the different organs. The pilocarpine-stimulated secretions have been found to be similar in composition to normal salivary secretions. The effect is rapid and the salivary flow effect lasts many hours. Pilocarpine is eliminated predominantly in the urine, with an elimination half-life of 0.76-1.35 hours following administration of 5-10 mg dose three times daily.

Only few studies have dealt with this issue in advanced cancer patients [Davies *et al.*, 2001]. Pilocarpine has been used as an adjuvant to morphine therapy, resulting in a better control of opioid-induced adverse effects. In an open study, pilocarpine has been found to be safe and effective and to have a short onset of activity in almost all patients with opioid-induced xerostomia. Improvement in constipation and nausea were also observed, perhaps due to the gastrointestinal effects of pilocarpine [Mercadante *et al.*, 2000].

In a multi-center study of both inpatients and home care patients, excluding those who had radiation-induced xerostomia, mucin-based artificial saliva and pilocarpine were given using a cross-over design. Both treatments were effective, although data could have been limited by the low number of patients who completed both phases of study (about 1/3), and the low initial VAS score. The timing of response to artificial saliva is immediate, but the duration of the response is short lived. The effects of pilocarpine can be prolonged also after discontinuation [Davies *et al.*, 1998]. Patients with drug-induced xerostomia should require smaller doses of pilocarpine.

Pilocarpine is not recommended in patients with cardiovascular disease, unstable hypertension, gastrointestinal ulcers, uncontrolled asthma, acute iritis and/or narrowangle glaucoma. Caution should be taken with concomitant administration of beta-adrenergic antagonists or other cholinergic agents.

Cardiac adverse effects

Many medications commonly prescribed for pain, such as tricyclic antidepressants, haloperidol, and selective serotonin reuptake inhibitors may produce QT prolongation. Among opioids, the use of methadone has been linked to a life-threatening polymorphic ventricular tachycardia known as torsades des pointes. Methadone inhibits cardiac cell membrane repolarization, by blocking potassium channels. Proper precautions should be taken. Patients receiving high doses of methadone should be monitored and with the evidence of a QT prolongation (>490 ms), methadone should be discontinued [Mercadante *et al.*, 2013].

Bladder dysfunction

Difficulty voiding or urinary retention are commonly reported in postoperative pain patients, or more frequently after epidural/spinal opioids are given. However, these effects may also occur after initiation of opioid therapy. Opioids decrease detrusor tone and the force of contraction, decreased the sensation of fullness and urge to void, and inhibit the voiding reflex. Central and spinal mechanisms are supposed, although changes in bladder function are due in part to a peripheral effect [Benjamin *et al.*, 2008].

Hormonal and immunological effects

Opioids are one of a number of substances which modulate the hypothalamic-pituitary-gonadal axis. Activation of opioid receptors in the hypothalamus, and potentially to other sites, modulates the gonadal function. Opioids reduce the release of GnRH, resulting in a decreased release of LH and FSH from the pituitary and a secondary fall in gonadal steroid production. Opioids have been shown to increase pituitary release of prolactin, which in turn decreased testosterone secretion. Opioids also may alter the adrenal production of an important precursor of testosterone and estradiol. Some observations suggest that hypogonadism is associated to opioid sensitivity and interference with opioid analgesia [Stoffel *et al.*, 2005].

Hypogonadotropic hypogonadism is principal manifestation of these endocrine effects. Decreased libido, depressed mood, impotence, and oligorrhea are common symptoms associated with opioid-induced hypogonadism. Infertility, anxiety, decreased muscle mass and strength,

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tiredness and fatigue, hot flashes and night sweats, galactorrhea, osteoporosis are other possible symptoms associated with hypogonadism.

Several studies in patients receiving long-term opioid therapy have shown that hormone levels were lower in opioid users than in control patients. Testosterone levels were lower and libido decreased and erectile dysfunction was reported. Of interest, significant improvements were found with hormonal substitutive treatments [Daniell, 2002; Daniell *et al.*, 2006; Daniell, 2008; Rhodin *et al.*, 2010]. Other studies in cancer survivors confirmed these findings [Rajagonal *et al.*, 2003; Rajagonal *et al.*, 2004]. These opioid effects seem to be reversible.

There are no standards for the management of presumptive opioid-induced hypogonadism. For patients with symptoms or evident laboratory abnormalities, the first option to change the analgesic treatment, for example with non-opioid options. There is no information about the possible advantages of opioid switching, although some opioids, like buprenorphine, seem to have less influence on hormonal function. Hormone therapy may be potentially useful, parenterally or transdermally. Hormonal supplementation may produce adverse effects, including local reactions, hematologic abnormalities and sexual disturbances [Katz and Mazer, 2009].

The immune modulatory effects of opioids are often linked to central to central neuro-endocrine-paracrine and peripheral mechanisms, although the exact mechanism still remains unclear. The importance of centrally mediated mechanisms is supported by the observation that opioids that cross the blood-brain-barrier exert more immune modulatory effects than opioids that poorly cross the barrier. Cellular immunity suppression may be the consequence of hypothalamic-pituitaryadrenal axis dysregulation producing an increased plasma concentration of glucocorticosteroids, affecting the immune system through gene modulation. Opioids can also cause sympathetic nervous activation that may suppress the activity of some immune cells. There are differences among opioids in immune modulatory effects [Al-Ashimi et al., 2013].

Summary

• Successful opioid therapy requires that the benefits of analgesia outweigh treatment-related adverse events. Opioid side effects impair the quality of life and increase morbidity, and may cause patients to discontinue therapy. Most adverse effects occur at initiation of opioid therapy or when significant dose increases occur.

- Sedation and impaired psychomotor function are a dose-dependent effect of opioids, and frequently occur at the beginning of treatment and/or when doses are increased. Tolerance develops rapidly, but this effect may often prevent dose increases necessary to pain control.
- Central adverse effects also include sleep disorders, hyperactive delirium, myoclonus, and respiratory depression.
- Opioids are one of the most important causes of gastrointestinal symptoms. While nausea tends to disappear spontaneously within 3-4 days, constipation is likely to persist chronically.
- Other problematic adverse effects include pruritus, dry mouth, cardiac effects, and bladder dysfunction.
- Concerns exist regarding hormonal and immunological effects with prolonged therapy with opioids.

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Nonopioid analgesics

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Introduction

The treatment of pain in palliative care is often a challenge to clinicians, patients, and their caregivers. Therapeutic approaches vary and range from drugs to interventional/ surgical procedures to complementary therapies. Although opioids are a mainstay of treatment, many patients succeed on non-opioid analgesics or improve when non-opioids are added to their regimen. As with any analgesic, the choice is based upon the type and severity of pain as well as patient specific risk factors involved with that treatment. This chapter will describe our current understanding and the utility of non-opioid analgesics, specifically non-steroidal anti-inflammatory drugs (NSAIDs) and acetaminophen.

Non-opioids such as NSAIDs and acetaminophen are analgesics and antipyretics indicated for mild to moderate pain of all types as well as for fever. Different from opioids, they have a maximal effect to their dose response; after achieving an analgesic ceiling, increasing the dose does not offer additional analgesia but increases the risk of adverse effects. These agents also do not produce physical or psychological dependence and therefore sudden interruption in treatment does not typically produce drug withdrawal or any abstinence syndrome.

Non-opioid analgesics can be used as monotherapy for mild pain and as an adjuvant for moderate to severe pain. The World Health Organization (WHO) guidelines recommend non-opioid therapy at all three steps on the analgesic ladder, either alone or in combination with an opioid or adjuvant medication or both [Ventafridda *et al.*, 1985]. It is suggested that unless contraindicated, any analgesic regimen should include non-opioid drugs, even when pain is severe enough to require the addition of an opioid [Acute Pain Management Guideline Panel, 1992]. In addition to non-opioids, adjuvant drugs that provide or enhance analgesia may be used at any step to treat concurrent non-nociceptive symptoms.

The first step on the ladder is the use of non-opioids for mild to moderate pain; when pain persists or increases, the ladder suggests a mild opioid such as codeine or hydrocodone be added to (not substituted for) the nonopioid. Opioids at step II are often administered in fixeddose combinations with acetaminophen, NSAIDs or aspirin as these combinations are thought to provide additive and perhaps synergistic analgesia. Upward titration of these combination products is usually limited by dose-related toxicity of the non-opioid component. When higher doses of opioids are necessary, the third step is approached whereby separate dosage forms of the opioid and non-opioid analgesic should be titrated individually to maximal efficacy and minimal toxicity. A fourth step of the ladder has been proposed to include consideration of interventional pain management and neurosurgical procedures such as nerve blocks, neurolysis, spinal cord or brain stimulators and other invasive techniques (Figure 1) [Vargas-Schaffer, 2010].

Acetaminophen

Acetaminophen is one of the most commonly used medicines in the United States. It is regularly known elsewhere around the world as paracetamol. Although acetaminophen has been shown to have analgesic and antipyretic activity, its mechanism of action remains largely unknown. The effects are thought to be centrally mediated, but there is some literature that describes a potential



Figure 1 New adaptation of the analgesic ladder. Reprinted with permission: Vargas-Schaffer G. Is the WHO analgesic ladder still valid? Can Fam Physician 2010;56:514-7.

peripheral mechanism of action [Watkins et al., 1995].

Acetaminophen is a weak inhibitor of prostaglandin (PG) synthesis in vitro and appears to have very little anti-inflammatory activity [Seegers et al., 1981]. The chemical name for the compound is N-acetyl-paraaminophenol (APAP). When used according to the label, it has a well-established record of safety and efficacy. It has not been shown to significantly affect platelet function, increase surgical bleeding, or affect kidney function with short term use [Cattabriga et al., 2007; O'Brien, 1968]. Acetaminophen risks increase with long term use, but it has a high therapeutic index that allows for safe and effective use in treating pain and fever in a wide range of patients. Although acetaminophen overdose is rare in the context of its broad usage, overdose can be toxic and is the leading cause of acute liver failure in the US [Fontana, 2008]. Acetaminophen may be preferred over NSAIDs in elderly patients with osteoarthritis because of fewer GI and renal side effects. The American Geriatrics Society recommends acetaminophen as the analgesic of choice for minor aches and pains in patients older than 50 years [AGS, 2009]. In cancer pain, acetaminophen can be added to a mild or strong opioid regimen to increase analgesic effects while decreasing side effects.

Acetaminophen is readily absorbed from the GI tract allowing administration orally and rectally. Pharmacokinetic studies of rectal administration of acetaminophen showed up to 9-fold variation of peak drug concentration, often not achieving therapeutic levels [van Lingen *et al.*, 1999]. The range in pharmacokinetic differences could be a result of the inherent variability of venous drainage from the rectum. Drugs administered distally in the rectum bypass the liver, whereas drugs administered in the proximal portion drain into the portal system and are subject to the hepatic firstpass effect [Morselli *et al.*, 1980].

An intravenous formulation of acetaminophen was approved in the United States in 2010 for the treatment of pain and as an antipyretic [Walson *et al.*, 2006]. IV administration is convenient in the immediate postoperative period, or in situations where a patient is unable to take medications by mouth (e.g., nothing by mouth status, severe nausea, odynophagia, or dysphagia), when a faster onset of analgesia is desired, or when the rectal route is not preferred [Pyati and Gan, 2007]. IV administration may also result in a more rapid onset of analgesia with higher peak plasma concentrations and more predictable pharmacokinetics than the oral or rectal formulations [Malaise *et al.*, 2007].

In January 2011, in an effort to promote its safe use, the

U.S. Food and Drug Administration (FDA) asked drug manufacturers to limit the strength of acetaminophen in prescription drug products, which are predominantly combinations of acetaminophen and opioids. The recommendation was to limit the amount in these products to 325 mg per tablet, capsule, or other dosage unit [FDA, 2011].

Despite this change, the prescribing recommendations of 1-2 tablets every 4-6 hours, not exceeding a daily dose of 4,000 mg was not changed. In addition, Boxed Warnings highlighting the potential for severe liver injury and a warning highlighting the potential for allergic reactions (e.g., swelling of the face, mouth, and throat, difficulty breathing, itching, or rash) were being added to the label of all prescription drug products that contain acetaminophen. The FDA also requires alcohol warnings for acetaminophen and anticipates that these actions will help to reduce the risk of severe liver injury and allergic reactions [FDA, 1999].

Aspirin

Aspirin is a potent inhibitor of both PG synthesis and platelet aggregation [Aspirin, 2013a]. It is a unique NSAID that irreversibly inhibits cyclooxygenase type 1 (COX-1) and cyclooxygenase type 2 (COX-2) [Pillinger *et al.*, 1998]. Platelets have markedly limited capacity for protein synthesis allowing this inhibition to last the lifetime of the platelet which is about 8 to 12 days. This property of aspirin supports its role in decreasing risk of thrombotic events such as myocardial infarction and stroke [Goldstein *et al.*, 2011].

The recommended dose of aspirin in adults varies by indication. The package insert [Aspirin, 2013a] recommends up to 3 g per day for osteoarthritis and up to 4 g per day for spondyloarthropathies. For acute analgesic and antipyretic purposes, most sources recommend 325-650 mg every four hours as needed up to 4 g/day [Aspirin: Drug information, 2013b]. Similar to other NSAIDs, gastric disturbances and bleeding are common adverse effects with therapeutic doses of aspirin. Regular aspirin use is associated with gastrointestinal (GI) bleeding, with risk more strongly related to dose than duration of use [Huang *et al.*, 2011].

Certain individuals display hypersensitivity to aspirin and present a wide range of clinical manifestations which can lead to severe bronchospasm or anaphylaxis. This may happen within minutes of aspirin ingestion or be a delayedtype response appearing after days or weeks [Kowalski *et al.*, 2011]. Aspirin intolerance is a contraindication to therapy with any NSAID because cross-sensitivity can provoke a life-threatening, anaphylactic reaction.

NSAIDs

Non-steroidal anti-inflammatory drugs are amongst the most widely used agents. Compared with placebo, NSAIDs have shown clear analgesic, antipyretic, and anti-inflammatory effects, although their mechanism of action may also lead to their toxicities. It is now established that prostanoids (i.e., PGs) play important roles in many cellular responses and pathophysiologic processes, including modulation of inflammatory reactions, erosion of cartilage and bone, GI cytoprotection and ulceration, angiogenesis and cancer, hemostasis and thrombosis, renal hemodynamics, and progression of kidney disease. NSAIDs, COX-2 inhibitors, and acetylsalicylic acid (aspirin) prevent the formation of prostanoids from arachidonic acid. This synthesis of PGs from arachidonic acid is controlled by two separate cyclooxygenase enzymes (COX-1 and COX-2) [Patrignani et al., 2005]. NSAIDs can be grouped by properties as shown in Table 1, but are generally classified by the way they interact with cyclooxygenase: non-selective (ns) COX-1 and COX-2 versus selective COX-2 inhibitors.

NSAIDs: physiology/mechanism of action

As mentioned in the chapter on pain pathophysiology, analgesics are thought to reduce the release of excitatory nociceptive chemicals and slow the transmission of pain signals from the periphery to the central nervous system. When damage to the cell membrane occurs, an inflammatory response is triggered, breaking down arachidonic acid by enzymes called cyclooxygenase (COX), including its isoforms COX-1 and COX-2. This cascade produces PG and its breakdown products prostacyclin and thromboxane. Whereas COX-1 enzymes are constitutivealways actively producing PGs that regulate renal, GI, and platelet function, COX-2 enzymes are inducible-activated following a trauma or an inflammatory stimulus [Middleton, 2003]. Once PGs are produced in response to a noxious stimulus, they sensitize the peripheral nerve endings that form primary pain receptors found in skin, connective tissues, and visceral organs. The cascade that ensues can then trigger a prolonged increase in the excitability of neurons in the periphery, as well as in central nociceptive pathways-phenomenon known as peripheral and central sensitization [Woolf, 2011]. Though traditionally viewed as peripherally acting agents, it is well recognized that

	Comments ^{b,c,d}	Hepatotoxicity is the main risk; maximum daily dose should be reduced in patients with hepatic failure or alcohol abuse, and possibly in older patients).25-0.3 h; Meta- 300-600 mg, 3 5-6 h; higher 5-30 h		es: 2-3 h; No effect on platelet aggregation es: add 30 h	es: 7-8 h; es: add 15-30 h	Available OTC	Available OTC and as a suspension							
	Half-life	t t	Parent: 0. bolites: 30 h; >1 g, 5 doses, 15	8-12 h	Low dose high dose	Low dose high dose	2 h	12-15 h	12-15 h	12-15 h	12-15 h	1-4 h	1-4 h	3-6 h	1.40-50 h
	Recommended maximum daily dose	4,000 mg	4,000 mg	1,500 mg	4,500 mg	4,000 mg	3,200 mg	1,500 mg	g 1,375 mg	1,100 mg	g 660 mg	300 mg	200 mg	300 mg	1 800 mg or 26 mg/kg
	Recommended daily starting dose ^a	325-650 mg; q4-6h	325-1,000 mg	250-500 mg; q8-12h prn	a-1,000 mg q8h or 1,500 mg bid	500-1,000 mg; q8-12h	200-400 mg; q4h	250-500 mg; q12h	550 mg, then 275 m(q6h	550 mg; q12h	440 mg, then 220 m q8-12h	25-75 mg; q6-8h	100-200 mg; qd	100 mg; q6-8h	600-1 200 mai ad
oid analgesic agents	Drug; brand name, manufacturer	Acetaminophen ^e ; Tylenol, McNeil ^í	Aspirin ^e ; Bayer ^f	Diflunisal°; Dolobid, Merck ^f	Choline magnesium triss licylate [®]	Salsalate°; Amigesic, Amide ^f	lbuprofen ^e ; Motrin, Ortho-McNeil; Advil, Whitehall-Robins ^f	Naproxen°; Naprosyn, EC-Naprosyn, Roche ^ŕ	Naproxen sodium ^e ; <i>Immediate-release</i> ; Anaprox, Roche	Naproxen sodium; <i>Extended-release</i> ; Anaprox DS, Roche	Naproxen sodium; <i>Extended-release</i> ; Aleve, Bayer	Ketoprofen; Immediate-release	Ketoprofen; Extended-release; Oruvail, Wyeth	Flurbiprofen ^e ; Ansaid, Pfizer ^f	Ovantozin:
Table 1 Non-opic	Class	P-Aminophenol derivative	Salicylates				Propionic acids					Propionic acids			

Nonopioid analgesics

Part	

Table 1 (continue)	(p;				
Class	Drug; brand name, manufacturer	Recommended daily starting dose ^a	Recommended maximum daily dose	Half-life	Comments ^{b.c.d}
Acetic acids (indoles)	Indomethacin; <i>Immediate-release</i> ; Indocin, Merck ^f	25-50 mg; q8-12h	200 mg	4-6 h	Higher incidence of adverse effects (GI, renal, CNS); cannot be considered as a simple analge- sic and should not be used in conditions other
	Indomethacin; S <i>ustained-rele</i> ase; Indocin SR, Forte; Pharma	75 mg; qd-bid	150 mg	4-6 h	than moderate to severe RA, ankylosing spon- dylitis, acute painful shoulder and acute gouty arthritis
	Indomethacin Suppository; Indocin, Merck	50 mg; q8-12h	150 mg	4-6 h	
	Sulindac; Clinoril, Merck [†]	150-200 mg; bid	400 mg	Parent drug: 7 h; active metabolite: 18 h	Pro-drug has to be metabolized by the liver for analgesic efficacy; active metabolite has long half-life
Acetic acids (naphthyl)	Nabumetone; Relafen, GlaxoSmithKline ^f	2,000 mg qd or 1,000 mg bid	2,000 mg qd or 1,000 mg bid	Active metabolite: 22-30 h	Pro-drug has to be metabolized by the liver for analgesic efficacy; active metabolite has long half-life; relatively low risk for GI toxicity
Acetic acids (phenyl)	Diclofenac; <i>Immediate-release</i> ; Cataflam, Novartis ^f	50 mg; q8-12h	200 mg	1-2 h	
	Diclofenac; <i>Delayed-rele</i> ase; Voltaren, Novartis	50-75 mg; q8-12h	200 mg	1-2 h	
	Diclofenac; <i>Extended-release</i> ; Voltaren-XR, Novartis ^f	100 mg; qd	100 mg	1-2 h	
Acetic acids (pyrroles)	Ketorolac tromethamine; Oral; Toradol, Roche ^f	10 mg; q4-6h	40 mg	2-8 h	Potent NSAID with potential to cause serious adverse events; should be used only for moder-
	Ketorolac tromethamine; Intramuscular; Toradol, Roche ^f	<50 or \geq 65 kg years old: 30-mg loading dose, then 10-15 mg q6h; >50 kg: 30- to 60-mg loading dose, then 15-30 mg q6h	<50 or ≥65 kg years old:150 mg in first 24 h, then 120 mg; >50 kg: 30- to 60-mg loading dose, then 15-30 mg q6h	2-8 h	ately severe acute pain that requires analgesia at the opioid level for a maximum duration of 5 d; should not be used for minor or chronic painful conditions
	Tolmetin doium; Tolectin, Tolectin DS, Ortho-McNeil ^f	200-400 mg; q8h	1,800 mg	1-2 h	
Table 1 (continue)	(p;				

	Comments ^{b.c.d}			High incidence of peptic ulcer with use of 40 mg for >3 wks	COX-2 selective at low doses	Should not be used for >1 wk		Compared with nonselective COX-1 and COX- 2 inhibitors: less risk for GI toxicity, similar risk for renal toxicity, no effect on platelet function. As with other prescription NSAIDs, may increase risk for serious cardiovascular thrombotic events myocardial infarction, and stroke [Solomon <i>et al.</i> , 2005]	
	Half-life	4 L	7 h	45-50 h	20 h	3.5 h	2-3 h	11 h	:
	Recommended maximum daily dose	1,200 mg or 20 mg/kg	1,000 mg	20 mg	15 mg	1,000 mg	400 mg	400 mg	
	Recommended daily starting dose ^a	200-400 mg; q6-8h	400-600 mg; qd	10-20 mg; qd	7.5 mg; qd	500 mg, then 250 mg q6h	50 mg; q6-8h	100 mg; bid	
0	Drug; brand name, manufacturer	Etodolac; <i>Immediate-release</i> ; Lodine, Wyeth ^f	Etodolac; Extended-release ^f	Piroxicam; Feldene, Pfizer ^f	Meloxicam; Mobic, Boehringer Ingelheim/ Abbott	Mefenamic acid ^e ; Ponstel, Parke-Davis	Meclofenamate ^e	Celecoxib°; Celebrex, Pfizer	-
Table 1 (continued)	Class	Pyrano-carbox- ylic acid		Oxicams		Fenamates		Selective COX-2 inhibitor	

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mum daily dose should be lowered. ^bContraindictions to NSAID administration: increased bleeding risk, concomitant use of an anticoagulant (e.g., warfarin), renal (gastric ulcer, gastritis), renal insufficiency, fluid retention, CHF, arterial hypertension, increased bleeding risk, hyperkalemia. All prescription NSAIDs may increase Pain is an FDA-approved indication in the United States. ¹Other branded and/or generic products are available. Based on product inserts and Wallenstein and insufficiency, recent gastric ulcer or gastritis, severe liver insufficiency, severe CHF, allergy to NSAIDs. ^oCommon adverse effects of NSAIDs: gastroduodenopathy the risk for serious cardiovascular thrombotic events, myocardial infarction, and stroke. This risk may increase with duration of use. ^aWith prolonged use and/or high doses, regular monitoring for occult GI bleeding (stool guaiac), renal function tests (blood urea nitrogen, creatine), and liver function tests are recommended. The starting dose should always be individualized. In older patients, patients with renal failure, and patients taking multiple drugs, the starting dose and maxi-Portenoy, 2002. [Lussier et al., 2008; Reprinted with permission from Pain Medicine News 2008;7:1-8.].

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NSAIDs also exert their analgesic effects through inhibition of COX in the spinal cord and brain (CNS) [Burian and Geisslinger, 2005].

NSAIDs are completely absorbed in the GI tract, with food only minimally affecting plasma levels, although an increase in gastric pH has been shown to reduce NSAIDs absorption [Tobert *et al.*, 1981]. From a pharmacokinetic standpoint, NSAIDs do not undergo first-pass elimination. They are highly bound to plasma proteins resulting in a low volume distribution, and this high affinity for plasma proteins disposes them to displace other drugs from binding sites, including warfarin and other NSAIDs [Diana *et al.*, 1989].

Most NSAIDs are broken down by the cytochrome P450 2C9 (CYP2C9) hepatic enzyme system to inactive metabolites that typically are excreted in the urine, though some drugs are also excreted in bile [Goldfrank et al., 2002]. Interactions with warfarin, beta blockers, antidepressants, antiepileptic drugs, and statins often involve the cytochrome P450 enzymes. Genetic variability (polymorphisms) in the cytochrome P450 enzymes may influence a patient's response to many commonly prescribed drug classes, including NSAIDs. As a review, the metabolism of these agents can be inhibited or induced by other drugs or compete with other drugs (known as substrates) for metabolism, resulting in clinically significant drug-drug interactions that can cause unanticipated therapeutic failures or adverse reactions. Polymorphisms in CYP2C9 (i.e., poor metabolizers) or the addition of other CYP450 enzyme inhibitors may cause adverse effects related to elevated drug serum levels. Knowledge of the most important drugs metabolized by cytochrome P450 enzymes (substrates), as well as the most potent inhibiting and inducing drugs, can help minimize the possibility of adverse drug reactions and interactions. This becomes more important as we consider the widespread use of NSAIDs along with an increase in polypharmacy in our aging population.

NSAIDs: therapeutic benefits

The role of NSAIDs in cancer and other conditions has been well established for the treatment of mild-moderate pain, for bone pain and in association with opioids in the treatment of moderate-to-severe pain. The use of NSAIDs has been shown to be opioid sparing in cancer and other pain syndromes, i.e., post-operative pain-reducing the overall need for opioids or allowing for the use of lower doses [Abrahm, 2005]. They lack the undesired opioid effects such as respiratory depression, somnolence, constipation, and the potential of developing physical dependence or addiction. Based on the evidence that osteolytic activity in bone metastases is mediated at least in part by PGs, NSAIDs are the first line of therapy in malignant bone pain and should be used in any cancer pain if no contraindication exists [Acute Pain Management Guideline Panel, 1992].

Interestingly, a 2010 drug class review noted highstrength evidence that there were no significant efficacy differences between individual oral NSAIDs [Peterson *et al.*, 2010].

NSAIDs: risks

The entire class of NSAIDs is now under increased scrutiny as unwanted side effects may not be class-specific. The most significant NSAID adverse events (AEs) are associated with platelet inhibition, GI, renal and cardiovascular toxicity. These have been attributed to NSAID induced blockade of PGs. The selective COX-2 inhibitors were developed under the assumption that the constitutive COX-1 enzyme would be spared causing fewer side effects than traditional NSAIDs [Vane and Botting, 1998]. However, recent studies have indicated that COX-2 is also constitutively expressed and that its inhibition may exacerbate inflammation, impair ulcer healing, and decrease the formation of prostacyclin. Therefore, all NSAIDs have increased risk for thrombosis, myocardial infarction, renal impairment, hypertension, stroke, and liver toxicity [Hinz and Brune, 2007].

In the GI tract, PGs exert a protective effect by reducing acid secretion, promoting gastric mucosal blood flow, and stimulating bicarbonate and mucus production [Whelton, 1999]. By inhibiting COX-1, NSAIDs suppress these protective PGs and also cause local irritation by direct contact with the GI lining. GI toxicity varies from mild (dyspepsia, nausea, abdominal pain, and reflux) to severe symptoms (ulcer, bleeding, and perforation). These events can occur at any time during use and without warning. Elderly patients are at greater risk for serious GI events and clinicians are advised to consider both the safety as well as effectiveness of NSAIDs in this population [Peterson et al., 2010]. The risk of GI adverse events is further increased in those with Helicobacter pylori infection, heavy alcohol consumption, or other risk factors for mucosal injury, including concurrent use of glucocorticoids [Deeks et al., 2002]. Co-administration of the PGE1 analog, misoprostol, or proton pump inhibitors (PPIs) in conjunction with

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NSAIDs can be beneficial in the prevention of these symptoms [Rostom *et al.*, 2002], although their benefits may be limited to areas exposed to gastric acid (i.e., the proximal GI structures).

Symptomatic ulcers and ulcer complications develop in only 2% to 4% of patients taking NSAIDs for a year [Paulus, 1985]. Even low-dose aspirin, with or without enteric coating, is associated with an increased risk of UGI bleeding. Although the risk appears small, the millions of U.S. patients taking NSAIDS for arthritis or aspirin for cardiovascular prophylaxis translate into a large number of patients at risk.

Nephrotoxicity has also been observed for all NSAIDs. In patients with congestive heart failure (CHF), hepatic cirrhosis, chronic kidney disease, hypovolemia, and other states of activation of the renin-angiotensin system, the PG effect on renal function becomes more significant. PGs are necessary for the renal excretion of several electrolytes, toxins, and drug metabolites. By inhibiting the synthesis of PGs, NSAIDs decrease the renal clearance of these materials. PGs normally cause vasodilation of the afferent arterioles of the glomeruli. This helps maintain normal glomerular perfusion and glomerular filtration rate (GFR), an indicator of renal function. The renal risks increase with chronic or high dose NSAIDs, urinary tract infections, and the use of certain diuretics and angiotensin converting enzyme (ACE) inhibitors [Patrono and Dunn, 1987]. Common adverse events noted with NSAID induced nephropathy include edema (sodium and fluid retention) and hypertension. The black box warning indicates that the use of NSAIDs can promote sodium retention in a dose-dependent manner, through a renal mechanism, which can result in increased blood pressure and/or exacerbation of CHF [Peterson et al., 2010]. Regular monitoring of blood pressure is necessary in all patients, especially the elderly, who are on antihypertensive therapy [MacFarlane et al., 1995].

In addition to risk of increased blood pressure and exacerbation of CHF, use of some NSAIDs is associated with an increased incidence of cardiovascular adverse events such as myocardial infarction, stroke or thrombotic events which can be fatal. The risk increases with dose and duration of use. Patients with risk factors or preexisting cardiovascular disease may be at greater risk [Peterson *et al.*, 2010]. A 2011 meta-analysis suggested that among a number of NSAIDs analyzed, naproxen seemed least harmful for cardiovascular safety [Trelle *et al.*, 2011].

Although the exact mechanism of this NSAID induced cardiac toxicity is not fully understood, it seems to be linked to the relative imbalance in prostacyclin and thromboxane production, resulting in a prothrombotic state [Graham *et al.*, 2005]. Therefore, caution should be exercised in prescribing NSAIDs to any patient with ischemic heart disease, CHF [congestive heart failure (NYHA II-IV)], or cerebrovascular disease. NSAIDs are contraindicated for treatment of perioperative pain in the setting of coronary artery bypass graft (CABG) surgery.

Clinicians have come to recognize that toxicity can occur at any time or with any duration of use with NSAIDs and from an overall risk standpoint, regardless of the NSAID chosen, the lower the dose utilized- the lower the risk to the patient.

In 2005, the FDA requested that manufacturers of all NSAIDs produce a patient medication guide for these products and make changes to their product label (package insert) for both prescription and over-the-counter (OTC) NSAIDs. They mandated inclusion of a boxed warning highlighting the potential for increased risk of cardiovascular (CV) events and the well described, serious, potential life-threatening GI bleeding associated with their use [FDA, 2012].

In 2013, the FDA approved an NSAID developed using a proprietary [SoluMatrix Fine Particle[™]] technology which altered the absorption properties of diclofenac, suggesting the prospect of pain relief at lower doses—at least 20% lower than currently available diclofenac products. Further clinical trials are warranted for this and other emerging NSAID technologies to determine their long term safety and efficacy. This technology was developed to address FDA's public health advisory recommending that NSAIDs be used at the lowest effective dose for the shortest duration of time consistent with individual patient treatment goals [Iroko Pharmaceutical LLC. Press release. 2013].

Topical NSAIDs

With the increased GI and cardiovascular risks associated with oral NSAIDs, topical NSAIDs are gaining in popularity with controversial evidence supporting their use. A recent review supported their use in knee and hand osteoarthritis, with no evidence of benefit for other chronic painful conditions [Derry *et al.*, 2012]. A 2010 review of NSAIDs noted that both diclofenac 1.5% topical solution and 1.0% topical gel had significantly greater mean changes in pain subscale scores than placebo [Peterson *et al.*, 2010]. Of the topical NSAIDs approved in the United States, both diclofenac gel and diclofenac solution have demonstrated efficacy in the management of OA of the knee. Current evidence shows that combining a topical NSAID with an oral NSAID confers no additional therapeutic benefit over either agent used alone, but it does increase the number of adverse events [Simon *et al.*, 2009].

Intravenous NSAIDs

Ketorolac tromethamine is an IV NSAID formulation that was approved for use by the FDA in 1989. It is indicated for the short term (five days) management of moderately severe acute pain. Of note, ketorolac has a much more potent effect on COX-1 than on COX-2, having important implications for clinical use [Warner *et al.*, 1999].

A formulation of IV Ibuprofen was approved for use in the US in 2009, indicated for the management of mild to moderate pain, moderate to severe pain as an adjunct to opioid analgesics and reduction of fever. The dose is 400 to 800 mg IV over 30 minutes every six hours for pain as necessary [CALDOLOR (ibuprofen) Injection, 2009]. Ibuprofen appears to have a more balanced affinity for COX-1 and COX-2. These intravenous agents carry the same warning for risks as oral formulations.

Summary

Non-opioid analgesics such as NSAIDs and acetaminophen can be used as monotherapy for mild pain and as adjuvants for moderate and severe pain. The use of these complementary agents is frequently overlooked in palliative care as well as in patients with postoperative and chronic pain. Although clinicians need to recognize the risks associated with these therapeutic agents, unless there is a contraindication, all analgesic regimens should include non-opioid drugs, even when the pain is severe enough to require the addition of an opioid.

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Introduction

Chronic pain is a global problem. Estimates suggest an adult worldwide prevalence of 20% (120 million). Additionally, the prevalence of new diagnoses is 10% (60 million) each year. One in three elderly adults have difficulty living independently due to chronic pain [Goldberg and McGee, 2011]. Chronic pain should be recognized as not just a symptom, but as a disease itself. The most effective treatment strategy for chronic pain is a multimodal and balanced approach combining pharmacologic and nonpharmacologic treatments.

Adjuvant analgesics are a diverse group of drugs that have a primary indication for use other than for pain, but have been found to have analgesic properties in some pain conditions. They often are co-administered with traditional analgesics and sometimes referred to as "co-analgesics". Even though these agents mainly are used as adjuvants in various pain conditions, some adjuvant analgesics also are being used as a first-line treatment option for management of specific pain, e.g., gabapentin for neuropathic pain. Using an adjuvant analgesic is important to the success in effective pain management.

Before using an adjuvant analgesic for pain control, providers must be familiar with the drug's clinical pharmacology, approved indications and off-label use, common side effects, drug interactions and specific dosing guidelines. Major classes of adjuvant analgesics include antidepressants, antiepileptic drugs (AED), corticosteroids, alpha (α_2) adrenergic agonists, N-methyl D-aspartate (NMDA) receptor antagonists, gamma amino butyric acid (GABA) agonists, local anesthetics, topical analgesics, benzodiazepines, neuroleptics, muscle relaxants, bisphosphonates, cannabinoids, psycho-stimulants, anti-cholinergics, calcitonin, radiopharmaceuticals and octreotide [Lussier *et al.*, 2004; Knotkova and Pappagallo, 2007]. These groups of drugs, along with examples of individual drugs that could be used as adjuvant analgesics, are summarized in *Table 1. Table 2* lists all the adjuvant analgesics approved by Food and Drug Administration (FDA) for the indication of pain. This chapter discussion will focus on the classes of drugs most commonly used and studied for adjuvant analgesia.

Antidepressants

Many antidepressants have well-established analgesic effects independent of antidepressant effects. Efficacy as an antianalgesic does not correlate with antidepressant efficacy. Various agents from the antidepressant class of drugs have been used for analgesia in chronic pain syndromes, for example, fibromyalgia, neuropathic pain and cancer pain. Antidepressants are less helpful for most acute musculoskeletal pain. They have the additional advantage of treating anxiety and insomnia along with depression. Antidepressants that work by increasing norepinephrine have better pain relieving capabilities than those which increase serotonin. This is likely why the selective serotonin reuptake inhibitors (SSRIs) have not been shown to be effective for pain, even though they are effective antidepressant drugs. Mechanisms of action of groups of antidepressants are explained in Table 3. At the time of discontinuation of an antidepressant, care should be taken to slowly taper the medication in order to avoid withdrawal syndromes [Mitra and Jones, 2012]. Direct comparison of

Table 1 Adjuvant analgesics: ma	ijor classes of drugs	
Class of drug	Example	Indication for type of pain
Antidepressants		Multipurpose analgesics
TCAs	Amitriptyline, nortriptyline, desipramine	
SSRIs	Paroxetine, citalopram	
Noradrenaline/SNRIs	Venlafaxine, duloxetine, milnacipran	
Others	Bupropion	
Anti-epileptics	Gabapentin, pregabalin, carbamazepine, oxcarbazepine, lamotrigine, topiramate, tiagabine, levetiracetam, zonisamide, phenytoin, valproic acid	Multipurpose analgesics
Corticosteroids	Dexamethasone, prednisone	Multipurpose analgesics
α_2 adrenergic agonists	Clonidine, tizanidine	Multipurpose analgesics
NMDA receptor antagonists	Ketamine, dextromethorphan, memantine, amantadine	Neuropathic pain
GABA agonists	Baclofen	Musculoskeletal pain
Local anesthetics	Lidocaine, mexiletine	Neuropathic pain
Topical analgesics	Capsaicin, lidocaine, lidocaine/prilocaine (EMLA)	Neuropathic pain
Benzodiazepines	Diazepam, lorazepam, clonazepam	Musculoskeletal pain
Conotoxins	Ziconotide	Neuropathic pain
Muscle relaxants	Cyclobenzaprine, carisoprodol, methocarbamol, metaxalone, orphenadrine	Musculoskeletal pain
Neuroleptics	Olanzapine	
Bisphosphonates	Pamidronate, zoledronic acid, clodronate	Bone pain
RANKL inhibitor	Denosumab	
Other adjuvant analgesics		
Psychostimulants	Methylphenidate, modafinil	
Anticholinergics	Hyoscine, glycopyrrolate	
Calcitonin		
Radiopharmaceuticals		
Octreotide	Strontium ⁸⁹ , samarium ^{153A}	
Cannabinoids		

Table adapted from Lussier *et al.* [Lussier *et al.*, 2004]; Abbreviations: TACs, tricyclic antidepressants; SSRIs, selective serotonin reuptake inhibitors; SNRIs, serotonin reuptake inhibitors; NMDA, N-methyl D-aspartate; GABA, gamma amino butyric acid; RANKL, receptor activator of nuclear factor kappa B ligand.

the analgesic efficacy of various antidepressant drugs has not been explored in many studies. *Table 4* describes adverse effects and drug interactions of antidepressants commonly used for pain management, while *Table 5* shows initial dose and usual effective dose of antidepressants used for pain management.

Serotonin noradrenaline reuptake inhibitors (SNRIs)

SNRIs, such as duloxetine and venlafaxine, have been shown

to possess analgesic properties in various studies. Both these drugs are devoid of anticholinergic and antihistamine effects of the TCAs. Venlafaxine has been found to be effective in painful polyneuropathy, diabetic neuropathy, and neuropathic pain, following treatment of breast cancer [McDonald and Portenoy, 2006]. It has potent serotonin reuptake inhibition, but weaker norepinephrine reuptake effects. Both immediate and sustained-release formulations of this drug are available, and the drug is known to be well tolerated. A comparison of venlafaxine and tricyclic

Table 2 List of adjuvant	ts with FDA approval for pain management
Adjuvant analgesic	FDA approved pain indication
Duloxetine	Neuropathic pain associated with diabetic peripheral neuropathy; fibromyalgia
Milnacipran	Fibromyalgia
Gabapentin	Neuropathic pain associated with post herpetic neuralgia
Pregabalin	Neuropathic pain associated with diabetic peripheral neuropathy and post herpetic neuralgia; fibromyalgia.
Carbamazepine	Neuropathic pain, trigeminal neuralgia, glossopharyngeal neuralgia
Bupivacaine liposome	Post-operative pain
(injectable suspension)	
Ropinirole	Pain associated with restless leg syndrome
Pramiprexole	Pain associated with restless leg syndrome
Migraine prophylaxis	Topiramate, divalproex
Ziconotide	Severe chronic pain in patients who are intolerant or refractory to all other available treatment including
	systemic analgesics, adjunctive therapies, intrathecal opiates

Table 3 Mechanism of action	of each group of antidepressan	its			
Mechanism of action	Site of action	SNRI	Bupropion	TCA	SSRI
MAO reuptake inhibition	Serotonin	+	-	+	+
	Noradrenaline	+	+	+	-
Receptor antagonism	Adrenergic (alpha-1)	_	-	+	-
	NMDA	+ (milnacipran)	-	+	-
	nAChR	-	+	-	-
Block/activate Ion channel	Na⁺ channel blocker	+ (venlafaxine)	-	+	+ (fluoxetine)
	Ca ²⁺ channel blocker	– (duloxetine)	-	+	+ (citalopram, fluoxetine)
	K ⁺ channel blocker	?	-	+	-
	Nicotinic receptor channel	-	+	-	-
Adenosine	↑adenosine availability and	?	-	+ (amitriptyline)	?
	local release; activation of				
	adenosine A1 receptor				
GABA B receptor	↑GABA B receptor function	?	-	+ (amitriptyline,	+ (fluoxetine)
				desipramine)	
Opioid receptor binding/	Activation of μ and δ opioid	+ (venlafaxine)	+	+	+ (paroxetine)
opioid-mediated effect	receptors				
Inflammation	↓PGE2 production	?	?	+	+ (fluoxetine)
	\downarrow TNF α production	?	+	+	?

Abbreviations: SNRI, serotonin and norepinephrine reuptake inhibitor; TCA, tricyclic antidepressant; SSRI, selective serotonin reuptake inhibitor; MAO, monoamine oxidase; NMDA, N-methyl D-aspartate; GABA, gamma amino butyric acid; nAChR, acetylcholine nicotinic receptors; PGE, prostaglandin E; TNF, tumor necrosis factor. Adapted with permission from Dharmshaktu *et al.* [Dharmshaktu *et al.*, 2012].

Drug/drug class	Adverse effects	Precautions	Potential drug interactions
Venlafaxine	Nausea, somnolence, hypertension, dry mouth, constipation, sexual dysfunction, blood dyscrasias, hyponatremia, SIADH	Caution in hypertension or seizure disorders, suicidal behavior, renal or liver disease, pregnancy (especially in third trimester)	MAOIs, TCAs, SSRIs, pimozide, tramadol, triptans, erythromycin, haloperidol, linezolid, trazodone, duloxetine, pseudoephedrine
Bupropion	Tachycardia, insomnia, agitation, tremor, dry mouth, headache, constipation, Stevens-Johnson syndrome	Contraindicated in seizure history, caution in suicidal behavior, renal and liver disease	MAOIs, SSRIs, beta-blockers, tramadol, warfarin, levodopa, pseudoephedrine
Duloxetine	Nausea, dry mouth, constipation, somnolence, insomnia, dizziness, sweating, fatigue, decreased appetite	Caution in hypertension and seizure disorders, suicidal behavior, renal and liver disease, pregnancy (especially in third trimester)	MAOIs, phenothiazines, amiodarone, beta- blockers, haloperidol, ritonavir, quinolones, TCAs, SSRIs, triptans, tramadol, propoxyphene, bupropion, venlafaxine, pseudoephedrine
Milnacipran	Nausea/vomiting, headache, constipation, insomnia, dizziness, palpitations, hyperhidrosis, hypertension, dry mouth, urinary retention, seizures, serotonin syndrome	Caution in ESRD, liver disease, alcohol abuse, glaucoma	MAOIs, triptans, venlafaxine, digosin, duloxetine, olanzapine, fluosxetine, sibutramine, SSRI
TCAs	Sedation, confusion, orthostatic hypotension, weight gain, tachycardia, arrhythmia, anticholinergic effects (dry mouth, blurred vision, urinary retention, constipation)	Caution in elderly, medically ill cardiovascular disorders, seizure history, narrow angle glaucoma, suicidal behavior	MAOIs, SSRIs, anticholinergic agents, antiarrythmic, clonidine, lithium, tramadol, linezolid, flumazenil, pimozide, carbamazepine, carbonic anhydrase inhibitors, rifampins, valproic acid, agents that prolong QTc interval
SSRIs	Nausea, headache, diarrhea, insomnia, dizziness, tremor, constipation, sexual dysfunction, hponatremia, SI- ADH, priapism, platelet dysfunction	Caution in seizure disorders, suicidal behavior, pregnancy	MAOIs, other SSRIs, ergot alkaloids, pimozide, TCAs, tramadol, aspirin, NSAIDs, buspirone, trazodone, triptans, aspirin, NSAIDs, buspirone, trazodone, triptans, linezolid, methylphenidate, phenothiazines, propoxyphene, pheytoins

Table 4 Common adverse effects and	drug	interactions	of antide	pressant
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Abbreviations: MAOI, mono amine oxidase inhibitors; SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants; SIADH, syndrome of inappropriate antidiuretic hormone secretion; ESRD, end stage renal disease; NSAIDs, non-steroidal anti-inflammatory drugs. Adapted with permission from McDonald and Portenoy [McDonald and Portenoy, 2006].

antidepressants has shown both drugs to possess analgesic properties, with venlafaxine having comparable efficacy [Sindrup *et al.*, 2003; Dharmshaktu *et al.*, 2012], but better toxicity profile [Koesters *et al.*, 2011]. The risk of gastrointestinal (GI) bleeding is significantly increased when used simultaneously with non-steroidal anti-inflammatory drugs (NSAIDs) [Haanpaa *et al.*, 2010]. If concomitant use of both these agents cannot be avoided, a GI prophylaxis agent should be considered [Haanpaa *et al.*, 2010]. Venlafaxine use, particularly in daily doses greater than 200 mg, is associated with dose-related hypertension and therefore, it is recommended that patients undergo regular blood pressure monitoring [Johnson *et al.*, 2006]. Providers should avoid venlafaxine in patients with uncontrolled

hypertension, as well as in patients who are at high risk of developing ventricular arrhythmia [Johnson *et al.*, 2006]. The cardiovascular side effects seen with venlafaxine are more common in elderly patients. In a prospective cohort study of elderly patients, 24% of initially normotensive participants and 54% of those with preexisting hypertension had an increase in blood pressure, whereas orthostatic hypotension developed in 29% of the patients [Johnson *et al.*, 2006]. A significant increase in the QTc interval was also found in some patients. Withdrawal symptoms may occur with abrupt discontinuation of venlafaxine [McDonald and Portenoy, 2006]. Venlafaxine is metabolized by CYP2D6 and patients with decreased CYP2D6 expression tend to have more side effects with its use [Shams *et al.*,

Table 5 Initial d	lose and usual effective	e dose of antidepressants
for pain control		
Drug	Starting dose	Usual effective dose
Venlafaxine	50-75 mg daily	75-225 mg daily
Bupropion	100-150 mg daily	150-450 mg daily
Duloxetine	60 mg daily	60 mg daily
Milnacipran	25 mg daily	50-100 mg daily
TCAs		
Amitriptyline	10-25 mg nightly	50-150 mg nightly
Nortriptyline	10-25 mg nightly	50-150 mg nightly
Desipramine	10-25 mg nightly	50-150 mg nightly
SSRIs		
Paroxetine	10-20 mg nightly	20-40 mg nightly
Citalopram	10-20 mg nightly	20-40 mg nightly
Abbreviations: T	CAs, tricyclic antidep	ressants; SSRIs, selec-
tive serotonin re	euptake inhibitors. Ad	lapted with permission

2006]. Despite a theoretical possibility of drug interaction with agents that inhibit or stimulate CYP2D6, no such drug interactions have been observed in clinical practice.

from McDonald and Portenoy [McDonald and Portenoy, 2006].

Desvenlafaxine is a salt form of the major active metabolite of venlafaxine [Pae *et al.*, 2009]. The oral formulation has quick and direct effects in neuronal systems of the brain. Unlike venlafaxine, desvenlafaxine is not metabolized by CYP450 enzymes and is associated with only minimal inhibition of CYP enzymes, leading to low risk of drug interactions and inter-individual pharmacokinetic variability [Pae *et al.*, 2009; Seo *et al.*, 2010]. Though it has been shown to be effective as an antidepressant, there is little evidence that desvenlafaxine is effective in management of pain syndromes [Seo *et al.*, 2010]. However, it is utilized off-label by physicians in management of neuropathic pain and fibromyalgia based on success of venlafaxine in these conditions.

Duloxetine is another SNRI that is a potent dual reuptake inhibitor of serotonin and norepinephrine. Randomized controlled trials (RCTs) of duloxetine versus placebo have shown relief in painful polyneuropathy. Duloxetine is also found to have an activating action helpful in hypoactive, depressed, or fatigued patients [Lussier *et al.*, 2004]. Duloxetine was the first antidepressant medication to be approved by FDA for the treatment of neuropathic pain, specifically associated with diabetic neuropathy [McDonald and Portenoy, 2006]. Common dose-limiting side effects associated with duloxetine include nausea and somnolence. It should not be combined with agents like CYP 1A2 inhibitors or nonselective, irreversible monoamine oxidase inhibitors [Masuda *et al.*, 2013]. Clinical trials have shown the analgesic efficacy of duloxetine for poly diabetic neuropathy and fibromyalgia along with improvements in quality-of-life measurements [Sultan *et al.*, 2008; Lunn *et al.*, 2009]. Duloxetine is a frequently preferred option in neuropathic pain management because it is efficacious and well tolerated. Milnacipran is the newest SNRI available that has a

strong selectivity for norepinephrine reuptake [Mitra and Jones, 2012]. Some RCTs have shown milnacipran to be highly effective in the treatment of fibromyalgia [Mease et al., 2009; Geisser et al., 2011]. When a systematic review of RCTs was performed in fibromyalgia patients receiving milnacipran 100-200 mg daily, it was found to be effective for only a minority of people for the treatment of fibromyalgia pain, providing moderate levels of relief when compared with placebo [Derry et al., 2012]. Milnacipran is the only antidepressant other than duloxetine that is FDA approved for treatment of fibromyalgia pain. Milnacipran does not undergo cytochrome P450 metabolism, and has a half-life of 6-8 hours. Fifty-five percent of each dose is excreted unchanged in the urine. Recently, a RCT concluded that addition of milnacipran to pregabalin in fibromyalgia patients who respond incompletely to the disorder showed improved pain, global status and other symptoms [Mease et al., 2013].

Tricyclic and tetracyclic antidepressants (TCAs)

TCAs are comprised of tertiary amines (amitriptyline, imipramine, clomipramine, doxepin) and secondary amines (nortriptyline, desipramine), both of which have analgesic properties. Secondary amines are generally better tolerated. Maprotiline and mirtazapine are tetracyclic antidepressants. Amitriptyline, nortriptyline, and desipramine inhibit both serotonin and norepinephrine reuptake to varying degrees and are effective for most neuropathic conditions. Their action is mediated by multiple pathways, which include increasing neurotransmitter availability in endogenous monoamine-mediated pain-modulating brain pathways that use serotonin or norepinephrine, interaction with endogenous opioid systems, and pharmacokinetic interactions with opiates leading to higher opiate concentrations [McDonald and Portenoy, 2006]. Studies have shown that the dose of TCAs required for analgesia

frequently are lower than the dose needed to manage depression, with a faster onset of analgesic action in comparison to antidepressant action. A provider should closely monitor patients when using TCAs and limit use in the elderly, due to their relatively frequent and poorly tolerated anticholinergic side effects. A study assessing the association between the use of antidepressants and future risk of cardiovascular disease (CVD) showed that TCAs are associated with a 35% increased risk for future CVD, which is not explained by psychiatric illness [Hamer *et al.*, 2011]. Therefore, TCAs should be avoided in patients with CVD.

Tetracyclic antidepressants like maprotiline and mirtazapine do not have strong evidence for use in pain management. A randomized double-blind, placebocontrolled trial in non depressed patients concluded that mirtazapine had better efficacy, in comparison to placebo, in decreasing the duration, intensity and frequency of chronic headaches when used as a prophylaxis [Bendtsen and Jensen, 2004]. Another uncontrolled study, with 594 patients, showed potential beneficial effect of mirtazapine in the treatment of patients with pain and concomitant depression [Freynhagen *et al.*, 2006]. However, there exists a need for placebo-controlled studies to confirm this benefit.

An older study compared maprotiline with amitriptyline, revealing that there was no significant difference between the two drugs in the treatment of painful neuropathy in diabetics and non-diabetics [Vrethem *et al.*, 1997]. Another study evaluated the effect of long term administration of maprotiline on sensory nerve function in patients with post herpetic neuralgia (PHN) via measurement of current perception thresholds (CPTs). Maprotiline, 60 mg daily, increased CPTs at two months in PHN patients when compared to controls, correlating well with decrease in pain score [Kudoh *et al.*, 2003]. Co administration of maprotiline has also been shown to increase the anti-nociceptive duration of morphine four-fold [Pettersen *et al.*, 2009].

Selective serotonin reuptake inhibitors (SSRIs)

Even though SSRIs possess potent antidepressant action, their analgesic action has been shown to be relatively ineffective. There are some positive RCTs of the combination of paroxetine and citalopram being effective for diabetic peripheral neuropathy [Sindrup *et al.*, 1990; Sindrup *et al.*, 1992; Holliday and Plosker, 1993]. Some studies of trazodone in cancer pain and fibromyalgia have shown positive results [Ventafridda *et al.*, 1987; Morillas-Arques *et al.*, 2010], whereas it has not been shown to be an effective analgesic in dysesthesic pain from traumatic myelopathy and burning mouth pain [Davidoff *et al.*, 1987; Tammiala-Salonen and Forssell, 1999]. A recent trial of trazodone in fibromyalgia showed that its combination with pregabalin enhanced the degree of improvement in the symptomatology associated with fibromyalgia, when compared with trazodone when given alone [Calandre *et al.*, 2011]. Data is limited on the analgesic efficacy of other SSRIs.

Other antidepressants

Bupropion is an antidepressant that inhibits serotonin, norepinephrine, and less potently dopamine. It is prescribed for smoking cessation and neuropathic pain [Semenchuk *et al.*, 2001; Shah and Moradimehr, 2010]. Isolated case reports have shown that bupropion has analgesic action in chronic headaches [Pinsker, 1998], but studies failed to show benefit in treatment of non-neuropathic back pain [Katz *et al.*, 2005]. Similar to duloxetine, bupropion is also activating. A major advantage of bupropion over other antidepressants is its low risk of somnolence and sexual dysfunction.

Antiepileptics

Antiepileptic agents have strong positive evidence in randomized trials and have been successful in clinical practice when used for neuropathic pain. Multiple antiepileptics are available, including typical antiepileptics (carbamazepine, oxcarbazepine, phenytoin and valproate) and atypical antiepileptics (gabapentin, pregabalin, topiramate, lamotrigine, and clonazepam). It is thought that they work so well for the management of neuropathic pain syndromes because of their ability to decrease the neuronal excitability. The hyperexcitable state of neuropathic pain is associated with reduced thresholds and ectopic discharges at the spinal dorsal horn or dorsal root ganglion pain neurons due to upregulation of sodium and calcium channels [Han et al., 2000]. While carbamazepine, oxcarbazepine, phenytoin and lamotrigine suppress the ectopic discharges by inhibition of sodium channels, gabapentinoids act through modulation of calcium channels [Burchiel, 1988].

Gabapentin and pregabalin, the gabapentinoids antiepileptics, are both efficacious in treating neuropathic pain. Unlike other anticonvulsants that have action at GABA or sodium channels, they instead inhibit release of nociceptive neurotransmitters, glutamate and substance

P, by reducing the calcium influx into presynaptic nerve terminals. Gabapentin is considered as first-line treatment for neuropathic pain syndromes, due to its favorable side effect profile and no major drug interactions [Rowbotham et al., 1998; Bennett and Simpson, 2004]. Gabapentin has been shown to be well tolerated and efficacious for the treatment of neuropathic pain in multiple placebocontrolled, randomized clinical trials [Backonja et al., 1998; Caraceni et al., 1999; Morello et al., 1999; Rice and Maton, 2001; Caraceni et al., 2004]. The drug is frequently used for postherpetic neuralgia, painful diabetic neuropathy, and cancer associated neuropathic pain. Addition of gabapentin has also shown a synergistic effect in patients already receiving opioids for cancer pain, where the combination is more effective than either drug alone [Gilron et al., 2005]. Poor oral bioavailability and nonlinear pharmacokinetics with dose escalation are a few limitations encountered with the use gabapentin, which makes it difficult to predict appropriate therapeutic dose and requires a prolonged titration time period.

Pregabalin, a drug structurally similar to gabapentin, was developed to overcome the issues of low potency and nonlinear pharmacokinetics encountered with gabapentin. It is widely used in treatment of neuropathic pain when gabapentin is not tolerated. As opposed to gabapentin, the pregabalin dose may be more rapidly escalated. Pregabalin is known to cause weight gain. Similar side effects have been seen with its counterpart gabapentin (*Table 6*).

An actively transported prodrug of gabapentin, gabapentin enacarbil, recently became available for treatment of restless leg syndrome (RLS). An integrated retrospective analysis of various doses of gabapentin enacarbil was performed to compare their efficacy and side effects. The results showed that gabapentin enacarbil 600 mg once daily significantly improved RLS symptoms in comparison with placebo [VanMeter *et al.*, 2012].

Lamotrigine has been shown to have efficacy in neuropathic pain not related to cancer [Zakrzewska *et al.*, 1997; Simpson *et al.*, 2000]. Lamotrigine works by blocking tetrodoxin-resistant sodium channels and inhibition of glutamate release from presynaptic neurons. It has been shown to improve pain associated with diabetic neuropathy, multiple sclerosis, spinal cord injury, central post stroke pain, polyneuropathy, complex regional pain syndrome, and refractory trigeminal neuralgia [Wiffen *et al.*, 2011]. The side effect profile is similar to other centrally acting analgesics that require a slow titration of the drug. Important concerns to monitor with lamotrigine, are the

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potential for rash and Stevens-Johnson syndrome. *Table* 7 shows initial dose and usual effective dose of anti epileptics used for pain management.

Corticosteroids

Corticosteroids can provide pain relief in many cancer pain syndromes, including bone pain associated with metastasis, neuropathic pain from either spinal cord compression or nerve infiltration by direct tumor infiltration, pain from lymphedema or due to bowel obstruction, headache due to increased intracranial pressure, and arthralgia [Lussier et al., 2004]. Their analgesic action is mediated by the decrease in edema around pain sensitive structures and potential decrease in the ephaptic neural discharges [Mitra and Jones, 2012]. No studies of analgesic effects have been performed, to date, about the relative potency, efficacy and dose response relationship among different corticosteroid agents. Providers often choose dexamethasone based on its theoretical advantage of possessing low mineralocorticoid activity, but prednisone or methylprednisolone can also be used [Lussier et al., 2004]. Dosing of steroid can be done variably. Dexamethasone is usually effective in a low dose regimen (at a dose of 2-12 mg daily) for achieving analgesia. Short term use of high-dose steroids is mainly recommended for patients whose have rapidly increasing pain along with functional impairment [Knotkova and Pappagallo, 2007]. Particular attention should be given to the risk of side effects like GI bleeding, severe dyspepsia and candidiasis. They should be avoided in patients who have delirium, infection, and uncontrolled glucose levels. In circumstances where a trial of corticosteroid therapy is not effective, it is reasonable to taper it off.

Bisphosphonates, denosumab and calcitonin

Bisphosphonates were originally used to treat hypercalcemia associated with cancer. Incidentally, they also were found to have analgesic effects on pain of bony origin. They are found to be efficacious particularly with bone metastasis [Amadori *et al.*, 2013], and multiple myeloma [Morgan *et al.*, 2010; Morgan *et al.*, 2012]. The available bisphosphonate agents that have shown efficacy in malignant bone pain conditions are zoledronate and pamidronate. Zoledronic acid is the most commonly used, as it has shown superiority in comparison to other bisphosphonates in management of skeletal related events [Lipton *et al.*, 2002; Rosen *et al.*, 2004]. Denosumab is a novel human monoclonal antibody

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Table 6 Comm	on adverse effects and potential drug interactions of antiep	ileptics	
Drug	Adverse effects	Precautions	Potential drug interactions
Gabapentin	Somnolence, dizziness, ataxia, weight gain, peripheral edema, dyspepsia, leukopenia	Lower doses in elderly and renal insufficiency; caution in pregnancy	Antacids, naproxen, may potentiate opioids, ethanol
Pregabalin	Dizziness, somnolence, peripheral edema, amblyopia, dry mouth, ataxia headache, confusion, diarrhea	Lower doses in elderly and renal insufficiency; caution in pregnancy	May potentiate opioids, ethanol, benzodiazepines
Lamotrigine	Somnolence, dizziness, ataxia, diplopia, headache, confusion, nausea and depression, Stevens-Johnson syndrome/severe rash (black box warning), bone marrow suppression, pancreatitis and hepatotoxicity	Reduce dose with valproic acid, oral contraceptives, or hepatic or renal disease, discontinue at first sign of rash; teratogenic	Rifampins, carbamazepine, ethosuximide, oxcarbazepine, phenobarbital, phenytoins, ethanol, lopinavir, ritonavir, pimozide, pyimethamine/sulfadoxine, trimethoprim, sulphamethoxazole
Topiramate	Somnolence, dizziness, ataxia, anxiety, speech disturbances, psychomotor slowing, abnormal vision, memory difficulty, paresthesia and diplopia, pancreatitis, hepatotoxicity, nephrolithiasis, osteomalacia, osteoporosis, hyperthermia, anemia, leukopenia, psychosis	Can cause metabolic acidosis, lower dose in kidney and caution in liver disease; teratogenic	Carbonic anhydrase inhibitors, oral contraceptives, phenytoin, valproic acid, carbamazepine, digoxin, metformin, lithium, amitriptyline, risperidone
Oxcarbazepine	Dizziness, somnolence, diplopia, fatigue, nausea, vomiting, ataxia, abnormal vision, abdominal pain, tremor, dyspepsia, angioedema, leukopenia, Ste- vens-johnsons syndrome, hyponatremia, increased liver enzymes	Lower dose in patients with renal disease; discontinue at first sign of rash, teratogenic	Amlodipine, atorvastatin, calcium channel blockers, oral contraceptives, clarithromycin, phenytoin, valproic acid, carbamazepine, Phenobarbital
Tiagabine	Dizziness, asthenia, somnolence, nausea, nervousness, irritability, tremor, abdominal pain, difficulty with concentration or attention, seizures (in non-epileptic patients), severe rash	Lower dose in liver disease; caution in non-epileptic patients; teratogenic; avoid abrupt withdrawal	Ethanol, ethosuximide, pimozide, carbamazepine, phenytoin, phenobarbital
Levetiracetam	Somnolence, headache, asthenia, infection, dizziness, emotional lability, psychosis, suicide at- tempts, leukopenia, neutropenia, pancytopenia, thrombocytopenia	Lower dose in patients with renal disease and in the elderly; avoid abrupt withdrawal; caution in pregnancy	None
Zonisamide	Somnolence, anorexia, dizziness, headache, nausea, agitation, irritability	Avoid if allergic to sulpha, discontinue at first sign of rash; caution in renal and liver disease, nephrolithiasis; teratogenic	Phenytoin, valproic acid, carbamazepine, phenobarbital, bosentan, CNS depressants, anticholinergics, diltiazepam, metoclopramide, protease inhibitors, rifampin
Adapted with p	ermission from McDonald and Portenov. [McDonald an	d Portenov. 2006l.	

Table 7 Initial dose and usual effective dose of anti-epileptics					
for pain control					
Drug	Starting dose	Usual effective dose			
Gabapentin	100-300 mg qhs	900-3,600 mg			
		daily divided bid-tid			
Pregabalin	150 mg daily	150-300 mg bid			
Lamotrigine	25-50 mg daily	200-400 mg daily			
Topiramate	25 mg daily	200-400 mg daily			
Oxcarbazepine	75-150 mg bid	150-800 mg bid			
Tiagabine	4 mg qhs	4 mg tid			
Levetiracetam	250-500 mg bid	500-1,500 mg bid			
Zonisamide	100 mg daily	100-200 mg bid			
Adapted with permission from McDonald and Portenoy.					
[McDonald and Portenoy, 2006].					

that inhibits bone resorption by binding to the receptor activator of nuclear factor kappa B ligand (RANKL). It is indicated for prevention of skeletal-related events in patients with solid tumor metastasis and helps in relief of bone pain [Fizazi *et al.*, 2011; Scott and Muir, 2011; von Moos *et al.*, 2013]. A recent systematic review of multiple RCTs showed that denosumab is more effective than zoledronic acid for bone pain interference and prevention of progression of bone pain severity [von Moos *et al.*, 2013].

Calcitonin has been found to be effective in treating bone pain associated with acute osteoporotic fractures, but not in chronic fractures [Blau and Hoehns, 2003; Knopp *et al.*, 2005; Knopp-Sihota *et al.*, 2012]. It has weak evidence in treatment of bone pain in cancer patients [Szanto *et al.*, 1992]. Studies of calcitonin in treating neurogenic claudication from lumbar canal stenosis have shown negative results [Podichetty *et al.*, 2004; Coronado-Zarco *et al.*, 2009]. It can be administered as intranasal spray, per rectal formulation, subcutaneous and intravenous injection. The most common side effects include nausea and skin hypersensitivity.

Alpha-2 adrenergic agonists

In the past, alpha-2-adrenergic agents were used primarily to treat hypertension, but their clinical use has now expanded widely in anesthesia, peri-operative and postoperative pain control, sedation, anxiolysis and treatment of chronic pain syndromes [Chan *et al.*, 2010]. Side effects include hypotension, bradycardia and sedation. Clonidine, tizanidine and the newer α -2 adrenergic, dexmedetomidine, are the most commonly used α -2 adrenergic agents in clinical practice. Both clonidine and dexmedetomidine are selective agonists of α -2 adrenergic receptors, with an α -2 to α -1 ratio of 200:1 and 1,620:1, respectively [Lowenthal, 1980; Virtanen *et al.*, 1988]. Therefore, dexmedetomidine is approximately eight times more specific than clonidine to α -2 adrenergic receptors. Studies of α -2 adrenergic agents implicate that their action are mainly central at the spinal-cord level [Chan *et al.*, 2010], but dexmedetomidine has both peripheral action and central action.

Clonidine improves the analgesic efficacy of local anesthetics and morphine, in addition to providing postoperative analgesia. The evidence supporting the postoperative analgesic effect is the strongest when clonidine is used regionally, particularly as adjunct to peripheral nerve and plexus blocks [McCartney et al., 2007; Popping et al., 2009], and intrathecal anesthesia [Sites et al., 2003; Elia et al., 2008], with a possible efficacy with epidural route [Wu et al., 2004; Dobrydnjov et al., 2005; Farmery and Wilson-MacDonald, 2009]. Unlike clonidine, dexmedetomidine is rarely given epidurally or intrathecally, likely due to the possible neurotoxic effects associated with epidural administration [Konakci et al., 2008]. Studies with dexmedetomidine have shown that when it is given as a single agent, there was a morphine-sparing effect, but no improvement in pain scores [Unlugenc et al., 2005; Gurbet et al., 2006; Dholakia et al., 2007]. However, the studies exploring postoperative analgesia of dexmedetomidine are far fewer in number than clonidine-implicating that analgesic benefit of dexmedetomidine in post-operative period needs to be further explored.

N-methyl-D-aspartate (NMDA) receptor antagonists

Trials are ongoing, with numerous compounds that specifically target mechanisms mediating neuropathic pain involving the NMDA receptor. NMDA antagonists have an interesting action of preventing sudden acute pain from progressing into chronic pain by blocking receptors of neurotransmitters that are essential for creating longterm pain pathways. NMDA antagonists also reduce opioid tolerance and may enhance opioid analgesia. Their utility is limited by significant dose-related, adverse effects, including lightheadedness, dizziness, tiredness, headache, bad dreams and sensory changes. Agents with clinically relevant NMDA blocking properties include ketamine, amantadine (an anti-influenza medication), memantine (an Alzheimer dementia medication), dextromethorphan (an anti-cough medication), and methadone (a mixed opioids and NMDA receptor antagonist). Among these drugs, ketamine and dextromethorphan remain the most studied NMDA antagonists in the clinical setting for the treatment of patients with neuropathic pain [Zhou *et al.*, 2011].

Ketamine is a strong NMDA antagonist that has been used orally and intravenously for the treatment of chronic regional pain syndrome (CRPS) and other neuropathic pain conditions. Adverse effects seen with ketamine include nausea, psychomimetic effects, intoxicated feeling, headaches, hypertension and elevated liver enzymes [Azari et al., 2012]. A recently published systematic review of trials of ketamine in refractory cancer pain confirmed it as a viable option for this indication [Bredlau et al., 2013]. A double-blind RCT of multi-day low dose ketamine infusion as an adjuvant to gabapentin in post-spinal cord injury related chronic pain confirmed the safety and efficacy of this regimen [Amr, 2010]. However, the study also showed that the effects of low dose ketamine and gabapentin ceased two weeks after infusion termination in comparison to gabapentin in combination with placebo. Some investigators have also explored the intranasal formulation of ketamine, finding it promising for the treatment of neuropathic pain [Huge et al., 2010].

Dextromethorphan, memantine and amantadine are weaker NMDA receptor blockers, and therefore have fewer CNS side effects. Dextromethorphan has efficacy in treatment of neuropathic pain conditions, like diabetic neuropathy, but not in post herpetic neuralgia [Sang et al., 2002; Thisted et al, 2006]. A small cross over study showed that high dose dextromethorphan, at 270 mg, provides analgesia in patients with neuropathic pain post traumatic injury [Carlsson et al., 2004]. A multicentric clinical trial studied two fixed dose combinations of dextromethorphan and quinidine (45 mg/30 mg and 30 mg/30 mg, respectively) for diabetic neuropathy leg pain and found both the doses to be effective with acceptable tolerability profile [Shaibani et al., 2012]. A well-designed phase 3 trial found AVP-923 to have potential for the treatment of diabetic neuropathy. AVP-923 is a combination of two compounds, the active ingredient dextromethorphan hydrobromide and the enzyme inhibitor quinidine sulfate (a CYP450 2D6 inhibitor), which serves to increase the bioavailability of dextromethorphan [Olney and Rosen, 2010]. The use of this drug recently was approved for agitation in patients with Alzheimer's dementia, but not yet approved in diabetic neuropathy.

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Currently, memantine is marketed for the treatment of dementia, and has been proposed as a medication for the treatment of neuropathic pain for its mechanism, safety, lack of serious adverse effects, and relatively rapid onset of action [Rogers *et al.*, 2009]. However, clinical trials have not been promising and its routine use in neuropathic pain is not currently recommended [Rogers *et al.*, 2009].

A novel drug, indantadol (V3381), which is an oral NMDA antagonist and non-selective monoamine oxidase inhibitor was being developed as a potential treatment of neuropathic pain [Mattia and Coluzzi, 2007]. Unfortunately, the phase II study showed that it failed in treatment of neuropathic pain in patients with diabetes.

0-conotoxins

Ziconotide is a synthetic equivalent of ω -conotoxin, a naturally occurring conopeptide [Kong and Irwin, 2009; Essack *et al.*, 2012]. It is a N-type calcium-channel blocker found in the conus magus, a piscivorous marine snail. Intrathecal infusion of ziconotide is approved by FDA for the treatment of severe chronic pain in patients who are intolerant or refractory to other treatments [Pope and Deer, 2013]. At this time, clinical evidence to support the use of ziconotide is limited. Ziconotide use is commonly associated with side effects like confusion, dizziness, nausea, nystagmus and contraindicated in patients with psychosis.

Summary

There are numerous pharmacotherapeutic options for the management of chronic pain. Proper evaluation, along with complete assessment of pain, is crucial to provide best possible analgesic approach. Optimization of analgesia in the long-term setting requires achieving a proper balance among efficacy, adverse effects, cost and other factors. Primary treatment directed at the specific etiology of pain is an important part of strategy to address poorly controlled chronic pain. In order to optimize the balance between pain control and toxicities, it is best to start the treatment with an adjuvant analgesic after opioids have been used and their doses well titrated.

Other than the introduction of an adjuvant analgesic, other approaches to additional pain control include rotation to an alternative opioid, trial of neuraxial infusion, and non-pharmacological therapies (conservative such as use of an orthotic or interventional such as neural blockade). Antidepressants and antiepileptics are the two most

important categories of drugs with current widespread clinical use for neuropathic pain management. No head to head comparison of antidepressants and anticonvulsants has been done in clinical trials for pain control, making it difficult to recommend one class over the other as first-line treatment. A provider may choose one class of drug over the other because of certain comorbidities and other non-pain symptoms. For example, patients with pain and concomitant depression may benefit from antidepressants and those with concomitant insomnia may benefit from sedating drugs. Drugs with known relatively higher toxicities should be started at a low dose and should be dose titrated as patients become tolerant to side effects. If an adjuvant analgesic produces a significant but incomplete analgesia, with side effects that are tolerable, it should be continued with consideration of addition of another adjuvant analgesic. The first step in a comprehensive pain assessment should be to determine the type of pain, then to get it under control as soon as possible, with opioids if needed. The provider's next thought should be to add an adjuvant analgesic.

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Topical analgesics

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Introduction

Pain signaling involves several processes, including activation and sensitization of sensory nerve endings (nociceptors), signal propagation and input into the dorsal horn of the spinal cord, supraspinal projection and integration, and descending modulation. Several recent reviews summarize advances in understanding the molecular and cellular neurobiology of initial steps involved in afferent signaling and in peripheral and central sensitization, and their contributions to inflammatory and neuropathic pain [Basbaum et al., 2009; Gold and Gebhart, 2010; von Hehn et al., 2012]. In view of these advances, there has been considerable interest in developing drugs that can selectively target the peripheral compartment to produce analgesia [Sawynok, 2003; Cairns, 2009]. Topical analgesics represent a class of pharmacological agents that are applied peripherally to cutaneous somatic sites, or to specialized compartments (e.g., oral cavity), and act locally on sensory nerve endings or adjacent structures to inhibit pain signaling. Topical analgesics come in several forms (creams, gels, patches) and differ from transdermal delivery systems where the drug is delivered to the skin but acts at remote sites within the central nervous system (e.g., fentanyl and buprenorphine patches). Topical delivery results in low systemic drug levels, and few systemic side effects or drug interactions. They are of interest as potential monotherapies and as combination therapies due to their low systemic adverse effect profile. They are generally well tolerated, although local adverse effects can occur. There is a considerable body of data validating topical analgesics for management of osteoarthritis [Derry et al., 2012] and neuropathic pain [Derry et al., 2013; Haanpää and Treede, 2012; Mick and Correa-Illanes, 2012].

Neuropathic cancer pain and treatment

With cancer, pain can be prevalent and impair quality of life; it is treated using World Health Organization guidelines for pain relief which recommend stepwise selection of analgesic drug classes and adjuvants [World Health Organization, Analgesics Ladder]. Cancer pain can arise from the disease process (e.g., tumor infiltration, nerve compression) or from treatments such as surgery, radiotherapy and chemotherapy [Urch and Dickenson, 2008; Lema et al., 2010; Fallon, 2013]. Neuropathic pain is defined as caused by injury or disease of the peripheral or central nervous system [Treede et al., 2008]. Cancer pain is characterized as nociceptive or neuropathic and often as mixed nociceptive/neuropathic; pain considered as neuropathic can occur in up to 40% of cancer patients [Caraceni and Portenoy, 1999; Bennett et al., 2012]. Neuropathic cancer pain is treated using therapies with proven efficacy in other neuropathic pain conditions (e.g., post-herpetic neuralgia, diabetic neuropathy), including adjuvants such as tricyclic antidepressants (e.g., amitriptyline, nortriptyline), serotonin noradrenaline reuptake inhibitors (e.g., duloxetine, venlafaxine), gabapentinoids (gabapentin, pregabalin), and other agents [Attal et al., 2010; Dworkin et al., 2010; Finnerup et al., 2010]. There are a growing number of trials informing this area that indicate benefits outweigh risks [Mitra and Jones, 2012; Jongen et al., 2013]. Combination therapies involving analgesics and adjuvants are also being explored for neuropathic pain in cancer [Arai et al., 2010; Bennett, 2010]. Topical analgesics are often considered as adjuvant analgesics or co-analgesics [Lussier et al., 2004; Mitra and Jones, 2012]. While there are a limited number of clinical trials using topical analgesics for neuropathic pain related to cancer, there has been some exploration of this indication. The following sections will review classes of agents used as topical analgesics in relation to cancer care.

Table I Ch	inical studies of indocanie 3 % inedicated	i plaster for neuropathic pain in can	
Report	Study design	Participants	Outcomes
Hans <i>et al.</i> , 2008	CASE REPORT; NeP following decompression surgery in metastatic pancreatic cancer	N=1 (54 yrs)	Pain relief (dysesthesia, allodynia) after 12 hrs; effective analgesia maintained several weeks
Cheville <i>et al</i> ., 2009	Prospective RCT, double-blind, crossover trial; four week treatment, persistent postsurgical pain in cancer patients	N=21 completed 1 st phase; N=18 completed crossover phase; mean age 61.8 (SD 9.5) yrs	Lidocaine patch did not significantly reduce pain intensity or alter most secondary end points (but some are improved)
Fleming and O'Conner, 2009	Retrospective CASE SERIES; pain in palliative care service in a comprehensive cancer centre [2001-2009]	N=97 total; N=26 post-surgical NeP, N=24 post-herpetic neuralgia, N=18 cancer-related NeP; median age 61 (range 19-99) yrs	Analgesia considered potent in 35-38% of those with post-herpetic neuralgia and post-surgical NeP, 27% in NeP from cancer treatment, 12% in cancer-related NeP; where allodynia present (>60%), partial or potent effect in 62%; terminated in 8% due to skin irritation
López Ramírez, 2013	Retrospective CASE SERIES; NeP in cancer patients presenting for radiotherapy over 6 months [2011]	N=15; 40% NeP related to cancer, 60% not related; median age 65.7 (range 48-86) yrs	Analgesia considered potent (≥4 VAS units) in N=8, partial (≥2 VAS units) in N=4; 80% exhibit efficacy; 7% with skin irritation
Kern <i>et al.</i> , 2013	Retrospective CASE SERIES; NeP following surgery or chemotherapy, report from meeting in Germany in 2010; participants invited to contribute reports 4 weeks prior to meeting	N=41; age 59.5±13.7 yrs; pain duration 1.8 (SD 2.8) yrs; 80% receive concomitant oral pain medications	N=20 much improved; N=10 very much improved; 73% improved; N=11 exhibit minimal or no change; oral analgesic dose reduction in 62%; allodynia, hyperalgesia, and pain quality considered to provide potential (not definitive) indicators of treatment success

Table 1 Clinical studies of lidocaine 5% medicated plaster for neuropathic pain in cancer

Abbreviations: NeP, neuropathic pain; RCT, randomized controlled trial; VAS, visual analog scale; yrs, years.

Topical analgesics and cancer care

Lidocaine medicated plaster

Topical 5% lidocaine medicated plaster is approved for use for localized or focal peripheral neuropathic pain, and is registered in the United States, and in European, Latin American, and Middle Eastern countries [Mick and Correa-Illanes, 2012]. It is licensed for treatment of post-herpetic neuralgia, but has been evaluated in clinical trials for a variety of pain conditions [Mick and Correa-Illanes, 2012]. Up to three plasters (10 cm × 14 cm, containing 700 mg lidocaine, 5% w/w) are recommended daily, for a maximum of 12 hours with a plaster-free interval of 12 hours; $3\% \pm 2\%$ of drug reaches the systemic circulation.

There are a limited number of reports on the use of lidocaine 5% medicated plaster in cancer patients (*Table 1*). There is a case report of early onset and sustained pain relief of post-surgical pain in a cancer patient [Hans *et al.*, 2008]. However, a prospective randomized-controlled trial did not demonstrate significant pain reduction compared

to placebo patches for persistent post-surgical pain in cancer patients [Cheville et al., 2009]. In fact, that study was terminated early, perhaps reflecting stringent entry criteria. There are three retrospective case series reports of lidocaine 5% medicated plaster use in cancer patients. Fleming and O'Conner [2009] analyzed 97 cases in a comprehensive cancer care setting, and noted partial or potent effects in 27-38% of those with post-herpetic neuraglia (N=24) or post-cancer treatment pain (N=26), and 12% of those with cancer-related pain (N=18). López Ramírez [2013] analyzed 15 cases of neuropathic pain in patients presenting for radiotherapy, and reported 80% partial or potent effects; 40% of neuropathic pain was related to cancer in this report. Kern et al. [2013] analyzed 41 cases of neuropathic pain following surgery, radiotherapy or chemotherapy for cancer; 73% were much or very much improved, and there was a dose reduction in systemic analgesics in 64% of cases where suitable information was available. In two reports, the presence of allodynia or hyperalgesia was considered to be somewhat predictive of treatment responses to lidocaine

Table 2 Clinical studies of topical capsaicin for neuropathic pain following surgery for cancer

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Report	Study design	Participants	Outcomes		
Watson et al.,	OPEN LABEL, capsaicin 0.025%	N=18, post-	8/14 (57%) completing trial report ≥50% reduction		
1989	for 4 weeks	mastectomy pain	in pain; at 6 months, 50% continue with pain relief		
Dini <i>et al</i> ., 1993	OPEN LABEL, capsaicin	N=21, post-	13/19 (68%) report reduction in pain (no worse than		
	0.025% for 8 weeks	mastectomy pain	mild at end); burning noted by 6/21 (29%)		
Watson and	RCT, capsaicin 0.075% vs. inert	N=25 post-	8/13 (62%) report \geq 50% reduction in pain vs. 3/10		
Evans, 1992	placebo, 6 weeks	mastectomy pain	(30%) in placebo group; 92% reported burning		
Ellison et al.,	RCT, capsaicin 0.075% vs. inert	N=99, 52% post-	Average pain reduction of 53% vs. 17% in placebo		
1997	placebo, 8 weeks; crossover trial,	mastectomy pain,	group at 8 weeks; burning common; at end of		
	but initial 8 weeks analysed	34% post-thoracotomy	crossover, 60% preferred capsaicin $\textit{vs.}\ 18\%$ placebo		
	separately	pain, 14% other			
Abbreviation: RCT, randomized controlled trial.					

5% medicated plaster [Kern *et al.*, 2013; López Ramírez, 2013]. While there are unique challenges to evaluating drug effectiveness in neuropathic pain in controlled trials in cancer patients, the results of these case series reports provide valuable pragmatic information related to clinical practice, and are sufficient to warrant conducting large, well-designed trials in this area.

Topical capsaicin

Topical formulations containing low concentrations of capsaicin (0.025-0.075%), especially as creams, are widely available as over-the-counter and prescription remedies for pain. Recent reviews of capsaicin 0.075% cream for neuropathic pain cite a limited number of trials with heterogenous data (sample size, pain conditions), modest effects (number-needed-to-treat or NNT 6.6) and common local skin reactions (erythema, burning; number-needed-to-harm or NNH 2.5) [Derry *et al.*, 2009; Derry and Moore, 2012]. Topical low concentration capsaicin creams are considered second- or third-line approaches for those who do not respond adequately to, or cannot tolerate, first- and second-line therapies [Attal *et al.*, 2010; Dworkin *et al.*, 2010; Finnerup *et al.*, 2010].

Several studies have examined effects of topical capsaicin 0.025-0.075% for post-mastectomy pain following surgery (*Table 2*). In small open-label trials (N=18-21), capsaicin 0.025% resulted in \geq 50% pain reduction over 4-8 weeks in 57-68% of subjects [Watson *et al.*, 1989; Dini *et al.*, 1993]. In a placebo-controlled trial (N=25), capsaicin 0.075% resulted in \geq 50% pain reduction in 62% (8/13) over six weeks [Watson and Evans, 1992]. In a larger post-surgical trial (N=99), which included 52% post-mastectomy patients,

capsaicin 0.075% over eight weeks resulted in an average pain reduction of 53% (vs. 17% for placebo) [Ellison *et al.*, 1997]. At 0.025%, some report burning pain with capsaicin; however, at 0.075%, most report burning sensations (which decline over time) [Watson and Evans, 1992; Ellison *et al.*, 1997]. In the latter study, discontinuation was similar in the placebo group, and 60% of subjects preferred the capsaicin cream (vs. 19% for placebo). In both controlled trials, an inert placebo was used, and there was concern that unblinding occurred due to the burning sensation.

Within the past few years, a high concentration capsaicin patch (8% capsaicin w/w) has been approved in the United States and several European countries [Haanpää and Treede, 2010; McCormack, 2010]. The patch is applied for 30-60 minutes, and acute application site reactions (erythema, pain, pruritis, and edema) are controlled by topical local anesthetics and oral analgesics. Patch application leads to long-lasting (over 12 weeks) analgesia in post-herpetic neuralgia and HIV distal polyneuropathy when compared to an active placebo patch (0.04% capsaicin) [Haanpää and Treede, 2010; McCormack, 2010]. Meta-analysis generates NNT values of 7.0-8.8 and 5.8-11.0 for 30-50% pain relief in these conditions, or a clinically meaningful pain reduction (≥30%) in 45% and 42% of patients, respectively [Derry et al., 2012; Mou et al., 2013]. There are, however, unknown risks in relation to epidermal nerve fiber innervation, which is reduced substantially by patch application, with repeated applications over long periods [Derry et al., 2013]. There are no trials reporting use of the high concentration capsaicin patch in cancer.

Topical opioids

Opioids, via actions at multiple opioid receptors, influence

pain, inflammation and wound healing responses by peripheral actions on nociceptive afferents, immune cells, and cutaneous cells [Stein *et al.*, 2003; Stein and Machelska, 2011; Stein and Küchler, 2013]. Initial studies focused on analgesic properties of peripheral opioids [Stein *et al.*, 2003; Stein and Machelska, 2011]. However, there is now data from both *in vitro* and *in vivo* studies indicating that peripheral opioids also reduce inflammation and tissue destruction, and peripheral opioids have become a potential target for drug development for treating inflammation and to promote wound healing [Stein and Küchler, 2013].

Cutaneous lesions in advanced illness can be painful, difficult to treat, and negatively affect quality of life [Maida et al., 2012]. Topical applications of opioids for cutaneous lesions in palliative care represent an area of emerging investigation. By 2009, a systematic review which focused attention on this issue had identified 19 relevant studies [LeBon et al., 2009]. A more recent review of this subject identified 23 studies (three controlled studies, 17 case series, three case studies) reporting beneficial effects on pain in palliative settings with topical opioid treatments [Graham et al., 2013]. There was considerable variation in size and aetiology of wounds, with the most common being of pressure and malignant origins; there was also a variety of opioids (diamorphine, morphine, oxycodone, meperidine, methadone), doses, vehicles to deliver opioids (IntraSite gel, hydrogel, novel gel formulations), and concomitant oral medications used in these studies [Graham et al., 2013]. Three additional controlled studies found that topical opioids were not effective for vascular ulcers, and it was surmised that this might reflect limited involvement of inflammation [Graham et al., 2013]. Some studies addressed altered dosage, frequency of application, local and systemic adverse effects, as well as impact on systemic medication use, but there was little documentation of patient responses. Overall results indicated that topical opioids are useful and safe for treating inflammatory pain in wounds, and systemic absorption occurs at a safe level. Morphine is not absorbed appreciably through intact skin, but an open wound provides no such barrier and systemic absorption can be a factor for large wounds [Farley, 2011]. In future studies, it will be important to report wound characteristics in detail to provide more complete information on conditions that benefit from this approach. Systematic and critical analysis approaches both conclude that there is a need for more studies in this area, for study designs to attend to multiple variables, and to use N-of-1 approaches for within-patient data, to provide further clinical guidance for this treatment method [LeBon et al., 2009; Farley, 2011;

Graham et al., 2013].

Investigational agents

Several additional drug classes, considered as investigational agents, also have been explored with topical delivery for various forms of neuropathic pain [Sawynok, 2013; Zur, 2013]. These include vasodilators, α -adrenergic agents, antidepressants, glutamate receptor antagonists, other centrally acting agents, and combinations of such agents. These agents have been examined in varied trial sizes (but most are small), diverse neuropathic pain conditions, and varied formulations. There are a growing number of case reports describing analgesia in neuropathic pain cases that have not responded to standardized oral therapies, and these are summarized systematically in recent reviews [Sawynok, 2013; Zur, 2013].

Some topical analgesic trials of investigational agents involve cancer care. Barton et al. [2011] examined a combination of baclofen, amitriptyline and ketamine in pluronic lecithin organogel vs. placebo as a topical treatment for chemotherapy-induced peripheral neuropathy in a trial involving 208 subjects. At eight weeks, there was an effect size of about 0.28 for the active arm over placebo in the sensory subscale (P=0.053) and 0.38 in the motor subscale (P=0.021). There were no undesirable toxic effects or evidence of systemic toxicity. Uzaraga et al. [2012] examined a combination of amitriptyline, ketamine and lidocaine in neuropathic pain resulting from radiation in 16 subjects. The combination cream significantly reduced pain intensity and several pain qualities (e.g., sharpness, burning, itchiness, unpleasantness) at 30 minutes post-treatment and burning pain following two weeks of treatment. Fatigue (in 32%) and site irritation (in 19%) were attributed to combination cream treatment. While results of these trials are considered promising, it is not clear what the optimal concentration of individual agents needs to be, the constituent individual agents that produce the most reliable and robust effects, or which delivery vehicles are most effective. These challenges recapitulate those observed in other neuropathic pain conditions.

Topical analgesics for oral mucositis

Oral mucositis involves acute inflammation and ulceration of the oral mucosa and often occurs as an adverse effect of chemotherapy or radiation therapy. It affects about 30% of patients during or after chemotherapy, and almost all of

Topical analgesics

those undergoing hematopoietic stem cell transplantation or radiotherapy of tumors in the head and neck region [Sonis, 2007]. Oral mucositis pain negatively affects oral dietary intake, maintenance of oral hygiene, and quality of life; it can also lead to dropout and suboptimal dosing. Most patients with moderate-severe oral mucositis require systemic analgesics (including opioids), and antimicrobial agents for colonization of oral ulcers by microbial flora. A systematic review of use of antimicrobial agents, mucosal coating agents, anesthetics and analgesics for management of oral mucositis has recently been published [Saunders *et al.*, 2013].

Several topical analgesics have been examined for potential benefits in oral mucositis. Multiple opioid receptor subtypes are present on human oral epithelial cells, and exposure to morphine increases cell migration [Charbaji et al., 2012]. Clinical case reports indicate reduced pain of oral mucositis following topical morphine (0.08% gel) [Krajnik et al., 1999] or methadone (sublingual tablet 5 mg crushed) [Gupta et al., 2010]. Two studies, including one randomized controlled trial (RCT), examined a 2% morphine mouth rinse for oral mucositis following radiation of head and neck cancer [Cerchietti et al., 2002; 2003]. The pilot trial (N=10, N=22) reported analgesia with morphine 2% and a dose-related effect (2%>1%) [Cerchietti et al., 2003]. The RCT compared morphine to "magic mouthwash" (lidocaine, diphenhydramine, and magnesium aluminum hydroxide); those treated with morphine reported less pain, had shorter-duration pain, less impairment, and less systemic opioid intake; no adverse effects were noted [Cerchietti et al., 2002]. Recent guidelines for treatment of oral mucositis have now added morphine 2% mouth rinse to treatment options [Saunders et al., 2013].

Doxepin is a tricyclic antidepressant with topical analgesic actions in neuropathic pain [McCleane, 2000]. Uncontrolled studies report doxepin 0.5% mouth rinse for oral mucositis due to chemotherapy or radiation, and report a strong beneficial effect with rapid onset, long duration, and improved pain management with repeated dosing [Epstein et al., 2001; 2006; 2007; 2008]. A recent doubleblind RCT of oral doxepin rinse (25 mg/5 mL, 0.5%) in 155 patients revealed a significantly greater reduction in pain compared to placebo, and also a significant pain reduction in crossover groups [Miller et al., 2013]. Doxepin was well tolerated but had more stinging/burning and unpleasant taste; it also caused more drowsiness than placebo. A majority of patients (64%) elected to continue doxepin in the optional continuation phase of the trial [Miller et al., 2013]. Recent guidelines include 0.5% doxepin mouth rinse

as a new treatment option for management of oral mucositis [Saunders *et al.*, 2013].

There are additional reports of oral mucositis pain management using investigational analgesic agents. There is one uncontrolled report of oral capsaicin delivered as a candy (taffy containing cayenne pepper) providing pain reduction in 11 patients in the short-term [Berger *et al.*, 1995]. There is also a case report of oral ketamine rinse (20 mg/5 mL, swished and spit after one minute) being highly effective in decreasing mouth pain at rest and with eating [Slatkin and Rhiner, 2003]. While these reports are insufficient to warrant guideline statements, they do provide data generally consistent with cutaneous topical treatments (see above), and this suggests further exploration of investigational agents for oral mucositis may be useful.

Summary

There are a limited number of controlled trials of topical analgesics for cancer patients, with use in such settings reflecting extrapolation from other neuropathic pain conditions. Up to 40% of cancer pain is considered to be neuropathic in nature, and this is a reasonable approach. The most information is available for lidocaine medicated plaster, and retrospective case series reports indicate efficacy (partial or potent) in significant numbers of patients. There is interest in trying to determine factors that might predict favorable responses to topical analgesics, and localized pain and pain characteristics are receiving attention. There are few controlled reports on topical capsaicin for pain following surgery for cancer, and these may be unblinded due to the burning sensations that capsaicin produces. There are no reports on the use of the high concentration capsaicin patch (8%) (0.04% patch controls for local sensations in neuropathic pain studies) at this time. There is a growing body of evidence relating to favorable effects of topical opioids for cutaneous lesions in palliative care, and further exploration of this approach is encouraged. There is some exploration of topical applications of investigational agents given in combinations in cancer care (potentially recruiting multiple mechanisms of action), but issues of composition and formulation remain a challenge. There are promising reports on use of topical morphine and topical doxepin for oral mucositis, and these are now included in recent treatment guidelines. Topical analgesics lead to a generally favorable adverse effect (systemic, local) profile and can be considered as add-on therapies to other approaches; however, the potential for adverse effects,

particularly in the elderly, needs to be monitored. Topical applications of analgesics, both to cutaneous somatic sites and to the oral compartment, constitute a promising area for continued exploration in cancer care.

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Interventional pain techniques

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Introduction

Palliative care is concerned with the treatment of a patient's symptoms without necessarily affecting the underlying cause. Pain is the most feared symptom and three quarters of patients with advanced cancer experience moderate to severe pain, often at multiple sites [Grond *et al.*, 1996].

Since the publication of the WHO pain ladder and advancements in the understanding of appropriate multimodal analgesia, the management of cancer pain has improved dramatically [Zech et al., 1995]. Despite this, 5-14% of patients do not have adequate pain control, even with optimised systemic medical therapy [Meuser et al., 2001]. A number of recent studies suggest that the above figure may be an understatement and that a greater proportion of people are affected than previously thought [Breivik et al., 2006; Valeberg et al., 2008; Breivik et al., 2009]. This has led to the suggestion [Miguel, 2000] that the WHO ladder should be modified with a fourth step, that of interventional procedures and techniques. This chapter focuses on commonly used interventional techniques, including nerve blockade and nerve destruction techniques and will cover epidural injections, radiofrequency ablation, cryo-lesioning and trigger point injections.

The palliative care patient

Moderate to severe pain can be treated in a number of ways: systemic analgesic medications, anti-cancer treatment and interventional procedures. Interventional procedures are required in only a small number (8-11%) of palliative care patients [Linklater *et al.*, 2002], who have intractable pain

or when systemic analgesia is dose-limited by undesirable side effects. These patients are commonly referred to a Chronic Pain Specialist, who will consider the options for nerve block, ablation or regional analgesia. Interventional techniques remain an important and frequently underused part of the multimodal management of cancer pain. However, the procedures themselves may be uncomfortable and distressing for the patient and have the potential to produce adverse effects. Very careful consideration needs to be taken when weighing up the benefits of performing an intervention for this group of patients.

Rarely will an interventional procedure alone be adequate in controlling a patient's pain and, as such, has must be viewed as a part of multimodal analgesia and patient care. Nevertheless, these procedures can give very substantial benefit and allow reduction of other analgesic drugs and their side effects [Eidelman *et al.*, 2007]. The majority of these patients will be on high dose opioids and careful monitoring and titration of drugs is required post intervention to prevent withdrawal phenomena or excessive sedation once the pain is reversed. A common approach is to halve the systemic opioid immediately after the procedure and to continue to reduce it thereafter if the procedure is successful.

The withdrawal of opioids may also lead to patients having greater clarity about their situation and there may be psychological implications of this. Care must be taken to ensure adequate consent and a realistic discussion of the aims of the treatment and potential side effects are discussed with patients and their relatives. Careful documentation of the outcomes of these discussions should be recorded. Patients in this group will frequently have significant comorbidities, and prior to performance of interventional procedures it is important to be aware of, and to document, neurological examination and laboratory blood work including clotting, platelet and neutrophil count. However, the context in which these procedures and their risks are being considered is very different from the non-cancer population. This will affect treatment decisions [Deer and Krames, 2007], relative contraindications, and consent [Chambers, 2008]. Of note, some of these interventions entail off label use of medications [British Pain Society, 2005].

Generally, neuropathic and bony metastatic pain are treated. In the palliative patient, bony metastases are a common source of pain, and there has been increasing interest in the use of minimally invasive techniques in its management. Approaches that have been tried with success include intralesional injection with ethanol under CT guidance which has been shown in one case study to provide prolonged relief in 70% of cases [Rowell, 1988; Gangi *et al.*, 1994].

Other approaches, such as radiofrequency with or without cementoplasty [Munk *et al.*, 2009; Thanos *et al.*, 2008] and acetabuloplasty for pain from metastatic involvement in this area, have been reported with varying degrees of success. Pain arising from metastases close to joints such as the sacroiliac or hip may also be helped by local injection of the joint with steroid [SIGN, 2008].

Vertebral metastases may give rise to severe movement related pain, which is often very difficult to manage with radiotherapy or drugs. These are increasingly being managed with percutaneous vertebral augmentation [Burton et al., 2005]. This technique involves percutaneous insertion of a cannula under image guidance into the vertebral body and injection of polymethyl methylacrylate cement (vertebroplasty) once the position is confirmed. This may be preceded by expansion of the vertebra by inflation of a balloon (kyphoplasty). A systematic review of these procedures showed an 87% improvement in pain relief with vertebroplasty and 92% with kyphoplasty whilst a case series of 283 patients showed substantial pain relief in 86% [Anselmetti et al., 2007; Hulme et al., 2006]. As well as treating vertebral collapse, it is thought other mechanisms such as microfracture stabilisation, interference of tumour blood supply and thermal or cytotoxic destruction of tumour cells may explain its effectiveness [Gangi et al., 2003]. Fortunately, although cement leak is commonly reported, serious complications are rare.

Although it carries a higher risk of cement leak than kyphoplasty, vertebroplasty is less time consuming, and

more likely to be performed under local anesthetic/ sedation. Therefore, it is more appropriate for patients with advanced disease [SIGN, 2008]. It has been recommended that patients with difficult to control pain from vertebral secondaries should be referred for consideration of vertebroplasty, if locally available [SIGN, 2008].

Epidural procedures

Rationale

Blockade of nerves is common practice in Pain Medicine and a range of nerves can be targeted from peripheral nerves to sympathetic nerves to the spinal nerve roots. Blockade may use local anaesthetic with or without the addition of corticosteroid, and may be extended with the use of implanted catheter techniques [Vranken *et al.*, 2000].

It has been observed that both central [Simpson, 2008; Linklater and Chambers, 2008] and peripheral [Okell and Brooks, 2009; Boys *et al.*, 1993; Arner *et al.*, 1990] nerve blocks may give analgesia of duration considerably in excess of that of the local block. Possible mechanisms for this include reduction in peripheral and central sensitisation or simply reduction in local nerve excitability via suppression of ectopic neural discharges from injured nerve fibres [Johansson and Bennett, 1997]. There is some evidence that the duration of benefit from nerve blockade may be prolonged by the addition of corticosteroid to the local anaesthetic [Twycross, 1994; Abram, 2000].

More permanent blockade of neural tissue may be performed using neurolytic agents (phenol 6-12%, ethanol 50-100%) or thermal methods using heat (radiofrequency ablation) or cold (cryoneurolysis) [Williams, 2003]. These methods aim to cause Wallerian degeneration of the nerve fibre, interrupting pain impulse transmission. The damaged nerves tend to regrow over months, with the potential for return of pain. Epidural injections with local anesthetics, steroids and other adjuvants have been shown to be successful in intractable cancer pain [Tei *et al.*, 2008; Buchanan *et al.*, 2009].

'Epidural Steroids' refers to the injection of corticosteroids, usually mixed with local anaesthetic +/adjuvants, into the epidural space to relieve pain. Commonly used steroids are dexamethasone, betamethasone, methylprednisolone and triamcinolone. Epidural steroids are more commonly used in the non-cancer setting for the treatment of radicular and discogenic pain emanating from the cervical, thoracic, and lumbar spine. In the palliative
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care setting, whilst not supported by strong evidence, epidural steroid injections with local anaesthetic are commonly performed for vertebral cancer induced bone pain. This is usually performed as a single shot injection.

The epidural route is also used for the administration of local anesthetics and opiates (+/- other adjuvants such as clonidine). Drug delivery can be achieved with a percutaneous epidural and an external syringe pump, which may be able to provide analgesia for a number of months. In a series of 91 patients who received 137 epidural catheters, the median survival was 38 days (1-1,000 days). Adequate pain relief was obtained in 76% of 58 patients with nocioceptive pain and 73% of the 33 patients with neuropathic pain [Smitt et al., 1998]. Studies have suggested that opioids and other drugs administered intrathecally may give better pain relief than epidurally [Baker et al., 2004; Bennett et al., 2000], and be less prone to complications [Nitescu et al., 1990; Dahm et al., 1998]. Epidural catheters have a potential for blockage due to encapsulation and fibrosis around the tip of the catheter [Crul and Delhaas, 1991; Mercadente, 1999].

Patient selection

Patients in this group will frequently have significant comorbidities and may be more susceptible to side effects. The context in which these procedures and their risks are being considered is, however, very different from the noncancer population. Contraindications to consider include known hypersensitivity to agents, systemic infection or local infection at the planned site of injection and bleeding diathesis/anticoagulation therapy. Due to the nature of the disease, many patient factors which would be considered a near absolute contra-indication to the use of epidural analgesia in the non-cancer setting need to be considered in a different light in palliative care. For example, the benefit of good analgesia in this group of patients may outweigh the risk of hematoma formation secondary to a coagulopathy.

There are a number of key differences between the patients in the palliative care setting and those in the nonmalignant setting. Firstly, those with malignancy are more likely to be immunocompromised and be coagulopathic. The epidural is more likely to be initially managed in a hospice rather than in theatres or pain clinic and consequently, monitoring is likely to be less intensive and aseptic technique less stringent. Despite this, serious complications are relatively low, and palliative care patients are more likely to have a successful outcome from the epidural than those in the traditional setting [Ballantyne and Carwood, 2005].

Technique

The three most common approaches by which steroids are introduced into the epidural space are the caudal route, the interlaminar approach, and the transforaminal approach. A caudal block is placed through the sacral hiatus (the developmental absence of lamina and spinous processes at S5 and occasionally S4). The main benefit of this injection is that the chance of dural puncture is substantially reduced while it is easy to perform under fluoroscopic or ultrasound guidance.

Published studies of caudal injections of corticosteroids have mostly been in non-malignant pain in the lumbar spine associated with radicular pain. A recent study found that caudal injections of corticosteroids in the management of malignant pain resulted in a good response in 56% of patients and a partial response in a further 25% [Back and Finlay, 2000]. The caudal route may be advantageous in patients who have significant metastatic disease in the lumbar vertebrae where the interlaminar or transforaminal approach may be difficult.

The interlaminar approach is the most common way of performing an epidural injection. It is performed by placing a Tuohy needle (16 or 18 G) between the spinous processes in the midline (or paramedian) of two vertebrae, with a loss of resistance to air or saline technique being the standard. The use of fluoroscopic guidance has been shown to enhance safety and improve the accuracy of placing the steroid at or nearer the site of the pathology.

The transforaminal approach targets foramina at a specific level and should always be done under fluoroscopic guidance. The foramina are the small lateral openings between the vertebrae through which the nerve roots traverse to exit the spinal canal. The benefits of the transforaminal approach may include decreased risk for dural puncture with delivery of smaller volumes of steroid to the appropriate site of considered pathology. Both the interlaminar and transforaminal approaches can be used at the cervical, thoracic, and lumbar levels. However, the use of transforaminal approach in the cervical area is not only dangerous but also not necessary in the majority of cases.

Manchikanti and colleagues compared the three different routes of administration [Manchikanti *et al.*, 1999]. His study showed better outcomes with the transforaminal

approach followed by the caudal approach. It is important to note that he used a blind interlaminar approach whilst using fluoroscopically guided caudal and transforaminal approaches.

Side effects and complications

Risks associated with epidural insertion include those caused by the needle placement and those that occur as a result of the injectate (contrast, local anaesthetic, steroid, or adjuvants). Trauma from needle placement can result in bleeding and hematoma. The incidence of epidural haematoma is 0.02% and is higher in those who are coagulopathic [RCoA, 2009]. Nerve injury, dural perforation and pneumothoraces with thoracic procedures are all potential complications.

Reactions to the drugs themselves also occur, but are fortunately rare. There is the risk of allergic reaction to the injectate, particularly with the contrast. Patients in this cohort are rarely opioid naïve, and as such, respiratory depression when epidural opioids are administered is usually not encountered. Cardiovascular changes are very rare unless drugs are inadvertently given intrathecally. Steroids can affect blood sugar levels in diabetics and should be monitored, as they have also been associated with fluid retention leading to exacerbation of symptoms of heart failure.

Injuries to the spinal cord have been reported after cervical and lumbar transforaminal injections. This may be due to direct cord trauma or cord infarction following injection of particulate steroid suspension into the vertebral artery, radicular artery or compression of the cord by a haematoma or abscess [Tiso *et al.*, 2004; Houten and Errico, 2002].

Infection can potentially be a major problem, especially if epidural catheters are inserted. Superficial infections following insertion of a catheter were seen in 10.8% of cases in one study [Linklater and Macaulay, 2005]. Deeper infection in the epidural space is less common and was seen in 2.1% of cases, the majority of which were due to a spinal epidural abscess requiring laminectomies and decompression [Smitt *et al.*, 1998]. It was the recommendation of the authors that only those patients with a life expectancy of less than a few months should receive indwelling epidural analgesia.

Controversies

Particulate steroids have been used in epidural injections

for decades but concerns have arisen after embolic events have been reported following intra-articular injection. Undetected vascular injections of the vertebral artery or spinal radicular arteries with particulate steroids are postulated to cause 'anterior spinal artery syndrome' resulting from embolic infarctions following cervical epidurals. Spinal cord injuries resulting in strokes and deaths have all been reported [Tiso et al., 2004; Houten and Errico, 2002; Tripathi et al., 2005]. Studies show that the size of particles in commonly used steroid preparations, like betamethasone, triamcinolone and methylprednisolone, equals or exceeds the caliber of many radicular arteries [Derby et al., 2008]. These particulate steroids tend to form aggregates larger than a red blood cell and are associated with a higher risk of embolic events than dexamethasone, which is water-soluble. A study compared particulate and non-particulate steroid injections into the vertebral arteries of pigs under general anesthesia. The animals injected with non-particulate steroids did not have ischemic events and recovered without apparent adverse effects. Their MRIs and histology were normal. In comparison, animals injected with particulate steroids never regained consciousness and their subsequent MRIs revealed brain stem and spinal cord edema whilst histology showed ischemic changes [Okubadejo et al., 2008].

Neurologic complications related to particulate steroid injections following lumbar or thoracic epidurals are thought to involve the artery of Adamkiewicz. This radicular artery typically arises at thoracic levels, but it can occur as low as L2 or L3 in about 1% of patients, and more rarely at lower level [Charles *et al.*, 2011]. Thus, paraplegia from transforaminal particulate steroid injections at lumbar levels has been reported in the literature [Houten and Errico, 2002].

Although most of this data is from epidural injections used in the chronic non-cancer pain setting much of the findings can be extrapolated to its use in cancer pain.

Care must be taken to prevent injection into the vertebral artery or spinal radicular artery. It appears prudent to avoid the use of particulate steroids when performing cervical epidurals and to excise caution if using them in thoracolumbar epidurals. Techniques, such as using fluoroscopy with or without digital subtraction angiography (DSA) or utilizing a test dose of local anaesthetic, may reduce the risk of catastrophic complications. Studies comparing the efficacy of steroids in epidural injections have shown no statistical difference between the use of dexamethasone or triamcinolone [Dreyfuss *et al.*, 2006].

Radiofrequency ablation

Radiofrequency (RF) ablation is increasingly used to treat painful neurologic and bone lesions in cancer patients. The goal of RF ablation is the destruction of neural tissue by a low-energy, high-frequency (50-500 kHz) alternating current. A needle electrode is placed alongside the nerve using radiographic screening and the final target is verified with sensory and motor stimulation. The current passes from the electrode to the tissues producing heat in the tissues. Thermal ablation is generally performed at 80 °C for 90 seconds. Feedback via a thermocouple in the needle tip allows accurate control of the temperature.

RF is used in lesioning in the central nervous system. Notably, percutaneous cordotomy RF of other areas, such as the trigeminal ganglion, has been extensively used for trigeminal neuralgia, and has also been used with benefit in head and neck cancer [Shapshay *et al.*, 1980]. RF and cryolesioning have also been used for treatment of lesions such as bone metastases [Iannessi *et al.*, 2013; Rosenthal and Callstrom, 2012; Dupuy *et al.*, 2010]. Clear evidence, however, is currently still lacking.

A more recent modification of RF is the use of pulsed radiofrequency (PRF) [Malik and Benzon, 2008; Cahana *et al.*, 2006]. In PRF alternating current is delivered to a target nerve without producing significant heating. The temperature at the needle tip is held below 42 °C to avoid neural damage. Typically, a 50 kHz current is delivered in 20 ms pulses at a frequency of 2 Hz, for a period of 120 seconds. The relatively long pause allows heat to dissipate. PRF does not appear to produce a histological lesion and thus its mechanism of action is unclear. Possible theories include alteration of descending or dorsal horn modulation of pain impulse traffic or selectively impairing C fibre transmission of pain.

In general, RF and PRF are performed in awake patients with local anesthetic used to anesthetize the skin prior to electrode insertion and injected down the electrode prior to radiofrequency lesioning. Sensory and motor nerve stimulation, at 50 and 2 Hz respectively, is performed to identify the nerve and confirm probe placement prior to lesioning. PRF and RF are generally well tolerated with few side effects.

There is little published evidence for the use of PRF or RF in cancer pain, but case studies appear to show a benefit for both techniques [Zeldin and Ioscovich, 2008]. Both PRF and RF of the thoracic dorsal root ganglia (DRG) have been shown to alleviate pain arising from the thoracic plexus [Van Kleef *et al.*, 1995]. More recently, PRF of paravertebral nerves has been used to treat painful metastatic breast disease [Izzo F *et al.*, 2001]. Nonetheless, ablation of the DRG with conventional RF is not recommended as it can result in significant neuropathy and subsequent neuropathic pain syndrome.

Cryolesioning

Another technique that can be used to provide long-term interruption of nerves carrying pain is the use of cold. Various names have been used for this, including cryoablation, cryoneurolysis or cryolesioning. The instrument used for this is termed a cryoprobe. Cryoneurolysis uses a probe whose tip is cooled towards –70 °C by expansion of pressurised nitrous oxide in its tip causing freezing and ice crystal formation within the axon. As is the case for RF, cryoneurolysis is relatively safe. Risks for bruising, bleeding and infection are low. Permanent nerve damage is exceptionally rare.

Peripheral sites

In general, peripheral nerve blocks have only a limited role in cancer pain. They can be of use in providing short-term analgesia while control of pain is gained by other means. Catheterisation and prolonged blockade of nerve plexuses and other peripheral nerves for the management of cancer pain have been reported [Chambers, 2008; Vranken *et al.*, 2005]. Implantation of catheters into the interpleural space [Myers *et al.*, 1993; Amesbury *et al.*, 1999] allows diffusion of agents through the parietal pleura to anesthetise the intercostal nerves: this may also diffuse onto and block the thoracic sympathetic chain located on the antero-lateral aspects of the vertebral bodies.

The intercostal nerves are another target for peripheral neurolysis and may provide analgesia for several weeks or months [Wong *et al.*, 2007]. The disadvantage is that the risk of neuritis is close to 30%, especially if a high concentration of alcohol is used [Doyle, 1982]. This may be less with cryoneurolysis, although chemical neurolysis was more effective than cryoneurolysis in one case series [Ramamurthy *et al.*, 1989].

Myofascial trigger points

Myofascial trigger points are localised painful areas of contraction in skeletal muscles and are common in patients with cancer pain. Infiltration of trigger points with local

anesthetic with or without steroids may provide pain relief [Han and Harrison, 1997]. Botulinum toxin and dry needling techniques similar to those used in acupuncture have also been used for trigger point deactivation. Acupuncture in general is not supported by strong evidence in malignant pain [Lee *et al.*, 2005].

Summary

Treatment of pain in terminally ill cancer patients poses significant challenges for pain specialists. Although there is very little evidence looking into the efficacy of interventional procedures in this group of patients, use of interventional techniques have proved an important and successful part of multimodal symptom control. Whilst the prognosis of these patients is often very limited, the benefit they can obtain from such procedures has the potential to be extremely worthwhile.

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Interventional procedures and minimally invasive techniques for persistent pain

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Introduction

Persistent cancer pain can be classified as nociceptive pain, which has both somatic and visceral components, or neuropathic pain. A common example of somatic pain in persistent cancer pain is pain originating from metastatic bone lesions, which is treated by percutaneous osteoplasty (POP), including vertebroplasty. A common feature of visceral pain is abdominal pain with ascites after sympathectomy, which is treated by implantation of an epidural port. A common example of neuropathic pain is radicular pain from metastatic tumors compressing the spinal nerve roots, which may be treated by endoscopic removal. Mixed pain originating from systemic metastasis can be alleviated by an implantable intravenous port.

Minimally invasive techniques for persistent cancer pain extend the field of active treatment for palliative care in debilitated patients and can be used as alternatives to open surgery, which is only performed in patients with an estimated life expectancy of at least 3 to 6 months.

Patterns of cancer pain: persistent or breakthrough pain (BTP)

Cancer patients may have constant or intermittent pain. BTP refers to sudden increases in the base level of pain or different but recurring pains. There are 3 types of BTP: (I) incidental pain; (II) end of dose failure; and (III) spontaneous pain [Fitzgibbon and Chapman, 2001] (*Table 1*).

Types of cancer pain: nociceptive or neuropathic pain

Cancer pain, like other non-malignant chronic pains, is also

classified as nociceptive or neuropathic pain. Nociceptive pain, which has both somatic and visceral components, arises from actual or possible damage to non-neural tissue and is due to the activation of nociceptors. Neuropathic pain is caused by a lesion or disease of the somatosensory nervous system [IASP, 2011] (*Table 2*).

Life expectancy, quality of life, and interventional pain management

Minimally invasive techniques for persistent cancer pain extend the field of active treatment for palliative care in debilitated patients with shortened life spans. The revised scoring system for preoperative evaluation of metastatic spine tumor prognosis proposed by Tokuhashi is useful for predicting life expectancy and deciding upon treatment strategies [Tokuhashi *et al.*, 2005] (*Table 3*).

The Karnofsky performance scale index allows patients to be classified by their functional impairment. This can be used to compare the effectiveness of different therapies and assess prognosis in individual patients. The lower the Karnofsky score, the worse the survival for most serious illnesses [Karnofsky and Burchenal, 1949] (*Table 4*).

Interventional procedures and minimally invasive techniques for somatic pain

POP with/without adjacent joint injections

Facet joint block before POP had two major roles: one is to let patients lie down during the procedure under local anesthesia and the other is to let the operator assess the exact pain level among the multiple fractures by elimination of radiating pain to the flank, abdomen, groin, or buttocks. In addition, if

Table 1 Three	types of breakthrough pain		
Incidental pain	Pain is directly related to an event or activity	Turning in bed, weight bearing, bowel movement, swallowing meals, etc.	Pain is well defined and predictable, so that physicians can anticipate and treat the problem prophylactically
End of dose failure	Pain emerges because of too much time between doses of medication	One can predict the pattern for the individual patient and readily prevent it by using time- contingent dosing at an appropriate interval	The key is monitoring symptoms in relation to the dosing schedule
Spontaneous pain	Pain occurs spontaneously without relationship to particular events or procedures	These pains are more difficult because of their unpredictable nature and their often fleeting character. In some cases, adjunctive analgesics effectively provide relief. Longer lasting pains require rapid-onset analgesics	Increasing the dose of time-contingent opioids often increases the overall side effects of these medications

Table 2 Types of cancer pain: nociceptive or neuropathic pain

Types of pain		Pain characteristics		Treatment		
Types of pair	1		Faill Characteristics	Pharmacologic	Interventional	
Nociceptive	Somatic	Superficial	Well-demarcated,	Acetaminophen, acetylsalicylic	Trigger point injection	
pain	pain pain		localized, sharp pain	acid, and non-steroidal		
		Deep	III-demarcated,	anti-inflammatory drugs	Facet joint injection, percutaneous	
			localized, blunt pain	(NSAIDs)	osteoplasty	
Visceral pain		Non-demarcated,	Opioids	Visceral sympathectomy, epidural		
		diffuse, dull pain		port implantation		
Neuropathic	pain		Allodynia, hyperalgesia,	Anticonvulsants and	Somatic sympathectomy, epidural	
			and hyperpathia	antidepressants	port implantation	

Table 3 A revised scoring system for preoperative evaluation of metastatic spine tumor prognosis and treatment strategy			
Characteristic	Score		
General condition (performance status)			
Poor (10-40%)	0		
Moderate (50-70%)	1		
Good (80-100%)	2		
Number of extraspinal bone metastases foci			
≥3	0		
1-2	1		
0	2		
Number of metastases in the vertebral body			
≥3	0		
1-2	1		
0	2		
Metastases to the major internal organs			
Unremovable	0		
Removable	1		
No metastases	2		
Table 3 (continued)			

Interventional procedures and minimally invasive techniques for persistent pain

Table 3 (continued)	
Characteristic	Score
Primary site of the cancer	
Lung, osteosarcoma, stomach, bladder, esophagus, pancreas	0
Liver, gallbladder, unidentified	1
Others	2
Kidney, uterus	3
Rectum	4
Thyroid, breast, prostate, carcinoid tumor	5
Palsy	
Complete (Frankel A, B)	0
Incomplete (Frankel C, D)	1
None (Frankel E)	2
Total	
Criteria of predicted prognosis	Strategy of treatment for spinal metastases
Total score 0-8; <6 months	Conservative treatment or palliative surgery
Total score 9-11; ≥6 months	Palliative surgery (single lesion, no metastases to the major
	internal organs)
Total score 12-15; ≥1 year	Excisional surgery

Table 4 Karnofsky performance status scale		
Definitions	Rating (%)	Criteria
Able to carry on normal activity and	100	Normal no complaints; no evidence of disease
going to work; no special care needed	90	Able to carry on normal activity; minor signs or symptoms of disease
	80	Normal activity with effort; some signs or symptoms of disease
Unable to work; able to live at home	70	Cares for self; unable to carry on normal activity or do active work
and care for most personal needs;	60	Requires occasional assistance, but is able to care for most personal needs
varying amount of assistance needed	50	Requires considerable assistance and frequent medical care
Unable to care for self; requires	40	Disabled; requires special care and assistance
equivalent of institutional or hospital	30	Severely disabled; hospital admission is indicated although death not imminent
are; disease may be progressing	20	Very sick; hospital admission necessary; active supportive treatment necessary
rapidly	10	Moribund; fatal processes progressing rapidly
	0	Dead

PVP is performed prior to facet joint blocks, the cement will obscure the targeted facet joints [Kim *et al.*, 2005].

POP as a technical extension of PVP, has been used as a treatment for painful extraspinal metastatic lesions at sites other than the vertebrae. PVP is performed in weightbearing vertebrae; extraspinal POP is usually performed in non-weightbearing flat bones. In recent years, it has become possible to safely apply bone cements to the flat bones, except in the case of irregular bones such as the vertebrae [Kim, 2011] (*Table 5*).

Preoperative painful osteolytic lesions are indicated by a history of aggravation of pain in a dependent position. The pain can present as incidental pain related to motion, a kind of BTP, during persistent pain. Severe tenderness of the osteolytic lesions is noted upon physical examination. To confirm the presence of metastatic osteolytic lesions, plain films, bone scans, and 3-dimensional computed tomography are helpful.

Informed consent after provision of information on the potential complications of POP, including nerve injury, bleeding, wound infection, and embolism, must be obtained

Table 5 Comparison between percutaneous vertebroplasty (PVP) and percutaneous osteoplasty (POP)		
	PVP	POP
Lesions	Painful vertebral lesions	Painful osseous lesions
Sites	Irregular bones such as vertebral body	All bones including flat bones
Pain provocation	Weight-bearing position	Dependent position
Adjacent joint pain	Facet joints	Articular joints



Figure 1 Scapuloplasty. The cement is injected into the posterior ribs through an 11-gauge needle via the lateral boarder of the right scapula. A. Lateral view; B. Anteroposterior view.

from the patients. Pneumothorax is also a potential complication of scapuloplasty and costoplasty. Internal organ damage is another complication of ilioplasty and ischioplasty.

The patient is placed in the prone position on a radiolucent table with an inflatable adjustable pillow. After aseptic draping, an outline of the osseous structure is drawn on the skin under fluoroscopic guidance. An additional inner line is drawn to indicate osteolytic bone defects confirmed by preoperative plain film and computed tomography. An 11- or 13-gauge, 10-cm-long bone biopsy needle is inserted from the nearest entry point or palpable bony structure to fill the osteolytic lesion with bone cement under fluoroscopic guidance.

The procedure is performed under conscious sedation and basic monitoring using electrocardiography, pulse oximetry, and noninvasive blood pressure measurement. Local anesthesia is provided with a total of 10-20 mL of 1% lidocaine, and intravenous analgesia with 30 mg of ketorolac and 100 µg of fentanyl.

After confirming needle placement and ensuring the absence of leakage of contrast medium into the blood vessels or other soft tissues, the cement (polymethyl methacrylate, PMMA) is injected with withdrawal of the bone biopsy needles [Choi *et al.*, 2010].

(I) Scapuloplasty (Figure 1): fracture of scapula



Figure 2 Costoplasty. The cement is injected into the posterior ribs through two 13-gauge needles. A. Anteroposterior view; B. Lateral view.

does not allow a patient to lie in the dependent position. In addition, adjacent glenohumeral or acromioclavicular joint and/or subacromial bursa injections may be needed;

- (II) Costoplasty (*Figure 2*): if the lesion is located at the anterior rib, the patient is placed in the supine position;
- (III) Ilioplasty (*Figure 3*): adjacent sacroiliac joint injection may be needed;
- (IV) Ischioplasty (*Figure 4*): fracture of the ischium causes aggravation of characteristic pain in a sitting position;
- (V) Humeroplasty and femoroplasty (*Figure 5*): POP in the proximal humerus shows favorable results; however, POP in the proximal femur shows an unexpected pathologic fracture on the femoral neck after weight-bearing. POP in the proximal humerus is recommendable to treat intractable metastatic osteolytic bone pain as a minimally invasive technique for palliative care; However, POP in the proximal femur requires a deliberate consideration of another option such as open surgery, if the general condition of the patient permits. Adjacent glenohumeral or acromioclavicular joint and/or subacromial bursa injections may be needed while performing humeroplasty.

Interventional procedures and minimally invasive techniques for persistent pain



Figure 3 Ilioplasty. The cement is injected into the left iliac bone via the posterior superior iliac spine through an 11-gauge needle. A. Anteroposterior view; B. Lateral view.



Figure 4 Ischioplasty. The cement is injected into the right pubic bone via the ischial tuberosity through an 11-gauge needle. A. Anteroposterior view; B. Lateral view.



Figure 5 Humeroplasty and femoroplasty. A. Local anesthetic is infiltrated into the skin and periosteum of the left greater tubercle. An 11-gauge, 10 cm long bone biopsy needle is slowly inserted into the same skin entry point and advanced into the medulla where the anticipated osteolytic lesions are located through the cortex under anteroposterior and lateral views. The contrast medium shows leakage into the vessels. After gelatin embolization, 10 mL of bone cement was filled under anteroposterior and lateral views; B. Local anesthetic is infiltrated into the skin and periosteum of the left greater trochanter. A bone biopsy needle is advanced from the skin to the lesser trochanter with comparison of anteroposterior and lateral views. Then, after testing for leakage is performed using contrast medium, 15 mL of bone cement is inserted; C. Local anesthetic is infiltrated into the skin and periosteum of the targeted entry point, 10 mL of bone cement is injected with withdrawal of the bone biopsy needle; D. Unfortunately, a new fracture developed on the left femoral neck on day 21 after percutaneous osteoplasty in the case of (B).

 Table 6 Two different approaches for percutaneous vertebroplasty

Trans-pedicular approach		Extra-pedicular approach
Uni-pedicular approach	Bi-pedicular approach	In case of pedicle screw fixation

Table 7 Comparison between percutaneous vertebroplasty (PVP) and percutaneous balloon kyphoplasty (PKP)			
	PVP	PKP	
Ability to restore collapsed vertebra	()	(+)	
Large cavity creation and filling with a greater volume of cement	()	(+)	
Ability to insert more hard cement	()	(+)	
Possibility of cement leakage into the anterior epidural space	(+)	()	
Re-fracture or pain recurrence due to separation of cement from the medulla	()	(+)	
Procedure time	Short	Long	
Cost	Low	High	

Table 8 Neurolytic sympathetic blocks			
Targeted plexus and nerves	Performed site	Visceral pain	Required volume of neurolytic agent (mL)
Celiac plexus and splanchnic nerves	T12 and L1	Upper abdominal pain	30-40
Superior hypogastric plexus and lumbar sympathetic chain	L5 and S1	Lower abdominal pain	10-20
Ganglion impar	Sacrococcygeal region	Anal and vaginal pain	2-4

Percutaneous vertebroplasty and percutaneous balloon kyphoplasty (PKP)

- (I) Two approach methods for PVP (are described in *Table 6* and *Figure 6*);
- (II) A comparison between PVP and PKP (is shown in *Table 7*).

Interventional procedures and minimally invasive techniques for visceral pain

Abdominal pain can be divided into visceral and somatic components, which can occur in isolation or in combination during an episode of pain. Somatic pain arises from stimulation of the parietal peritoneum and accurately localizes to a specific part of the abdomen, whereas visceral pain has a diffuse nature and is experienced over a large portion of the abdomen [Mayer and Wong, 2010]. Therefore, chemical sympathectomy is only useful for visceral pain, while epidural port implantation is helpful for patients who also have ascites, which causes somatic pain with underlying visceral pain.

Chemical sympathectomy (Table 8, Figure 7)

(I) Celiac plexus and splanchnic nerves: common adverse

effects include temporary hypotension, diarrhea, back pain with dysesthesia, hemorrhage, and impotence [de Courcy, 2011];

- (II) Superior hypogastric plexus and lumbar sympathetic chain;
- (III) Ganglion impar.

Epidural port implantation

Subcutaneous access port implantation for epidural administration (SCAPIFEA) is designed for long-term, repeated access to the epidural space for delivery of opioids and local anesthetics. An epidural port can be connected to a portable infusion pump to adjust infusion rates based on patient's need for analgesia.

A completely implanted intrathecal catheter with an implanted programmable infusion pump is suitable for long-term use and allows virtually unrestricted mobility of the patient. However, it may be better to select epidural analgesia using both an adequate amount of local anesthetics and opioids for neuropathic pain, instead of intrathecal analgesia using opioids alone or with a small amount of local anesthetics for nociceptive pain [Christo and Mazloomdoost, 2008].

Informed consent for early complications such as

Interventional procedures and minimally invasive techniques for persistent pain



Figure 6 Percutaneous vertebroplasty can be performed via the pedicle in most of cases. (A) In the case of the pedicle involvement by osteolytic lesions, it is preferable to perform vertebroplasty in the non-involved pedicle; (B) However, when a pedicle screw is already been inserted, it is common to use the extrapedicular approach.

dural puncture, hemorrhage, or wound infection and late complications such as kinking, occlusion, or dislodging of the catheter or epidural abscess should be obtained from all patients before implantation.

An implantable access port system (Celsite ST 304-19[®], B Braun Medical, Boulogne Cedex, France) was used for SCAPIFEA. The patient is placed in the lateral recumbent position. The skin is prepared and draped for midline approach in a sterile fashion. The needle entry point is determined by the target dermatomal level of pain, and is usually located 2 or 3 levels below the targeted posterior epidural space. After the skin is anesthetized, an 18-gauge Tuohy needle kept at an angle less than 30° is directed toward the posterior epidural space by using the loss of resistance method. Advancement of the needle is confirmed by lateral viewing using a fluoroscope. Once the position of the needle tip is confirmed, an epidural catheter is inserted via the Tuohy needle. After aspiration to confirm the absence of blood or cerebrospinal fluid regurgitation, contrast medium is injected for the confirmation of needle placement into the posterior epidural space. A test dose of a mixture of 3 mL (1 mg/kg) of 2% lidocaine and 10 µg of



Figure 7 Neurolytic sympathectomy for visceral pain. (A) Celiac plexus, greater splanchnic nerve, and superior mesenteric ganglion neurolytic block at the level of the thoracolumbar junction; (B) Superior hypogastric plexus and inferior mesenteric ganglion neurolytic block at the level of the lumbosacral junction; (C) Ganglion impar neurolysis at the level of the sacrococcygeal junction.

epinephrine is injected to reconfirm any extravasation and intrathecal or subdural injection [Guay, 2006].

An adequate volume (from 3 to 10 mL for the cervical to lumbar dermatome) of 1% lidocaine for analgesia is injected into the epidural space according to the dermatome used during the rest of the procedure. An imaginary line is drawn with a sterile marking pencil from the needle entry point through the flank to the abdomen for the thoracic or lumbar spine (or through the neck to the anterior chest below the clavicle for the cervical spine) where an access port is ready to be imbedded. The outline of the port is also drawn in the umbilical region (or infra-clavicular fossa). A skin incision



Figure 8 Steps involved in subcutaneous access port implantation for epidural administration. (A) Once the position of the needle tip is confirmed, the epidural catheter is inserted via a Tuohy needle. After aspiration to confirm the absence of blood or cerebrospinal fluid regurgitation, contrast medium is injected; (B) The contrast medium spreads into the posterior epidural space from the tip of the epidural catheter; (C) After dissection to create a pocket of the port, a tunneling rod is then routed subcutaneously to the portal implantation site; (D) The catheter is tightly connected to the portal using a wrench. A technical tip to prevent epidural catheter migration from the epidural space is to place a sufficient length of catheter below the subcutaneous access port; (E) A 90° angled needle is inserted into the portal septum to ensure placement, patency, and flow with the epidural catheter in the epidural space; (F) After insertion into the pocket, the portal is then anchored to the underlying fascia with nonabsorbable sutures. The portal pocket site is sutured.

is made along the insertion site of the epidural needle, and the subcutaneous tissue below the incision is dissected to the deep tissue above the muscle. After removing the needle while leaving the epidural catheter, subcutaneous tunneling into the abdomen for implantation of the subcutaneous access port is performed using a 28 cm-long tunneling rod, after connecting it with the epidural catheter. Subcutaneous tunneling is usually carried out with a 1-stop connection on the flank because the length of the rod is insufficient to reach from the thoracic spine to the abdomen or fatty abdomen.

After closing the skin on the back and flank and dressing the wound, the patient is turned to lie in the supine position. After the skin is anesthetized, a skin incision is made on the midline of the previous drawn outline of the port. The subcutaneous tissue is dissected to make a pocket for the port. The proximal end of the catheter is then routed subcutaneously to the portal implantation site, and the catheter is connected to the portal. A 90° angled needle is inserted into the portal septum while ensuring placement, patency, and flow with the epidural catheter in the epidural space. The portal is then anchored to the underlying fascia using nonabsorbable sutures. The portal pocket and catheter insertion sites are sutured (*Figure 8*).

This system is connected to a portable patient-controlled analgesia pump, containing a mixture of 0.2% ropivacaine and a half dose of morphine sulphate with respect to the equianalgesic requirement for previous opioids after the procedure, with a basal infusion rate of 1 mL/h, bolus infusion of 1 mL, and lock-out interval of 15 min.

Interventional procedures and minimally invasive techniques for neuropathic pain

Most metastatic spine diseases arise from the vertebral column, with the posterior half of the vertebral body and/or the paravertebral region being the most common initial focus, and tract along the spinal nerves to enter the spinal column via the intervertebral foramina. The thoracic spine is the most common site of disease (70%), followed by the lumbar spine (20%) and the cervical spine (10%) [Klimo and Schmidt, 2004].

Treatment options available for metastatic spine tumors



Figure 9 Endoscopic tumor removal. (A) Intraoperative steps for placing a spinal endoscope using the transforaminal approach. Upper first to third: oblique, anteroposterior, and lateral views) A 6-inch long, 18-gauge needle was placed into the intervertebral foramen under fluoroscopy in the same manner as a transforaminal epidural block at T11. Upper fourth and fifth: lateral and anteroposterior views: contrast medium is injected to confirm needle placement in the posterior epidural space. In this case, the contrast infiltrated into the posterior epidural space below the injection level and the distal part of the spinal nerve; however, it could not be disseminated into the anterior epidural space or the posterior epidural space above the injection level. Middle first: the skin is incised around the inserted needle. Middle second: a guide-wire is inserted through the needle after the needle stylet is removed. Middle third and fourth: an obturator dilator is inserted over the guidewire and its location is confirmed under fluoroscopy. Middle fifth: a working sleeve was inserted over the dilator. Lower first: the working sleeve is tightly fixed with a holder. Lower second: after the dilator is removed, the working sleeve with the guidewire inside the intervertebral foramen is observed on the lateral fluoroscopic view. Lower third: the guide-wire is removed. Lower fourth: a 30° spinal endoscope with a 2.7 mm working channel is inserted into the working sleeve and a bipolar radiofrequency system for ablation and coagulation is inserted into the endoscope. Lower fifth: the endoscope with the radiofrequency system tip inside the working sleeve on the lateral fluoroscopic view; (B) Intraoperative endoscopic views. Upper left: tumor emboli are located from the 3 o'clock to the 9 o'clock position and blood-tinged bright-yellow epidural fat is located at the 12 o'clock position within the working channel. Upper middle: in this case, after the tumor and epidural fat had been removed, yellow-colored ligamentum flavum was located from the 2 o'clock to the 9 o'clock position. Upper lower: a white transforaminal ligament is seen on the right of the tip of the bipolar radiofrequency instrument. Tumor emboli obscure the bottom of the endoscopic field from the 3 o'clock to the 9 o'clock position. Middle left: a white, waxy, soft, and detached transforaminal ligament, suggestive of the superior corporo-pedicular ligament, is hanging from the 9 o'clock position into the middle of the visual field. It is difficult to identify the nerve structures due to the tumor emboli. Middle middle: forceps are used to remove the tumor emboli from the dorsal root ganglion. Middle right: In a distant view, a transforaminal ligament at the 9 o'clock to the 10 o'clock position and the ventral root and dorsal root ganglion in the middle from the 11 o'clock to the 5 o'clock position are shown. Lower left: in a more distant view, tumor emboli surround the nerve structures at the bottom. (Lower middle) In the close view, after removal of the tumor mass at the bottom of the field, a tumor mass is seen over the dorsal root ganglion. Lower right: the congested dorsal root ganglion is seen more closely from the 1 o'clock to the 7 o'clock position, while the ventral root passes parallel to the dorsal root ganglion from afar from the 11 o'clock to the 8 o'clock position. The tumor mass has been removed from the nerve structures. A small white intraforaminal ligament is observed between the dorsal nerve ganglion and the ventral nerve root at the center of the endoscopic field.

include radiation therapy, surgery, and chemotherapy. Radiotherapy is accepted as the first-line choice for most patients with metastatic spinal tumors [Bilsky *et al.*, 1999].

- (I) Diagnostic and therapeutic block and ablation;
- (II) Endoscopic tumor resection.

For the endoscopic removal of thoracic metastatic tumors, at least 3 ports, including an endoscopic port, a working port, and a suction port, are placed using deflation of the ipsilateral lung under general anesthesia with somatosensory-

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evoked potentials and motor-evoked potentials monitoring [Barrenechea *et al.*, 2006].

However, both single-port minimally invasive endoscopic spine surgery using the transforaminal approach without the need for lung deflation and patient-cooperative monitored anesthesia care using dexmedetomidine and intravenous opioid/nonopioid analgesics in the prone position dramatically improve surgical outcomes for elderly, debilitated patients with cancer [Joo *et al.*, 2012] (*Figure 9*).

Table 9 Commonly used intravenous analgesics for intractable cancer pain				
Intravenous	Analgonia machanism of action	Starting dose		
analgesics				
Morphine	Opioid receptor agonist	10		
Ketamine	NMDA receptor antagonist	25		
Nefopam	Inhibition of synaptosomal uptake of dopamine, norepinephrine, and serotonin; Inhibits calcium	60		
	influx, cGMP formation, and NMDA receptor-dependent neurotoxicity following activation of			
	voltage sensitive calcium channels.			
Midazolam	Increases inhibitory action at the GABA receptor	15		
Ketorolac	Anti-inflammatory, antipyretic, and analgesic effects	90		
Abbreviations	NMDA N-methyl-D-aspartate recentor: cGMP cyclic guanosine monophosphate: GABA gan	ma-aminobutyric		

Abbreviations: NMDA, N-methyl-D-aspartate receptor; cGMP, cyclic guanosine monophosphate; GABA, gamma-aminobutyric acid.



Figure 10 Intravenous port implantation. After puncture with a metal needle at the subclavian vein, a catheter is inserted into the superior vena cava above the heart via the brachiocephalic vein under fluoroscopic monitoring. Leaving the metal needle within the catheter, a skin incision including the needle is made below the clavicle. A portal with a septum is inserted into the subcutaneous space. A 90° angled needle is inserted into the septum. An intravenous patient-controlled analgesia pump is connected to the needle. After every infusion/injection, the port is flushed with heparin solution; this is conducted once every 4 weeks if the port is not used regularly.

Interventional procedures and minimally invasive techniques for systemic pain

Intravenous port implantation is helpful for patients with complaints of systemic pain due to metastasis to the whole of the body. The subclavian vein rather than the internal jugular vein is more comfortable for patients (*Figure 10*). According to pain components, opioids, non-steroidal antiinflammatory drugs (NSAIDs), ketamine, nefopam, and/or midazolam can be administered intravenously (*Table 9*).

Summary

Minimally invasive techniques for persistent cancer pain extend the field of active treatment for palliative care in debilitated patients and can be used as alternatives to open surgery, which is only performed in patients with an estimated life expectancy of at least 3 to 6 months. Persistent somatic cancer pain originating from metastatic bone lesions is treated by POP, including vertebroplasty. Persistent visceral pain is treated by sympathectomy or by implantation of an epidural port with regards to presence of ascites. Persistent neuropathic radicular pain from metastatic tumors compressing the spinal nerve roots may be treated by endoscopic removal after diagnostic and therapeutic sensory blockades. Mixed pain originating from systemic metastasis can be alleviated by an implantable intravenous port.

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Neuromodulation of pain

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Introduction

Electrical stimulation has played a role in pain modulation and finds its roots back to approximately 15 AD. A man who suffered from excruciating pain in his big toe from gout accidentally stepped on a torpedo fish and found significant alleviation of his pain from the electrical shock. Today, neuromodulation is a burgeoning and exciting field that offers potential for innovative applications in medicine. The International Neuromodulation Society defines neuromodulation as electrical or chemical alteration of signal transmission within the nervous system by using implanted devices to affect improvement in symptoms and render optimal functioning [Sakas *et al.*, 2007]. Seemingly any part of the nervous system may be stimulated in an attempt to modulate function to improve quality of life.

The field of neuromodulation continues to grow through a wide arena of scientific disciplines as cutting edge developments in biomedical technology occur. Currently, most types of stimulation are used to improve a handful of conditions which have some common basis. Spinal cord stimulation (SCS) for complex regional pain syndrome (CRPS) and failed back surgery syndrome (FBSS) has led the way as the most common application of neuromodulation. Motor cortex stimulation (MCS) and peripheral nerve stimulation (PNS) have also been used for treatment of intractable pain syndromes. In the past, deep brain stimulation (DBS) was employed most commonly for similar purposes, but the majority of its current use is for treatment of movement disorders such as Parkinson's disease (PD). Neuromodulation of pain, though not advocated previously because of cost and questionable efficacy with disease progression, may provide significant relief to the palliative care population especially as survival expectancy increases. This population typically has diminished organ reserve and vulnerability to drug-drug interactions from the exorbitant number of medications to manage conditions and associated side effects. Thus, using a different modality of treatment such as an electrical stimulation device may be quite beneficial.

In this chapter, we explore the pre-clinical and clinical data that supports the potential use of neuromodulation in palliation. We discuss the major sites of stimulation (DBS, MCS, SCS, and PNS), examine their current uses, and assess the noted effects on pain which may benefit people at end of life from refractory debilitating symptoms.

DBS

DBS is known for its treatment effects in movement disorders, specifically on PD and essential tremor by targeting the subthalamic nucleus (STN), and ventralis intermedius nucleus of the thalamus respectively. The mechanism of action of DBS clearly warrants continued investigation. What is known however is that the clinical effects on patients may be dramatic. Most experience a motor improvement of 50-80%. Medication is typically reduced from 30-70%.

Previously, DBS was most commonly used for the treatment of chronic pain. Most studies examine its impact on neuropathic and on nociceptive pain separately [Levy Neuromodulation of pain



Figure 1 (A) PVG/PAG and nocioceptive pain. Stimulation of the PVG/PAG produces a release of enkephalin, activating serotonergic neurons in the nucleus raphes magnus. These in turn project to the dorsal horn of the spinal cord, activating interneurons in the substantia gelatinosa. The release of endogenous opioids by these interneurons suppresses Substance P release by incoming axons, terminating the pain signal; (B) VPL and neuropathic pain. Ascending pain information in the lateral spinothalamic tract reaches the VPL before being relayed to primary somatosensory cortex. While the primary mode of analgesia is not clear, stimulation of the VPL can alter many facets of somatosensory thalamo-cortical pathway activity and inhibit spinothalamic tract components, disrupting the flow of pain information to the cortex. Abbreviations: PVG, periventricular gray; PAG, periaqueductal gray; VPL, ventral posterior lateral.

et al., 2010]. Two randomized clinical trials (RCTs) of DBS for pain show no statistical difference in pain amelioration when studied in a population. However, applications have demonstrated some success at the individual level in certain patients with refractory pain. There is little documentation on cancer pain specifically (*Table 1*). We do know that at least ten to fifteen percent of people suffering from cancerrelated pain fail to achieve adequate pain control with conventional analgesics and opioids. DBS may provide an alternative modality to achieve better pain management in patients refractory to current standard treatment (both in patients with nociceptive and neuropathic pain). It is also important to note that DBS for treatment of pain remains off-label.

The typical sites used in the past (*Figure 1A,B*) are the ventral posterior lateral and medial (VPL/VPM) thalamic nuclei for deafferentation pain [Hosobuchi *et al.*, 1973] and periaqueductal gray/periventricular gray (PAG/PVG) regions for nociceptive pain [Hosobuchi *et al.*, 1977]. DBS of the posterior hypothalamus shows promise in managing

chronic cluster headache [Leone *et al.*, 2006]. A recent prospective study examines DBS for neuropathic pain in 85 patients in the United Kingdom where DBS for pain has regulatory approval [Boccard *et al.*, 2013]. In these cases, 33 received PAG implants, 15 VPL/VPM, and 37 both. Fifty-nine of 85 underwent successful trial and ultimately implantation with 39 having significant benefit at one year on visual analogue scale (VAS), McGill pain questionnaire, Short-form 36, EuroQol-5D and health state.

Preclinical data supports these targets. In one study, the PAG was stimulated in rats three weeks after spared nerve injury. Three minutes of stimulation was applied to the PAG and spontaneous paw withdrawal movements (i.e., a standard index of pain) decreased for 30-40 minutes after the stimulation period. The reduction in mechanical allodynia and spontaneous pain suggests that PAG stimulation modulates pain by increasing activity of inhibitory pain pathways [Lee *et al.*, 2012].

The basal ganglia also play a role in nociceptive pain modulation. Patients with PD were compared on subjective heat pain thresholds with deep brain stimulators OFF and ON and also had PET scanning during pain exposure [Dellapina *et al.*, 2012]. Patients were categorized as with or without neuropathic pain and evaluated by clinical and neuroimaging results. DBS raised the subjective heat pain threshold significantly and PET revealed decreases in activity in regions usually activated by pain. No changes in pain threshold or cerebral activity were noted on patients without nociceptive pain. These findings suggest that pain modulation and perception are decreased by STN DBS [Dellapina *et al.*, 2012].

The brain appears to have a network "pain matrix" that processes the sensation of pain in the milieu of multiple sensory stimulation acquired by different modalities. Using vision in conjunction with touch mitigates the affective component of pain and reduces the level of perceived pain [Longo *et al.*, 2009]. Studies with human subjects show that viewing their stimulated hand in a mirror box while receiving nociceptive laser stimulation rate their pain as lower than when they view an object in the same location [Longo *et al.*, 2009]. This hypothesis was further supported by another study using contact heat pain thresholds [Mancini *et al.*, 2011]. A component of analgesia occurs merely by visualizing the impending nociceptive stimulus.

Functional MRI studies contribute collaborative data that activity in the ipsilateral primary somatosensory cortex (SI) and the contralateral operculoinsular cortex decrease when visualizing the body at the time of noxious

Table 1 DBS f	or cancer pain				
Author, year	Study design	No. with cancer pain [total number of patients in series]	Placement	Outcomes for cancer patients	Length of follow-up
Baskin <i>et al.</i> , 1986	Case series	6 [7]	PVG/PAG	6 with initial 100% pain relief; 3 with reduction in analgesic effect at 6-10 week follow-ups	1-5 months (survival range)
Boivie and Meyerson, 1982	Case series	5 [5]	PVG/PAG	4 of 5 patients with >50% relief, with 2 with 100% pain relief. At 17 months, 1 patient who had previously had 100% relief had 50%	3 weeks to 17 months (survival range)
Coffey, 2001	Review of clinical trial	4 [194] in model 3380 trial with "visceral, midline, or cancer pain"	PVG/PAG and/or VPL/VPM	Number of cancer patient implants internalized was not reported	2 years
Hosobuchi et al., 1977	Case series	4 [6]	PVG/PAG	4 with initial complete relief (at 4-5 weeks less effective, but adding off-stim periods reduced analgesic tolerance)	3-18 months
Hosobuchi, 1986	Retrospective cohort from prospectively collected data	7 [122]	cancer patients all had bilateral PAG	All with relief with trial; 5 patients had long-term pain relief success, 2 did not by final follow-up	2-14 years for the full study, ranges by etiology of pain not specified
Hosobuchi, 1987	Case series	7 [7]	Dorsal PAG	7 with initial pain relief, but 5 with unpleasant sensation precluding internalization; 2 internalized; of those 1 lost efficacy at 2 months; 1 with success until death	2-7 months
Kumar <i>et al.</i> , 1997	Retrospective cohort from prospectively collected data	1 [68]	Dual PVG & VPL	No relief; not internalized	NA
Levy <i>et al.</i> , 1987	Retrospective cohort from prospectively collected data	6 [141]	PVG/PAG or VPL	3 with initial pain relief and internalized implant (1 VPL, 2 PVG/PAG); 2 had continuing pain relief until death	6 weeks, then 2-14 years for the full study, ranges by etiology of pain not specified
Richardson and Akil, 1977a	Case series	2 [5]	PAG targeted, sometimes sites within posterior medial thalamus chosen instead	Both with acute pain relief from chosen stimulation target	N/A
Richardson and Akil, 1977	Case series 'b	2 [8]	PVG/PAG	2 with pain relief until death	2 months (death)
Young <i>et al.</i> , 1985	Retrospective cohort from prospectively collected data	7 [48]	PVG/PAG and/or sensory thalamus or internal capsule	6 implanted for initial success; at last follow-up 3 with excellent relief; 3 with 50%	2-60 months for the full study, ranges by etiology of pain not specified
Abbreviations:	DBS. deep brain	stimulation: PVG. periventricula	ar arav: PAG. periagueductal g	rav: VPL. ventral posterior lateral.: VPM. ventral pos	erior medial.



Figure 2 Mapping regions of motor cortex. Intra-operative photograph of electrophysiological monitoring showing activation of hand region during motor cortex stimulation to aid in proper placement of device over motor cortex.

stimulus [Longo *et al.*, 2012]. Longo *et al.* specifically investigated two cortical networks previously implicated in sensory processing—the "pain matrix" and the "visual body network." The brainstem, thalamic nuclei, somatosensory cortices SI and SII, insular and anterior cingulate cortices comprise the "pain matrix" while posterior cortical regions, including posterior parietal nodes, responsible for visual processing constitute the "visual body network." Visualizing the body enhances the effective connectivity of the "pain matrix" and the "visual body network" so as to functionally couple the two separate networks. It is the symbiosis with extensive activation and interaction between these two networks that modulates the perception of pain, and not the overall reduction of cortical activity [Longo *et al.*, 2012].

MCS

MCS has a long history that dates back to the seminal work of Wilder Graves Penfield [1891-1976] at the Montreal Neurological Institute where he localized the epileptogenic and functionally eloquent areas of the cortex. Over 12 years and 164 consecutive patients for pre-surgical evaluation of epilepsy, 4,160 cortical stimulations in all lobes of the brain were analyzed by assessing videotaped subjective and behavioral responses [Mazzola *et al.*, 2012]. It was discovered through this research that stimulation of the medial parietal operculum and posterior insula triggers activation of the pain cortical network and the experience of somatic pain. The few pain responses that were recorded (1.4%) demonstrated a rostrocaudal decrement in the medial parietal operculum and posterior insula. However, the interplay of pain modulation and processing delves much deeper than the cortical surface and can alter the affective experience of pain in each individual.

MCS for pain syndromes has garnered attention, but remains off-label (*Figure 2*). Although results from MCS studies have shown some efficacy, there is great variability across studies and there has been a lack of large, controlled, multicenter trials [Nguyen *et al.*, 2011]. MCS may be particularly effective in treating central pain syndromes such as thalamic pain syndrome and trigeminal neuropathic pain (TNP). Eight of eleven patients with thalamic pain received excellent pain control with chronic MCS. This effect was sustained in five patients over a two-year followup period while the other three had gradual decline in effect over several months. Postcentral gyrus, i.e., sensory cortex, stimulation had no effect or worsening of the pain syndrome [Tsubokawa *et al.*, 1993].

Meyerson and colleagues investigated ten patients with different forms of neuropathic pain and their response to MCS. Three patients with cerebrovascular disease mediated central pain did not gain any relief from MCS. One patient with a peripheral nerve injury achieved approximately 50% pain relief while a second patient with peripheral nerve injury did not have any change. Five patients with TNP all had significant pain relief ranging from 60-90%. Each patient had one or two generalized seizures during the trial phase but did not suffer further seizures after permanent implantation [Meyerson *et al.*, 1993]. Six of eight patients with either thalamic or peripheral deafferentation pain had significant pain alleviation (two had excellent results, two had good and two had fair relief) with MCS [Saitoh *et al.*, 2000].

In a prospective study of MCS in assessing long-term outcomes, 31 patients with medically refractory neuropathic pain were evaluated by using five measures [Nuti et al., 2005]. Patients (I) assessed pain scores using VAS; (II) rated postoperative reduction in VAS scores; (III) rated the percentage of pain relief; (IV) measured the decrease in analgesic use and (V) replied "yes" or "no" to whether they would undergo surgery given similar circumstances. Ten percent of patients achieved excellent pain relief (greater than 70% improvement), 42% had good relief (40-69% improvement), 35% had poor relief (10-39% improvement) and 13% had negligible relief (0-9% improvement). Fifty-two percent of patients were able to decrease their analgesic intake with 36% being able to stop all analgesics. Forty-five percent of patients did not have any alteration and data was unavailable in 3% of the study population.

Seventy percent of the population would have the operation again if the same beneficial outcome could be guaranteed. The degree of pain relief achieved in the first month was a strong predictor of long-term outcome of pain relief with MCS [Nuti *et al.*, 2005].

In a retrospective analysis of 17 patients with chronic neuropathic pain [ten TNP and seven with post stroke pain (PSP)], 50% of patients with TNP and 43% of patients with PS had pain alleviation of 50% on the VAS [Rasche *et al.*, 2006]. The mean follow-up period was 3.6 years with one patient having positive stimulation effect for up to 10 years. To study possible mechanism of action of MCS, Reyns and colleagues recorded and compared post-movement beta synchronization (PMBS) in eight patients with refractory neuropathic pain [Reyns *et al.*, 2012]. They hypothesized that implanted MCS modulates PMBS in patients with neuropathic pain and did discover that the degree of analgesia seemed to correlate with increased spatial distribution and amplitude of PMBS in the motor cortex.

In a systematic review of published literature on MCS to date, 210 patients were assessed as to the amount of pain relief they achieved with MCS [Fontaine *et al.*, 2009]. Fifty-five percent of patients had 40-50% pain relief and in 45% of 152 patients still had the same effect at 1-year follow-up. There was an average pain amelioration of 57% in responders according to the VAS. Adverse effects occurred in 157 patients and included infections (5.7%), hardware-related problems (5.1%) and seizures in the early postoperative period (12%). The authors concluded that MCS appears to be effective and safe for the treatment of chronic refractory neuropathic pain, however further investigation by way of blinded, controlled studies are necessary to confirm preliminary results from case series and reports [Fontaine *et al.*, 2009].

SCS

SCS is the most commonly used modality of neuromodulation and is generally used for treatment of chronic refractory pain. In a systematic review of 11 RCTs from approximately 6,000 citations, evidence suggests efficacy of SCS in ameliorating chronic neuropathic pain in FBSS and CRPS type 1 [Simpson *et al.*, 2009]. There is less evidence of effectiveness of SCS in ischemic pain given current lack of well-defined studies but there may be potential for critical limb ischemia and refractory angina [Simpson *et al.*, 2009]. These indications are more common in clinical practice in Europe.

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Multiple case reports implicate possible effectiveness of SCS in treatment of patients with cancer-related pain, whether from actual disease burden or from treatment for cancer. Two case reports describe SCS implantation for pain caused by chemotherapy [Cata *et al.*, 2004] and three reports for neuropathic pain as a result of radiation induced transverse myelitis or surgical resection [Yakovlev and Elias, 2008; Hamid and Haider, 2007].

The first report is of a 65-year old patient diagnosed with primary melanoma treated with interleukin-2. Constant pain of bilateral lower extremities developed after four weeks of treatment and the sensations severely affected activities of daily living and quality of life. The patient had inadequate pain control with morphine, hydrocodone, fentanyl, gabapentin, and tiagabine. The patient's pain level ranged from 4.5-9.3/10 on medications prior to SCS implantation. At 4-month follow-up, his VAS was 2/10 and he was only taking hydrocodone. In addition, the patient's gait, leg flexibility and touch detection had improved [Cata et al., 2004]. A 46-year-old patient with Ewing sarcoma of the right infraclavicular area developed pain in the lower extremities after two weeks of vincristine chemotherapy. This patient had SCS implantation at T11 and six hours later had improvement of pain from 4.6-8.8/10 to 2.4/10 that continued to improve at two weeks post-implantation. This patient also had improvement in leg function and was able to reduce pain medication intake [Cata et al., 2004].

A 51-year-old patient developed burning inguinal pain at the site of an inguinal metastasis after anteriorposterior resection and radiation for treatment of squamous cell carcinoma of the anus. Pain was rated 2-8/10 on the VAS score with ibuprofen, acetaminophen, gabapentin, cyclobenzaprine, amitriptyline, darvocet, fentanyl patches and ilioinguinal and iliohypogastric nerve blocks. SCS resulted in 100% relief of pain, discontinuation of all pain medications and return to pre-cancer treatment function. The patient had mild regression at 12 months postimplantation, rating pain at 1-2/10 [Yakovlev and Elias, 2008].

Another patient, 43 years old, status post debulking and radiation of a metastatic epidural tumor in the low thoracic spine developed pain ranging from 5-9/10 that did not respond to a plethora of various pain medications and epidural steroid blocks. Implantation of a SCS at the T9-10 level alleviated 90-100% of the patient's pain and opioid medications were discontinued. This patient's results were sustained over 1-year follow-up and also derived improvement in sleep and level of daily function [Yakovlev and Elias, 2008].

SCS has been employed to treat neuropathic pain induced from transverse myelitis from radiation therapy [Hamid and Haider, 2007]. A 54-year-old patient with nonsmall cell lung carcinoma was treated with chemotherapy, surgical resection and then radiation. Two months after receiving 5,040 cGy in 28 fractions, the patient developed gradual onset of terrible dyesthesia and hypersensitivity with subsequent weakness and bladder dysfunction. A MRI study revealed transverse myelitis at T4. Despite exhaustive conservative measures with little benefit, SCS was successful enough for the patient to discontinue the majority of medications [Hamid and Haider, 2007].

Chronic pelvic pain (CPP)

The pelvic region of the human body includes visceral and somatic structures that receive intertwined innervations from the sympathetic, parasympathetic and somatic nervous systems that can make this area vulnerable to complex pain syndromes. SCS has been attempted for CPP because this intractable pain closely resembles neuropathic pain for which SCS treatment has had good success [Hunter *et al.*, 2013]. The case series included in this review is comprised of four females and one male who had SCS implantation ranging from T6 to T7 to T12-L1 for pain in vaginal, rectal, pelvic and lower extremity areas as a result of endometriosis, yeast infection treatment related sores, rectal fistula and hemorrhoidectomy (T12-L1). All patients achieved significant pain relief and were able to reduce oral analgesia as well as increase physical activity [Hunter *et al.*, 2013].

A case series describes six females suffering from chronic pelvic pain with a history of endometriosis, dyspareunia and multiple abdominal explorations that underwent treatment with SCS [Kapural *et al.*, 2006]. Prior to SCS implantation, all patients received hypogastric blocks with good pain relief for 1-6 weeks and had psychological evaluations. Four patients had implantation centered at T11, one at T11-12 and one at L1. All patients reported greater than 50% pain relief and VAS scores decreased from 8 to 3. The Pain Disability Index decreased significantly from 57.7 to 19.5 and opioid use plummeted from 22.5 to 6.6 mg equivalents per day. Effects were sustained through the average followup time of 30.6 months [Kapural *et al.*, 2006].

These case series support the idea of CPP as an indication for SCS treatment. As with other neuromodulatory techniques and for various indications, the optimal location



Figure 3 Fluoroscopic intra-operative image from a peripheral nerve stimulation procedure. This image shows bilateral occipital nerve electrodes being inserted for the treatment of chronic migraine. The patient had failed all other conservative management options, including botulinum toxin.

and stimulation parameters have yet to be defined. Trials are completed in a step-wise fashion at an individual's specific pace.

PNS

Most recently, PNS has become more commonly used. It has generally been used for the treatment of refractory chronic head pain as well as nerve injuries. It is likely that these targets will further evolve based on clinical experience, functional imaging and electrophysiological correlates. As a means of exploring potential sites for stimulation the potential is seemingly endless. All current uses are off-label uses of FDA-approved SCS electrodes. The majority of experiences today in the head and neck have been with the occipital nerve, supraorbital/infraorbital branches of the trigeminal nerve, and the trigeminal nerve root at the foramen ovale. PNS of the sacral nerve, most often S3, alongside the sacral foramen, has also been used for treatment of bladder dysfunction and to treat pain associated with nerve injuries. Results with PNS of the occipital nerves seem to improve over time; perhaps secondary to plasticity [Magis et al., 2011].

Surgical trial for PNS starts with a slit-like incision and

is followed by electrode implantation subcutaneously via a Tuohy needle (*Figure 3*). Although typically percutaneous electrodes are used, paddle leads are also available. Guidance and confirmation of location is based on C-arm fluoroscopy. If a longer trial is necessary or there are temporary contraindications to total internalization, a permanent lead can be used and tunneled to an extension. Eventual lead removal and full internalization in the operating room is required in these cases.

Electrophysiological and psychophysical experiments in healthy human volunteers demonstrated alteration of central pain modulation after long-term depression induction with PNS. Subjects received painful electrical test stimulation and conditioning low frequency stimulation (LFS) through a concentric electrode to the right hand. The greatest decrease in LFS-induced pain perception was shown after LFS when compared against pre-LFS, post-LFS or control (no stimulation). One way to explore new arenas for the use of PNS is to assess where transcutaneous nerve stimulation (TENS) has been useful. As a treatment option, TENS appears to have benefit over placebo (Level C) but has less effect than electro-acupuncture [Cruccu *et al.*, 2007]. The role of TENS to predict outcome following implantable neuromodulators has not been defined.

One study assessed 20 patients with subacromial impingement syndrome of the shoulder. They were randomized between low-frequency TENS and sham TENS and underwent functional magnetic resonance imaging while noxious stimuli were applied both before and after treatment with TENS or sham TENS. Results indicate that TENS can reduce perceived pain intensity by decreasing ipsilateral supplementary motor area activation, contralateral primary sensory cortex, and bilateral caudal anterior cingulate cortex activation. The change in VAS was significantly correlated with change in activity in the ipsilateral posterior parietal cortex and the contralateral prefrontal cortex and thalamus [Kocyigit *et al.*, 2012].

Limitations

Currently, the application of neuromodulation in palliative care is hampered for a number of reasons. First and foremost, little evidence by way of clinical trials exists to support its use since this technology is still in its infancy for these particular indications. Ideas have developed from unexpected or incidental benefits in certain symptoms while studying other indications, however more research is necessary for each possible new application. The second

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hurdle is cost. All neuromodulatory devices have expensive up front costs that may range from \$15,000-\$35,000 depending on the device. The internal pulse generator (IPG) or battery that generates the electrical stimulation comprises most of that cost. Cost-benefit analysis for neuromodulation in a pallliative context is difficult to evaluate and would depend largely upon how the technology succeeds in reducing hospitalizations, nursing costs, outpatient care costs, medication costs and drug interaction adverse effects costs compared to improved quality of life. These studies are often difficult to perform.

Summary

Though some obstacles do exist, the idea of neuromodulation for treatment of pain in palliative care warrants further consideration. Case series suggests the potential for meaningful, relatively long lasting benefits. The potential is quite exciting. More research, including cost analysis studies, is necessary.

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Neurosurgical options

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Introduction

The palliative patient poses multiple challenges to the caregiver, calling not only for the most feasible medical options, but also reconciling patient wishes, family's beliefs and pragmatism. Occasionally, severe debilitating pain secondary to systemic disease processes, radiation and/or chemotherapy necessitates the use of multiple infusions of potent opioids and other medications to achieve palliation. Such methods not only potentially cloud the patient's mental status during end-of-life, impeding familial communication, but often mandate inpatient care [Kanpolat *et al.*, 2009]. When traditional pain interventions have failed, neurosurgical interventions should be considered.

Neurosurgical management of pain dates back to the 19th century when surgeons performed ganglionectomies for the treatment of trigeminal neuralgia. Harvey Cushing, widely heralded as the father of neurosurgery, would later modify the procedure in 1900, thereby solidifying neurosurgery's niche in pain management. Since that time, various ablative and intrathecal drug-delivery techniques, some of which have been popularized in modern medicine, have seen development in further efforts to control chronic malignant pain. This chapter reviews various neurosurgical interventions available to the palliative pain patient who has failed traditional pain management strategies. Specifically, we discuss ablative procedures—cordotomy, myelotomy and denervation—and intrathecal therapies.

Cordotomy

History

One of the oldest and most studied ablative procedures for pain control includes cordotomy. First described as an open procedure by Spiller in 1912, cordotomies are both the first recorded neurosurgical ablative procedure employed for the treatment of cancer-related pain and the most robustly studied [Raslan and Burchiel, 2010] (*Table 1*). That being said, the volume and quality of literature remains limited to the one prospective trial and five retrospective cohorts with a focus on cancer pain relief until death [Ischia *et al.*, 1984a; Ischia 1984b; Stuart, 1993; Raslan, 2008; Kanpolat *et al.*, 2009; Raslan *et al.*, 2011].

Since Spiller's original description, the method by which cordotomies are performed has certainly seen advancement. The use the fluoroscopic guidance to accomplish cordotomies was first introduced in the 1960s; however it was not until nearly a decade and a half later, in the hands of Gildenberg, that this advancement gained popularity [Gildenberg, 1976; Raslan and Burchiel, 2010]. Gildenberg's description detailed two procedures: a high cervical method in which a lesion was made using a 0.41 mm diameter electrode guided through an 18-gauge spinal needle introduced laterally between C1 and C2 as well as a low cervical method in which the guiding needle was introduced anteriorly through the intervertebral disk space. In the former method, needle placement was performed under fluoroscopic guidance after a small amount of either intrathecal air or radioopaque dye was use to visualize the cord and dentate ligament. For the latter, needle and electrode placement were made solely under assumed anatomical relationships within the spinal canal. Both were performed under local anesthesia, since it was necessary for the patient to document their response, and relied on the assumed uniformity of the spinothalamic tract with regard to location and somatotopic organization within the cervical spinal cord [Gildenberg, 1976].

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Table 1 Summary of reported cordotomy findings [1981-2012]					
	Authors & year	Study design	No. of patients with cancer pain [%]	Follow-up	Outcomes
	Collins <i>et al.</i> , 2012	Case series	6 [100]	2-12 mos	6 (100%) reported 90-100% immediate pain relief with 50-100% of original relief continuation until death
	Atkin <i>et al.</i> , 2010	Case report	1 [100]	Death (5 wks)	Complete relief of pre-operative pain until death with no new neurological symptoms
	Kanpolat <i>et al.</i> , 2009	Retrospective cohort	193 [93]	6 mos	 192 (92.5%) complete/satisfactory pain relief 15 (7%) unsatisfactory/no pain relief Significant improvement in mean pre- vs. post-op VAS and KPS scores 3 (1.4%) temporary urinary retention (<1 mos) 2 (0.9%) temporary hypotension (<1 mos) 5 (2.4%) both transient paralysis/motor weakness and ataxia (<3 wks) 4 (1.9%) permanent dysesthesia
	Meeuse <i>et al.</i> , 2008	Case report	1 [100]	5 yrs	Immediate left-sided analgesia and numbness Loss of sexual sensation Paresthesias developed 2 wks post-op and persisted No motor or autonomic dysfunction
	Raslan, 2008	Prospective cohort	41 [100]	6 mos 1 pt death before 6 mos	Statistically significant improvement in pre- vs. post-op mean sleep time and VAS immediately, 1, 3 and 6 mos post-op No motor or sleep apnea complications 2 (5%) transient dysesthesias
	Bekar <i>et al.</i> , 2007	Case report	1 [100]	3 mos	Complete pain relief 1 wk, 1 and 3 mos post-op No complications reported
	Crul <i>et al.</i> , 2005	Case series	43 [100]	Death (2 d-4 yrs) 2 deaths before secondary follow-up 1 lost to follow-up	 41 (95%) reported NRS ≤4 immediately post-op (mean 8 pre-op vs. 0 post-op) 34/40 pts NRS ≤4 to death 1 (2.3%) permanent ipsilateral LE paresis Transient bladder weakness (2.3%), mirror pain (16.3%), apnea (2.3%) and weakness (4.7%)
	Raslan, 2005	Case series	8 [100]	6 mos	6 (75%) complete or satisfactory pain relief through 6 mos 1 (12.5%) recurrence within 2 wks 1 (12.5%) no relief
	Jones <i>et al.</i> , 2003	Case series	9 [100]	Death (28-830 d)	 9 (100%) near complete relief of LE pain 2/3 (67%) complete relief of peritoneal pain 8 (89%) required less morphine post-operatively at 2 wks 6 (67%) new pain development—controlled with analgesics
	Yegul and Erhan, 2003	Case series	234 [100]	Uncertain	 114 (49%) complete, immediate pain relief 94 (40%) satisfactory, immediate pain relief 22 (9%) repeat procedure – 13 ipsilateral, 9 contralateral: 9/22 pts complete/satisfactory relief after repeat procedure
	Table 1 (continu	ued)			

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Table 1 (continued)					
Authors & year	Study design	No. of patients with cancer pain [%]	Follow-up	Outcomes	
Kanpolat <i>et al.</i> , 2002	Case series	19 [100]	1-12 mos 6 pts lost to follow-up	 18 (95%) complete, immediate pain relief 1 (5%) partial, immediate pain relief 13/13 (100%) pts pain free at follow-up 1 (5%) permanent dysesthesia 	
McGirt <i>et al.</i> , 2002	Case series (MRI-guided)	6 [100]	5-11 mos	6 (100%) excellent, immediate pain relief 5/6 (83%) sustained relief at 6 mos follow-up 1 (17%) post-operative weakness	
Jackson <i>et al.</i> , 1999	Case series	52 [100]	Death (2 d-52 wks)	 43 (83%) decreased opioid dosage ≥½ pre-op 18 (35%) recurrence of pain (5 d-26 wks) 4 (7.6%) mild post-op weakness 2 (4%) post-op dysesthesias 	
Sanders and Zuurmond, 1995	Case series	80 [100] 62 unilateral 18 bilateal	Death (3 wks-18 mos)	 54 (87%) satisfactory, immediate pain relief (unilateral) 9 (50%) satisfactory, immediate pain relief (bilateral) 6 (9.7%) partial, immediate pain relief (unilateral) 6 (33%) partial, immediate pain relief (bilateral) 5 (6%) no pain relief (uni/bilateral) 6 (7.5%) lasting urinary retention (uni/bilateral) 7 (8.8%) lasting hemiparesis (uni/bilateral) 5 (6%) lasting mirror pain 	
Fenstermaker et al., 1995	Case series	6 [100]	Death (4-10 mos)	5 (83%) excellent/satisfactory, immediate relief until death 1 (16.6%) fair, immediate pain relief until death 1 (16.6%) new-onset transient bladder dysfunction	
Nagaro <i>et al.</i> , 1994	Case series	10 [100]	Mean 13.5 wks 7 deaths during follow-up period	Average pain scale score reduced from 8.5±0.9 to 3±2.7 1 wk post-op 1 (10%) recurrence of pain 4 (40%) no analgesics required post-op 2 (20%) transient hemiparesis (3 wks) 5 (50%) transient general fatigue 1 (10%) permanent general fatigue	
Lahuerta <i>et al.</i> , 1994	Case series	140 [96]	Death (1-512 d) 1 pt lost to follow-up	97/140 (69%) complete, immediate relief 29/140 (21%) partial, immediate relief 14/140 (10%) no pain relief 12/145 (8%) recurrence of pain (1-180 d) 3/146 (2.1%) deaths within 48 hrs 3/146 (2.1%) deaths within 3-7 d post-op	
Krol and Arbit, 1993	Technical note	13 [100]		Technical note	
Table 1 (continued)					

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Table 1 (contin	iuea)			
Authors & year	Study design	No. of patients with cancer pain [%]	Follow-up	Outcomes
Stuart <i>et al.,</i> 1993	Retrospective cohort	273 [100]	Death or up to 5, 6 and 8 yrs	 250 (91.6%) successful procedures (initial/repeat) 245 (89.7%) complete, immediate relief (initial/repeat) 2 (0.7%) partial, immediate relief (initial/repeat) 3 (1.1%) no relief (initial/repeat) 23 (8.4%) failed procedures 2/11 (18%) sleep apnea in bilateral cordotomy pts with mortality at 2 & 4 mos 3 (1.1%) urinary retention 4 (1.5%) persistent hemiparesis
Nagaro <i>et al.</i> , 1993	Case series	66 [100]	Up to 1 wk	7 (10.6%) pts report reference of pain following cordotomy (ROPC) immediately [6] or within 6 hrs [1] of PCC
Amano <i>et al.</i> , 1991	Case series	60 (bilateral), 161 (unilateral)	Death or greater than 6 mos	 57 (95%) complete/almost complete relief in bilateral pts 132 (82%) complete/almost complete relief in unilateral pts 3 (5%) persistent, intolerable pain in bilateral pts 29 (18%) persistent, intolerable pain in unilateral pts
Hogberg <i>et al.</i> , 1989	Case series	24 [100]	Death or greater than 6 mos 1 pt lost to follow-up	19 (79%) complete, immediate relief 4 (16.7%) moderate or no pain relief 10/19 (52.6%) remained pain free until death
Ischia <i>et al.</i> , 1985	Retrospective cohort	119 [100]	Death (≤12 mos) 5 pts deaths 24-48 hrs 11 pts lost to follow-up	33/103 (32%) pain free until death (10 d-7.5 mos) 4 (4%) recurrence within 24 hrs 7 (7%) recurrence within 2 wks 3 (3%) recurrence within 1 mo 1 (1%) recurrence within ≥ 2 mos 33 (32%) transient ipsilateral weakness 9 (9%) permanent urinary retention 3 (3%) ipsilateral paralysis
Lahuerta et al., 1985	Case series	95 [95]	Death or up to 26 mos	63/95 (66%) complete relief 21 (22%) partial relief 11 (11.6%) no relief 95 (100%) ipsilateral Horner's syndrome 17/100 (17%) mirror pain 4/100 (4%) ipsilateral weakness lasting >1 mo 6/100 (6%) dysesthesias
Ischia <i>et al.</i> , 1984b	Retrospective cohort	69 [100]	Death (4 d-3 yrs)	 55 (80%) complete, immediate relief contralateral to lesion 4 (6%) partial, immediate relief contralateral to lesion 8 (11.6%) no relief contralateral to lesion 31 (45%) pain relief until death (15 d-2 yrs) 65 (94%) ipsilateral Horner's syndrome

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Table 1 (continued)					
Authors & year	Study design	No. of patients with cancer pain [%]	Follow-up	Outcomes	
Ischia <i>et al.,</i> 1984a	Retrospective cohort	36 [100]	Death 4 pts deaths in 1 st week	 15/32 (47%) complete relief until death (2 wks-9 mos) 4/32 (12.5%) partial relief until death (2 wks-1 mo) 13 (36%) transient ipsilateral weakness 36 (100%) ipsilateral Horner's syndrome 14/24 (58%) new permanent urinary retention 13 (36%) new orthostatic hypotension 	
Cowie and Hitchcock, 1982	Case series	33 [59]	Death or until 3 yrs	31/33 (95%) effective, immediate relief24 (73%) effective relief at 6 mos18 (55%) effective relief at 1 yr2/56 (3.5%) operative deaths	
Meglio and Cioni, 1981	Case series	52 [100]	Death or until 15 wks	38 (73%) "excellent" results at 1 wk post-op 33 (63%) "excellent" results at 15 wks post-op	

Abbreviations: mo, month; wk, week; yr, year; pt, patient; d, day.

The next significant advancement in how neurosurgeons approached performing cordotomies came 20 years after Gildenberg's first paper. In 1996, Kanpolat and his colleagues pioneered the concept of utilizing CT-imaging when performing percutaneous cordotomies. Due to the coinciding introduction of intrathecal opioid systems, however, the notion went largely unnoticed in both the United States and Europe [Kanpolat and Cosman, 1996; Raslan et al., 2011]. Over the next decade, Raslan and his mentor, Kanpolat went on to produce separate manuscripts detailing lesioning of the cervical spinothalamic tracts under CT-guidance. Both procedures were nearly identical, describing the introduction of a standardized 0.27 mm diameter Kanpolat CT Electrode (KCTE) laterally between C1 and C2 under CT guidance after the intrathecal introduction of a water-soluble contrast agent in a patient under conscious sedation. Though serial CT-imaging during instrument advancement allowed for a more accurate representation of targetinstrument relationships, the specific location of lesioning within the cord continued to be dictated by anatomic and somatotopic assumptions. For instance, the depth of electrode penetration within the cord was to be less than half the transverse diameter of the cord in the mediallateral plane with location in the anterior-posterior plane dictated by the somatotopic target: 1 or 2-3 mm anterior to the dentate ligament for lesioning of the lumbosacral

or thoracocervical fibers respectively [Raslan, 2008; Kanpolat et al., 2009].

Evidence and current uses

Currently, the most commonly employed technique aims to disrupt the lateral spinothalamic tracts at the C1-2 level. Since these tracts decussate within the cord, the approach is taken from the side contralateral to the patient's pain. Ideal candidates include those with unilateral intractable nociceptive cancer pain resulting from either chest wall or lower extremity malignancies.

Complications from unilateral CT-guided procedures are generally temporary and minor, including headache, hypotension and dysesthesias that can last up to two weeks post-operatively [Raslan, 2008]. Other potential risks include weakness and incontinence. Pain in a pattern along the level of the cordotomy may also occur, though typically this is temporary. Recurrent pain has been reported months after the procedure, but is generally well controlled with adjuvant oral medications. Encephalitis has also been documented [Nakamura *et al.*, 2010].

Bilateral cordotomies do remain an option for patients suffering from bilateral symptoms; however, the surgeon must exercise extreme caution when lesioning the cord at the C1-2 level bilaterally due to an increased risk of serious complications. The most feared complication is



Figure 1 CT of spinal cord at C1-C2 level with intrathecal contrast for direct visualization of spinal cord structures. Artist's rendition of needle placement 1 or 2-3 mm anterior to the dentate ligament for lesioning of the lumbosacral (A) or thoracocervical (B) fibers respectively. Approximation of anterior and posterior horns as well as left spinothalamic tract fibers to show relationship of structures and needle placement.

Ondine's curse—the loss of spontaneous respiratory drive. It has been postulated that respiratory dysfunction can be mild and go unnoticed after the first cordotomy, thereby giving a sense of false security when pursuing the other side [Nathan, 1963; Batzdorf and Weingarten, 1970]. If a bilateral procedure is planned, the two parts are staged approximately one week apart, with monitoring in the intensive care unit post-operatively to assess for signs of respiratory distress and/or spinal shock [Kanpolat *et al.*, 2009; Atkin *et al.*, 2010].

A recent systematic review identified several case series and reports of cordotomies totaling over 3,600 patients, including patients with and without cancer [Raslan et al., 2011]. Patients with oncologic pain were generally reported to fare better than those with non-malignant sources of pain, in which relief was not only more commonly moderate/fleeting, but also more likely to be complicated by dysesthesias. This review included several large retrospective cohorts that demonstrated lasting relief of malignant pain over follow-up periods exceeding six months. Also included were the results of a prospective trial that demonstrated improvement in pre- versus post-operative visual analogue scale (VAS) scores, Karnofsky Performance Scale (KPS) scores, Activities of Daily Living (ADL) and total sleeping hours [Raslan et al., 2011]. Although there were no randomized controlled trials, in an Australian report of 273 patients undergoing percutaneous cordotomy, 245 (89.7%)

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patients achieved immediate, complete pain control postoperatively. In the failures, significant psychosocial stressors were identified, further underscoring the role of psychiatric and social support for these patients before, during and after surgery. Complication rates were typically low and included anesthesia dolorosa and burns/fractures in the anesthetic limb(s) (<1%), significant hemiparesis (1.5%) and urinary incontinence (1.1%). Sleep apnea was found to occur in 2 of the 11 (18%) patients who underwent bilateral cervical cordotomy [Stuart and Cramond, 1993].

Kanpolat reported his 20-year experience performing percutaneous CT-guided cordotomy in 207 patients, with 92.5% demonstrating complete or satisfactory pain relief. Though there were no operative mortalities, complications included transient motor paresis (2.4%) and ataxia (2.4%). These deficits were reported improved after three weeks. The bilateral cordotomy group had three cases of temporary hypotension (1.4%) and two cases of urinary retention (0.9%), all of which resolved in one month. The only reported permanent complication was dysesthesia in four patients (1.9%) [Kanpolat *et al.*, 2009].

A Dutch group reported their prospective experience with 80 terminally ill oncologic patients who received either unilateral or bilateral percutaneous cordotomy for refractory pain over a five year period. Eighty-seven percent of patients achieved satisfactory outcomes in the unilateral group, while only 50% of the bilateral group achieved similar results. All patients (both unilateral and bilateral) developed postoperative Horner's Syndrome. Complications included 41.9% and 33.3% of patients reporting transient lower limb weakness and 22.6% and 44.4% of patients experiencing remitting urinary retention in the unilateral and bilateral cohorts respectively. Permanent deficits included hemiparesis in 8.1% and 11.1% of patients as well as urinary retention in 6.5% and 11.1% in the unilateral and bilateral cohorts respectively. Yet despite these seemingly high rates of hemiparesis, all patients reportedly remained ambulatory with the aid of crutches or other assistant devices [Sanders and Zuurmond, 1995].

Today, most cordotomies are performed under CTguidance. After sedation, the patient's head is immobilized and radioopaque dye is injected via lumbar puncture before a fine-cut CT is obtained. When the patient's exact cord dimensions have been measured, the cordotomy needle is inserted inferior to the mastoid process perpendicular to the axis of the spinal cord (*Figure 1*). The skin-to-dura distances ranged from 43-66 mm in Kanpolat's series [Kanpolat *et al.*, 1989].

Once the needle is positioned anterior to the dentate ligament, stimulation is used to confirm electrode



Figure 2 Intra-operative picture of midline myelotomy. Posteriorly, the dura has been opened, exposing the spinal cord at midline.

placement. Stimulation leading to pain, paresthesias and/or warmth, is consistent with placement within the spinothalamic tract [Fitzgibbon, 2009]. Permanent lesions are then created with temperatures greater than 60 degrees Celsius for 30 seconds. During lesioning, frequent testing of pain, perception, motor function and hot/cold discrimination at the target area is undertaken. Lesioning can be repeated at higher temperatures for longer times if insufficient analgesia is achieved during the initial attempts.

Midline myelotomy

History

Abdominopelvic malignancies can result in significant pain that is refractory to intrathecal and systemic narcotic regimens. Such visceral pain had previously been thought to be mediated solely by the spinothalamic and spinoreticular tracts; however, recent evidence suggests involvement of additional pathways. The dorsal column's role in response to noxious pain has been documented through pre-clinical behavioral studies, tracing studies, electrophysiological response testing of the ventral posterolateral nucleus and functional MRI. These findings lend credence to the attempted disruption of dorsal, ascending, midline visceral pain pathways with the goal of ameliorating malignant, visceral pain [Willis *et al.*, 1999]. This has led to the proposal, implementation, and eventual success of using midline myelotomy as a tool in palliative pain management [Armour, 1927; Gildenberg, 2001; Hwang *et al.*, 2004].

The open midline myelotomy was first conceived in 1927 by Armour with the intent of disrupting the decussating fibers of the spinothalamic tract for the relief of visceral nociceptive pain [Gildenberg 1984]. The long recovery time associated with a multi-level operation and the significant peri-operative risk of traditional myelotomy led to advancement in the procedure over time. In 1970, Hitchcock introduced the term "commissural myelotomy" in reference to a similar procedure in which he accomplished stereotactic instrumentation of the high cervical cord through the occiput and C1 interspace with the patient in a seated position [Hitchcock, 1970; Gildenberg and Hirshberg, 1984]. Eight years later, Schvarcz renamed the procedure yet again, coining the term "extralemniscal myelotomy" due to the realization that the lesion target, which he too approached stereotactically, was an as-yet undescribed ventral medial dorsal pathway within the dorsal columns.

In 1981, Gildenberg described his open "limited myelotomy", in which both mechanical and radiofrequency lesioning was carried out under direct visualization of the cord following T9-T10 laminectomy. By 1997, in concordance with his previously described work, Kanpolat described the CT-guided radiofrequency lesioning of the midline dorsal columns at the C1 level [Gildenberg and Hirshberg, 1984; Gildenberg, 2001]. Three years later, the term "punctuate myelotomy" was used by Nauta to describe a myelotomy performed using a 16-gauge needle following an open laminectomy [Nauta *et al.*, 2000] (*Figure 2*). Since then, others have advocated using fine-tip forceps rather than a needle when lesioning [Hong and Andren-Sandberg, 2007].

Evidence and current uses

Midline myelotomy is generally most effective for patients whose pain is visceral in the abdomen or pelvis from the level of the stomach to the uterus [Becker *et al.*, 1999]. Often, the most appropriate patients are those who present complaining of diffuse, lancinating abdominal pain and cramping after extensive chemotherapy and/or radiation. Of note, patients with abdominopelvic malignancies that have invaded the lumbosacral plexus may not respond as well as those in which the plexus remains uninvolved. Candidates for surgery are refractory to other, more conventional methods of pain control and are considered medically stable enough to undergo an invasive procedure. Some surgeons advocate limiting patient selection to those whose life expectancy is greater than or equal to three months in the hopes of allowing patients to live out their remaining days at home rather than in a facility or ICU following intervention. As less invasive techniques are introduced, however, easier recovery may negate this requirement, thereby allowing a greater number of patients a surgical option [Kim and Kwon, 2000; Nauta *et al.*, 2000; Vilela *et al.*, 2001; Hong and Andren-Sandberg, 2007].

Unlike cordotomy, midline myelotomy is significantly less reported, limited mostly to case reports and series (*Table 2*). One of the larger series reported on myelotomy in 20 patients using mechanical interruption or radiofrequency ablation [Gildenberg and Hirshberg, 1984]. Of the 14 patients who received traditional thoracic midline myelotomy, six (42.8%) had excellent results with no residual pain, and four (28.6%) reported good relief with only mild residual pain. Of the remaining four patients, two (14.3%) reported slight relief and two (14.3%) patients none. Of note, four patients in this series received cordotomy and midline myelotomy in the same setting. However, because significant lower extremity weakness developed in two (50%) of these patients, the author was led to abandon this approach.

Viswanathan *et al.* reported on a series of 11 patients, nine of whom underwent commissural myelotomy for pain due to metastatic cancer within the abdomen or pelvis. The remaining two patients underwent myelotomy for pain due to unresectable spinal tumors. Five of the eleven total patients (45%) had complete relief of pain and three (27%) had significant improvement and reduced opioid requirements. The remaining three had poor or fair outcomes. Three patients experienced postoperative weakness, but these symptoms were seen to improve by time of discharge. Though two patients did have pain recurrence, one at two weeks and one at six months, long-term efficacy is difficult to interpret given the median survival of 43 days [Viswanathan *et al.*, 2010].

Hwang *et al.* reported his center's experience with six hepatobiliary/pancreatic cancer patients treated using punctate midline myelotomy for refractory pain. Under general anesthesia, these patients underwent a T2-T3 laminectomy. The midline was determined after identifying the two root entry zones, and a 16-gauge spinal needle was then advanced to a depth of 6 mm at midline before being adjusted laterally by 0.5 mm on either side of midline. All patients experienced immediate pain relief, and those who experienced recurrence reported adequate control with conventional medications. There were no neurologic complications reported [Hwang *et al.*, 2004].

These results mirrored those of several other series, which collectively report pain relief from 70-100%. Unlike the more aggressive myelotomies, these less traumatic lesions of the cord provided excellent coverage and control of abdominopelvic visceral pain while sparing proprioception [Schvarcz, 1976; Gildenberg and Hirshberg, 1984]. Not uncommonly with myelotomy, pain has been found to recur; however, such recurrences are generally well controlled with traditional medical adjunctive therapies. Other reported complications have included dysesthesias, proprioception issues, incontinence and even death [Gybels and Sweet, 1989].

Peripheral denervation

The treatment of pain caused by metastatic disease also necessitates the management of severe peripheral mono- and poly-neuropathies. Conservative approaches, including medications, injections and holistic methods, are often initially attempted; however, in cases of failure, neurosurgical intervention—rhizotomy, neurectomy or sympathectomy—may be worth consideration. Patients whose pain has proven refractory to conservative therapy and demonstrates a dermatomal distribution may be appropriate candidates.

Dorsal rhizotomy

Dorsal rhizotomy is one method of denervation and involves partial laminectomy with severing of the sensory roots at, two levels above, and two levels below the painful level. In that, surgical outcomes rely heavily on the accurate identification of the involved nerve roots, in questionable cases, diagnostic extradural nerve root injections are performed to ensure proper localization prior to surgical planning. Because the procedure requires general anesthesia and a multi-level laminectomy, the recovery can be as long as four to six weeks. Thus, it is essential that patient life expectancies are believed to be conducive with this type of exposure.

To date, three large case series have been reported for a total of nearly 100 patients. Results are promising, with 40-64% of patients reporting excellent pain relief, 15-50% good relief and 7-10% poor results when cohorts are combined [Barrash and Leavens, 1973; Esposito *et al.*,

Table 2 Summary of reported myelotomy findings [1974-2010]

Authors & Year	Study design	No. of patients with cancer pain [%]	Follow-up	Outcomes
Viswanathan	Case	11 [100]	Death	8 (73%) excellent/good pain relief
<i>et al.</i> , 2010	series		(11-39 mos)	4 (36%) mortality within 30 d
			(9 pts)	2 (18%) recurrence (2 wks and 6 mos)
			1 pt lost to	1 (9%) urinary retention
			follow-up	3 (27%) new transient motor weakness in LE
				1 (9%) pulmonary edema requiring intubation post-operative day 3
Hwang et al.,	Case	6 [100]	Death	6 (100%) complete, immediate pain relief
2004	series		(2-18 wks)	3 (50%) pain recurrence (2-12 wks)
				No neurological complications
Vilela et al.,	Case	2 [100]	2-4 mos	Pain relief until 2 mos (1 pt) or death (1 pt)
2001	report			Complications: transient unsteadiness
Nauta <i>et al.</i> , 2000	Case series	6 [100]	Death (3-31 mos)	Significant pain reduction
Kim and	Case	8 [100]	Death	5 (63%) excellent/good post-op pain relief
Kwon, 2000	series		(3-18 wks)	3 (38%) fair/poor post-op pain relief
				2 (25%) transient paresthesias
				1 (13%) sustained paresthesias
Becker et al.,	Case	1 [100]	Death	Pain decrease from 10/10 to 2-3/10
1999	report		(5 wks)	Transient urinary retention and LE paresthesias
Nauta <i>et al.</i> , 1997	Case report	1 [100]	10 mos	Good pain relief with no recurrence or new dysesthesias
Kanpolat and	Case	14 [100]	Uncertain	6 (43%) total pain relief
Cosman,	series			4 (29%) partial/satisfactory
1996				4 (29%) no pain relief
				1 (7%) post-operative hyperalgesia/hypesthesia
Watling et al.,	Case	2 [100]	Death	Pain relief reported immediately post-op with continuation and, in
1996	report		(~29 and 48 d)	second patient, increasing opioid use with disease progression
Gildenberg	Case	14 [100] <i>limited</i>	Death	Thoracolumbar pain relief:
and	series	myelotomy	(2-13 mos),	10 (71%) excellent/good;
Hirshberg,		19-110	(6-24 mos)	4 (29%) Fair/Poor
1004		2 [100] cervical	(0 24 1103)	Cervical pain relief:
		myelotomy		2 (100%) fair/poor
				No sensory loss, weakness or incontinence
		4 [100] myelotomy		Myelotomy & cordotomy
		& cordotomy		2 (50%) good relief
				2 (50%) fair/poor relief
Fires ()	0-	10 [100]		2 (50%) significant ipsilateral weakness of leg
Elras et al.,	Case	12 [100]	Death (2-14 mos)	(30%) total pain relief (3-14 mos); 1 until death
1900	Selles		1 living at 14 mas	5 (4270) good relief
			niving at 14 mos	5 (4270) recurrence of pain
T 11 2 (· ·				nansient gait uistrubances/uysmetria

 Table 2 (continued)

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Table 2 (continued)				
Authors & Year	Study design	No. of patients with cancer pain [%]	Follow-up	Outcomes
Cook and	Case	16 [67]	Death (12 pts)	11 (69%) good immediate pain relief
Kawakami,	series		Uncertain for	3 (19%) fair immediate pain relief
1977			remaining 4 pts	2 (13%) poor immediate pain relief
				1 (6%) known recurrence before death
Schvarcz,	Case	35 [78]	Death in all	30 pts (67%) "satisfactory" pain relief
1976	series		but one case	5 (12%) partial recurrence
			(1-18 mos)	No motor weakness or proprioceptive alterations
Papo and	Case	9 [90]	Death or up	3 (33%) complete relief until death
Luongo,	series		to 1 y	6 (67%) severe relapse before 4 wks
1976				No bladder or respiratory difficulties
Lippert et al.,	Case	12 [75]	10 pts total	12 (100%) Excellent/Good initial pain relief
1974	series		(1-7 mos)	1/6 (17%) CA pts with follow-up had recurrence
			6 CA pts	Transient paresthesiae in 55%
				No new sphincter complications
Hitchcock,	Case	"most" (26 total)	Death or up to 4 y	13 (68%) excellent/good pain relief
1974	series		2 lost to	4 (21%) poor pain relief
			follow-up	2 (11%) no relief
Broager,	Case	31 [91]	Death	16 (47%) excellent relief until death (12 pts) or up to 12 mos
1974	series		(4 d-12 mos) (21 pts) or up to 18 mos	9 (26%) excellent relief with recurrence (1-6 mos)
				3 (9%) good relief until death (1-12 mos)
				2 (6%) severe dysethesia until death (3-6 mos)
				1/31 (3.1%) death 4 d post-op
				All had loss of proprioception
Abbreviations: mo month: wk week: vr vear: of patient: d day				

Abbreviations: mo, month; wk, week; yr, year; pt, patient; d, day

1988; Arbit *et al.*, 1989]. While pain relief generally lasts for several months, patients should expect numbness in the corresponding dermatomes post-operatively. However, this side effect is not usually reported to be particularly troublesome as long as relief is achieved. Other concerns include the development of a spinal fluid leak and unintentional nerve root injury resulting in weakness or incontinence [Barrash and Leavens, 1973].

Selective posterior rhizotomy

Malignant thoracic and chest wall pain respond particularly well to treatment via a selective posterior rhizotomy. In these cases, a multi-level hemilaminectomy is performed, the ventral and posterior roots separated and the appropriate posterior rootlets identified for sectioning (*Figure 3*). In 1988, Esposito demonstrated successful treatment of Pancoast's syndrome with the lesioning of C8-T4 posterior rootlets in a series of ten patients. The included patients had a life expectancy of one year or greater. All ten patients reported greater than 90% pain reduction in the immediate post-operative assessment. Over a follow-up period of 8 to 36 months, four patients experienced complete relief until death. Five patients estimated their residual pain to be approximately 10% of its original intensity throughout follow-up, while one patient approximated the residual pain at 20%. Four of the ten patients experienced new ipsilateral leg weakness, though a lack of gait impairment was reported. [Esposito *et al.*, 1988].

A modified rhizotomy technique has also been introduced with successful results in patients with chest wall pain secondary to thoracic nerve root pathology. Given


Figure 3 Intra-operative photograph of a dorsal rhizotomy. The ventral and dorsal nerve roots have been separated. Shown here are individual dorsal nerve rootlets being separated for stimulation prior to sectioning.

evidence that pain may be conducted through motor roots and sympathetic nerves, in place of the more traditional approach in which only the posterior rootlets are sectioned, Arbit *et al.* proposed a modified rhizotomy. In this method, Arbit details the sectioning of both the anterior and posterior pre-ganglionic nerve roots using an extradural approach. In this series, 14 patients experiencing pain from malignant disease affecting thoracic nerve roots, as indicated by radiographic studies, underwent a modified rhizotomy [Arbit *et al.*, 1989]. Strict pulmonary parameters were used in selecting these patients. Specifically, all patients required an arterial P_aCO₂ <50 mmHg, P_aO₂ >50 mmHg and a FEV₁ >1 L [Arbit *et al.*, 1989].

Sixty-four percent of the studied patients in Arbit's series experienced excellent pain relief with rapid weaning of narcotic medication. Fifty percent experienced pain relief until death. In 30% of patients, pain recurred, but was markedly less severe when compared to its original quality. Complications included infections, though these were successfully treated with antibiotic therapy. One failure was the result of improper identification of the offending nerve root. Arbit and his colleagues suggest that the modified rhizotomy in the thoracic region seems as effective as the more traditional approach while decreasing the potential for CSF leak and complications related to exposure [Arbit *et al.*, 1989].

Neurectomy/sympathectomy

Thoracic pain syndromes in cases of malignancy are a unique entity in that many traditional surgical approaches used to address pain can prove problematic. For instance, while cordotomies may be theoretically suitable for addressing such pain, because many of these patients have only one functioning lung, such extensive procedures are often contraindicated. For this reason, certain minimally invasive techniques may prove to be a more appropriate option in this patient population.

Lai *et al.* have reported on a video-assisted thoracoscopic neurectomy in a patient suffering from significant pain due to pronounced local bone and intercostal nerve involvement by a chest wall mass despite extreme dosages of intravenous morphine. Radiofrequency ablation and nerve root injections provided minimal relief, but aided in the identification of the offending nerves. With neurectomy, the patient experienced significant relief with the rapid weaning of a substantial amount of opioids and was able to be transferred to a hospice facility in significantly less pain [Lai *et al.*, 2006].

In abdominal malignancy, sympathetic splanchnicectomy is a viable option in certain patients [Lin et al., 1994; Krishna et al., 2001; Lang-Lazdunski et al., 2002; Lai et al., 2006; Mann et al., 2006; Kang et al., 2007; Katri et al., 2008]. In one series, patients suffering from severe, refractory abdominal pain secondary to unresectable tumors were selected for splanchnicectomy if they reported a KPS of greater than 60 and were healthy enough to undergo general anesthesia. Via thoracoscopic guidance, the sympathetic and splanchnic nerves were identified, allowing for the localization of the main trunk of the greater splanchnic nerve. All communicating branches were then severed from the base of the thoracic cavity prior to sectioning of the greater and, if found, lesser and least trunks of the splanchnic nerve. In a series of 21 patients, 76.2% were either weaned off of, or to substantially lower doses of narcotic medication. Patient-reported pain scores were significantly reduced post-operatively (8.5 to 1.7) [Kang et al., 2007]. In another report of 14 patients with pancreatic or other abdominal cancers, endoscopic, bilateral sympathetic splanchnicectomies resulted in 64% of patients experiencing complete pain relief and another 21% experiencing "good" pain relief [Lin et al., 1994].

In the palliative population of oncologic patients, longterm assessments of efficacy are difficult given limited survival. However, splanchnicectomies have also been used for pain control in chronic pancreatitis patients. In Buscher's prospective study of 75 patients treated with bilateral thoracic splanchnicectomies for chronic pancreatitis, 52% remained well-controlled at 12 months, 38% at 24 months and 28% at 48 months [Buscher *et al.*, 2008].

Intrathecal therapies

Implantable intrathecal pain pumps (ITP) are the most commonly used surgical modality in the palliative care situation. The majority of pain pumps are placed in the spine, though there are case reports of devices being used in the brachial plexus and in the ventricles of the brain. Of the catheters placed in the spine and connected to a pump, most are intrathecal. In cases where a patient's lifespan may be shorter, epidural catheters connected to an external pump have also been of some benefit. Though many substances have been administered intrathecally, those that are FDAapproved are currently limited to include morphine, ziconotide and baclofen. Clonidine has been approved for epidural administration by the FDA [Smith *et al.*, 2008].

Several important ramifications should be considered when pursuing the route of intrathecal drug delivery for pain control. First, because only a finite amount of medication exists in the reservoir, routine follow-up and access to care become necessities. Furthermore, medication requirements may change with disease progression, requiring an expert be available for management. Lastly, systems can fail; and though fluoroscopic-dye studies can be used to interrogate the system in the hopes of identifying a correctable problem, troubleshooting may prove cumbersome and lack of delivery can result in intense, sometimes life-threatening withdrawal.

Intrathecal drug therapy for pain has been studied and reported extensively in the literature. A randomized doubleblinded, placebo-controlled trial evaluated the therapeutic use of intrathecal ziconotide in patients suffering from refractory pain related to either cancer or AIDS. Onehundred-and-eleven patients were enrolled, fitted with an intrathecal catheter and randomly selected to receive an infusion of either ziconotide or placebo for a maximum of two weeks. Visual Analog Scale scores improved significantly in the ziconotide group, with moderate to complete relief of pain in 52.9% of patients [Staats *et al.*, 2004].

While studies of intrathecal drug therapy for chronic pain exist, fewer series report their efficacy exclusively in the oncologic setting. Becker *et al.* report their success in 43 patients receiving intrathecal opioid therapy for the management of cancer-related neuropathic and nociceptive pain conditions. A median pain reduction of 77.8% in patients with nociceptive pain and 61.1% in patients with neuropathic pain was demonstrated. Long term results illustrated continued relief in the nociceptive group with a median pain reduction of 66.7%. The neuropathic group, however, did not demonstrate a high degree of sustained analgesic effect, boasting a median of only 11.1% reduction in pain [Becker *et al.*, 2000].

Penn and Paice reported their results with chronic intrathecal morphine as well. In their series, 35 of 43 patients treated with implanted pumps for continuous infusion of intrathecal morphine suffered from pain secondary to malignancy. In this subset, 80% experienced good or excellent relief. Adverse events included catheter kinking, CSF leak and drug tolerance, though in all but two patients this was adequately managed with adjustments in

drug delivery and concentration [Penn and Paice, 1987].

In 2002, Smith *et al.*, reported on a randomized clinical trial comparing implantable drug delivery systems with comprehensive medical management for refractory cancer pain. Of the 202 patients enrolled in the trial, there was significantly improved pain control in the implanted group versus the medical arm (84.5% *vs.* 70.8%; P=0.05). The implanted group also achieved greater reductions in drug toxicity, fatigue and depressed levels of consciousness. Moreover, though not significant, the implantable group trended towards improved survival at six months (53.9% *vs.* 37.2%; P=0.06) [Smith *et al.*, 2002].

Though intrathecal pumps are generally preferred, in the oncology patient that may have a very short life span, cost analysis should be considered. Hassenbusch found that the break-even point with regard to differences in cost between intrathecal/implanted pumps versus epidural/external pumps lies between three and six months [Hassenbusch, 1999; Knight et al., 2007]. In some cases, epidural catheters with ports may be equal in efficacy to intrathecal-delivery systems. In one series of 91 patients with epidural catheters and a subcutaneous port, adequate pain relief was achieved in 76% of patients. Complications included superficial infections in 39 (43%) patients and deep infection in 12 (13%) patients, 11 of whom required further surgery. Given the significant complication profile, it was recommended that this therapy be used for patients with shortened life expectancies [Smitt et al., 1998; Anghelescu et al., 2010]. Overall, a systematic review of the existing literature regarding intrathecal drug delivery systems for cancer-related pain offered moderate recommendation for its use in this patient population [Hayek et al., 2011].

Intraventricular infusions

Though many groups of pain specialists are familiar with traditional intrathecal pumps, intraventricular administration of pain medications is less utilized. Neurosurgeons and oncologists, jointly, have used Ommaya Reservoirs for intraventricular administration of chemotherapeutics for decades. In the 1980s, however, clinicians began injecting opioids through these reservoirs in attempts to control refractory oncologic pain of the head and neck and found fair success [Leavens *et al.*, 1982; Cramond and Stuart, 1993; Karavelis *et al.*, 1996]. In patients receiving intraventricular therapy, initial dosages of morphine ranged from 0.10-0.5 mg, with titration thereafter determined by clinical response [Su *et al.*, 1987; Kilic *et al.*, 1993, Smith *et al.*, 1999].

Comparative studies indicate similar effectiveness for spinal intrathecal versus intracerebroventricular (ICV) administration [Ballantyne and Carwood, 2005]. Thirteen trials of 337 total patients assessing the efficacy of ICV pain medication were compared to 31 trials of 1,343 total patients receiving epidural medication and 28 trials of 722 total patients receiving intrathecal medication. Excellent pain relief was achieved in 73% of patients receiving ICV therapy and 72% of patients receiving intrathecal therapy. The epidural cohort experienced both a significantly lower rate of success (62%; P=0.03) as well as a significantly greater degree of overall dissatisfaction (P=0.005). Generally, patients included in the ICV group suffered from bilateral, midline, diffuse orofacial or cervicofacial pain, although patients with subdiaphragmatic pain were also included in some series where lumbar intrathecal therapy had either failed or was contraindicated [Lobato et al., 1983; Lazorthes et al., 1985; Lenzi et al., 1985; Lazorthes et al., 1995].

Lazorthes et al. reported their IVC experience in 82 patients with refractory pain secondary to an inoperable malignant tumor. The pain was somatic, nociceptive in nature and was typically confined to the upper body/head/ neck. Patients with lower extremity pain were included if they had failed standard IT therapy. Using sterile technique, patients received 0.12, 0.25, 0.5, or 1 mg boluses of morphine through the reservoir followed by titration of the dose so as to achieve adequate pain relief over one week, with close respiratory and neurologic monitoring throughout. Some patients' families learned the technique to allow for administration in the outpatient setting. Relief was measured by the VAS, improvement in KPS and systemic medication decrease. Side effects most commonly reported included nausea, vomiting, constipation, headaches, disorientation and drowsiness. A limited number of patients suffered severe drowsiness, myosis and respiratory depression, but these symptoms were successfully reversed with naloxone administration. Two cases were complicated by purulent meningitis, requiring intraventricular antibiotics and one case required replacement due to catheter kinking. Overall, of the 82 patients studied, 80% reported good to excellent analgesia with 17% reporting moderate analgesia. Only two treatment failures were reported. Of note, patients did require increased dosages of morphine injected into the reservoir over time, although whether this was secondary to progression of disease or tolerance remains unclear [Lazorthes et al., 1995].

Karvelis *et al.* found that intraventricular morphine administration provided significant benefit to their series of 90 patients, 90% of whom achieved adequate (>50%) pain relief. The most common side effect was nausea, though this was generally described as transient. Other complications included cerebral hematomas, misplacement in one patient and infection in two patients [Karavelis *et al.*, 1996].

The decision for spinal versus intraventricular analgesic administration rests on good clinical judgment. While the majority of cases seem to respond to standard IT therapy, IVC administration may be appropriate in patients suffering from refractory, malignant upper body/head/neck pain as well as in patients that already have a reservoir in place. Given the potential for critical complications using an intracerebral approach, some advocate that failure of intraspinal administration should be considered criteria for consideration of intraventricular administration.

Brachial plexus infusions

It should also be noted that pain pumps do not necessarily need to be constricted to the central nervous axis. A randomized, double-blinded, placebo-controlled study addressing the management of shoulder pain after rotatorcuff surgery in 40 patients found significantly improved pain control and decreased requirement for narcotic medication after infusion of 0.2% ropivacaine at 10 mL/hr into the interscalene brachial plexus when compared to the placebo group receiving only normal saline. Dislodgement occurred in two patients another patient complaining of dyspnea suspending his enrollment in the trial [Klein *et al.*, 2000].

This technique has also seen successfully employment in the case of malignant pain. Buchanan *et al.* report their experience treating a case of incapacitating shoulder pain in a patient with a pathologic glenoid fracture secondary to renal metastasis. A catheter was reportedly tunneled to the brachial plexus at the scalene muscle using radiographic guidance and 0.2% ropivacaine at 5 mL/hr was injected, resulting in immediate pain relief, return of activity and improved range of motion. The only significant side-effect was numbness. After two days of therapy, the medication was discontinued and his pain was significantly improved with gradual weaning of his previous oral opioid medication [Buchanan *et al.*, 2009]. Such methods could prove useful in patients with painful, unresectable primary of metastatic tumors involving the brachial plexus.

Future directions

Today, the use of neurosurgical procedures remains an option in treating malignant, refractory pain. For the nearly two-thirds of cancer patients estimated to suffer from chronic somatic or visceral nociceptive pain related to the progression of their disease, the mainstay of treatment remains non-surgical in nature. As per the World Health Organization, treatment of malignancy-induced pain focuses on a three-step pharmacological approach with escalation from non-opioid medications to mild opioids and finally strong opioids including the introduction of intrathecal analgesics [Raslan et al., 2011]. Certainly, intrathecal delivery systems remain a viable option for many patients. They are relatively easy to place and manage in the short-term and have provided many patients in the palliative setting considerable benefit. As discussed, less traditional forms of intrathecal therapies such as intraventricular and plexus catheters may also be considered in more difficult cases. Currently in both Europe and the United States, destructive neurosurgical procedures are undertaken only for those patients whose pain remains refractory to even the most aggressive attempts at medical management.

With today's ever-growing emphasis on evidencedbased medical practices, common procedures are discussed commonly. Neurosurgical ablative procedures to take a back-seat to those modalities with more clearly demonstrated efficacy and safety. This, in turn, has led to an understandable uncertainty among referring pain specialists and oncologists. Yet, as the preceding pages have demonstrated, these procedures can significantly improve quality of life in terminally-ill patients.

To be sure, since their original descriptions the two most popular neurosurgical ablative procedures—cordotomies and myelotomies—have seen advancement [Gildenberg 1976; JR. 1976; Gildenberg and Hirshberg, 1984; Nauta *et al.*, 1997; Nauta *et al.*, 2000; Gildenberg, 2001; Vilela *et al.*, 2001; Kanpolat *et al.*, 2002; Mann *et al.*, 2006; Kanpolat, 2007; Kanpolat *et al.*, 2009; Raslan and Burchiel, 2010; Viswanathan *et al.*, 2010; Raslan *et al.*, 2011]. With the increasing use of intra-operative monitoring and neuronavigation, the appeal of neuroablative procedures is expected to only expand. These technological improvements stand to increase the safety of procedures while greatly reducing the recovery and hospitalization time—essential components in end-of-life care.

Under the best of circumstances, these patients are poor surgical candidates. With the average post-operative survival of this patient population currently measured in weeks, it becomes necessary to not only improve pain but to avoid causing additional burden [Viswanathan *et al.*, 2010]. It falls to the surgeon to use those resources at his or her disposal to optimize outcome while minimizing

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the invasive nature of the procedure. The emergence and growing popularity of minimally invasive and/or endoscopic procedures in neurosurgery may thus prove invaluable in advancing surgical treatment of pain. Intra-operative MRI technology is also ideally suited as an adjunct for ablative procedures of the cord. Such a method would offer realtime feedback, the potential for thermal imaging as well as increased comfort for both the patient and the surgeon.

Utilization of intra-operative neuromonitoring and imaging may allow today's neurosurgeons the opportunity to offer an added modicum of comfort for the patient. We anticipate that further development of diffusion-tensor imaging, tractography and functional information may allow for further efficacy and safety of the procedures. As an example, perhaps one of the most obvious and important areas requiring refinement with regard to the future success of midline myelotomies is the expansion of our knowledge of those pathways involved. Is it possible to more clearly delineate the common dimensions of the target fibers so as to minimize damage to adjacent pathways? Is it necessary to lesion to the depth of the commissure to obtain full analgesic effect? Uncertainty about the exact nature and location of the target pathway remains. Addressing these issues requires both a basic science avenue of investigation as well as an increased volume of clinical analysis. The advancement of functional MRI with regard to specific spinal cord pathways related to pain and temperature-a modality of imaging that has seen exploration in rat models but has yet to be used to investigate the human neural axis-may also be of value [Malisza and Stroman, 2002].

Summary

As the treatment of malignant pain continues to evolve in the 21st century, involvement of any of the neurosurgical procedures discussed hinges on three interwoven factors that are anything but diminutive. Firstly, optimization of operative techniques with the goal of increasing the accuracy of lesion placement while decreasing the extent of undesired neurological effects is a necessity. As the preceding discussion has exemplified, neuroablative procedures are well suited for incorporating the imaging and intra-operative monitoring technologies of today as well as tomorrow.

Secondly, as procedures are standardized and modernized, it falls to the neurosurgical community to provide evidence of safety and efficacy. Since the 1960s less than 6 studies examining the outcomes of neuroablative procedures for cancer-related chronic pain have emerged with patient populations greater than 200 patients. The majority of those studies report patient populations of only ten to 50 patients. In that time, with the exception of the 1970s, in which the average number of studies was doubled, only 20-25 studies have emerged in any given decade for all of the neurosurgical ablative procedures combined [Raslan *et al.*, 2011]. Thus, both the volume and quality of literature demand improvement.

Lastly, the rejuvenation of these procedures makes their incorporation within neurosurgical residency program curriculum essential. Training residents to correctly and safely perform such procedures on the appropriate patient population assures not only their continued utilization, but also provides the necessary catalyst for the enactment of the first two necessary factors.

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Tai Chi

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Introduction

Tai Chi is an ancient martial and health art involving gentle flowing circular movement of the upper limbs, constant weight shifting of lower limbs, meditation, breathing, moving of qi (the internal energy in Chinese belief) and various techniques to train mind-body control. It is a mild to moderate aerobic exercise and the constant shifting of body weight helps the practitioners to improve the balance and minimize the risk of fall. Because the movements are slow and gentle, cancer patients can pace according to their physical fitness. Tai Chi helps individual to focus and improve their body-mind control. The role of higher centers in pain modulation is well supported by an abundance of literature and practicing Tai Chi can potentially help cancer survivors to optimize the coping mechanisms. Meditation, breathing and visual imagery are essential components of Tai Chi. Tai Chi is associated with improvements in psychological well-being including reduced stress, anxiety, depression and mood disturbance, and increased self-esteem. Literature specifically examining the effects of Tai Chi in cancer population is limited and more research is required to understand the full effects of Tai Chi in the cancer population.

Prevalence of complementary and alternative medicine (CAM) in palliative care

CAM in palliative care

CAM has emerged as a popular alternative among cancer survivors [Gansler *et al.*, 2008]. It refers to a group of diverse medical and healthcare treatments, practices, and products not considered part of conventional medicine but often used to prevent illness, promote health, avert disease recurrence, and manage symptoms related to illness [Fouladbakhsh *et al.*, 2005]. CAM practices are often grouped into broad categories, such as natural products, mind-body medicine, and manipulative and body-based practices [National Center, 2012]. Tai Chi is an example of mind-body medicine.

An analysis of the data from National Health Interview Survey (NHIS; N=31,044) revealed that the prevalence of CAM use in cancer survivor was 40 percent [Barnes *et al.*, 2004]. Female, middle-aged, Caucasian and well-educated subjects with pain, depression, and insomnia would tend to use CAM as a complementary treatment [Fouladbakhsh and Stommel, 2010; Gansler *et al.*, 2008]. User of CAM is often associated with experiencing greater symptom distress, a desire for spiritual transformation, or unfulfilled needs from the existing health care system [Mao *et al.*, 2008].

The Internet is an important tool in modern world to search for information. Patient and family tend to look for information in the Internet themselves. This is because health care practitioners usually try to avoid discussing CAM with their patients as they themselves are not well informed [Ernst, 2003]. Unfortunately, information that can be useful for cancer survivor especially on CAM can be misleading or fraudulent in the Internet [Walji et al., 2004; Meric et al., 2002]. Cancer patients are inclined to search for websites that are trustworthy. In a detailed analysis of websites in 41 National Cancer Institute (NCI) designated comprehensive cancer centers in US, 71% of 41 leading cancer centers provide information on CAM [Brauer et al., 2010]. However, the quality and ease of navigation of these sites remain highly variable and there are rooms for improvement.

Tai Chi and palliative care

Using the NHIS data, approximately 2.5 million individuals



Figure 1 The symbol of Tai Chi, showing the close relationship of yin and yang.

have practiced Tai Chi for health reasons in US, and this number is increasing [Barnes et al., 2004]. Among these, it was estimated that approximately 200,000 cancer survivors practice Tai Chi, and two-third of the practitioners are female [Fouladbakhsh and Stommell, 2010]. The practice of Tai Chi is far less common than the use of diet, herbal medicine and deep breathing, possibly because Tai Chi may require expenses for class attendance or purchase of audio-visual instructional materials. In a survey about complementary therapies in Canadian palliative care settings, only 11% of the surveyed palliative care settings provided complementary therapies whereas another 45% allowed the usage of complementary therapies by patients in their settings. Out of this, only 5% provided Tai Chi as part of the complementary therapy offered [Oneschuk et al., 2007].

History and philosophy of Tai Chi

Philosophy of Tai Chi

Tai Chi literally means "ultimate supreme", and in both Taoist and Confucian Chinese philosophy, Tai Chi is considered as the driving force of the universe [Cheng, 1985]. In this regard, Tai Chi is believed to generate two opposing forces, the Yin and Yang, which form the symbol of Tai Chi (*Figure 1*). Tai Chi exercise itself teaches "stillness in movement" and constant transfer of body weight, reflecting the simultaneous separation and merging of yin and yang energy in the form of "qi" [Tam, 2002; Horwood, 2008]. In Chinese belief, "qi" is the internal energy of the body.

History of Tai Chi

Tai Chi is both an ancient martial and health art which engages gentle flowing circular movement of the upper limbs, constant weight shifting of lower limbs, meditation, breathing, moving of "qi" and various techniques to train mind-body control. The history literature attributed the origin of Tai Chi around the period towards the end of Ming Dynasty (1597-1664 AD). There are five major styles of Tai Chi, each named after the Chinese families from which it originated: Chen, Yang, Wu, Sun and Wu/Hao [Zhu *et al.*, 2010]. The major family styles share much underlying theory, but differ in their approaches to training: postures, forms, pace and order of movements [Peng, 2012]. There are now dozens of new styles, hybrid styles and offshoots of the main styles.

In 1956, the government of the People's Republic of China sponsored the Chinese Sports Committee, who brought together four Tai Chi teachers to create a simplified form of Tai Chi as exercise for the masses. They truncated and abbreviated the traditional Yang family style Tai Chi forms to 24 postures; taking between four and five minutes to perform [Wolf *et al.*, 1997]. Tai Chi can be practiced everywhere, indoors and outdoors, alone or as a group. No special equipment is required. All that is needed is a small flat area of about four square meters, loose clothing and flat-heeled shoes [Peng, 2012]. Because of this official promotion, Tai Chi has become a very popular exercise in China.

Health benefits of Tai Chi

The various health benefits of Tai Chi have recently been reviewed [Peng, 2012]. There are three components that Tai Chi can contribute to the well-being of the cancer survivors: exercise, mind-body control and meditation.

Exercise

Tai Chi improves physical functioning

Depending on the duration, pace, experience and time spent in practice, Tai Chi is an exercise of mild to moderate intensity [Lan *et al.*, 2008]. The metabolic equivalent of task (MET) for Tai Chi ranges from 2.5-6.5, which is equivalent to exercise of moderate intensity such as dancing or brisk walking [Ainsworth *et al.*, 2000]. Long-term Tai Chi training was shown to enhance aerobic capacity (as measured by the peak oxygen uptake, VO_{2peak}) by 16-27%

and 16-21% in a cross sectional study and a longitudinal study, respectively [Lan *et al.*, 1996; Lai *et al.*, 1993].

Tai Chi practice involves slow exercise speed and constant weight shifting, which increases the load on the lower limbs. Therefore, Tai Chi training can improve musculoskeletal strength of lower limbs and balance [Wu, 2002; Lan *et al.*, 2000; Peng 2012]. The integration of cognitive and physical components in Tai Chi could represent additional value of Tai Chi over other exercise programs, which mainly focus on physical aspects only. Tai Chi enhances self-awareness of balance and thereby decreases the fear of falling [Li *et al.*, 2005; Zijlstra *et al.*, 2007]. Improving physical functioning is important for terminal patients as it preserves a sense of meaning and dignity to them by allowing them a sense of independence to carry out more basic activities in daily living.

Exercise improves health-related quality of life (HRQoL) in cancer patient

A systematic review examining the effects of exercise interventions on HRQoL for people with cancer during active treatment suggested that exercise compared with control had a positive impact on HRQoL and certain HRQoL domains [Mishra et al., 2012]. Exercise in general resulted in improvement in global HRQoL, body image/self-esteem, emotional well-being, sexuality, sleep disturbance, and social functioning up to 3 to 6 months follow-up. Furthermore, exercise intervention is beneficial in the management of cancer-related fatigue, which is significantly improved following an exercise program carried out either during cancer therapy or following cancer therapy [Cramp and Byron-Daniel, 2012]. The connection between physical functioning, fatigue and existential meaning or dignity had been explored previously [Lindqvist et al., 2004].

In a small prospective case study of 21 medically stable patients with terminal cancer, a 18-week Tai Chi training had significantly improved functional status, resulting in better flexibility in the upper limb and trunk, better mobility and balance, as well as lower handicap levels [Hui *et al.*, 2008]. In addition, Tai Chi improved the orientation, social integration and occupational domains. This study suggested that Tai Chi is safe and practicable even for terminally ill patients, with physical and psychosocial benefits.

Mind body control

Higher center and pain

Higher centers play an important role in pain perception.

Current scientific literature supports that the relationship between nociceptive information and pain perception is profoundly affected by affective and cognitive factors [Tracey and Mantyh, 2007]. Two important higher center processes are of particular important in pain modulation: attention and expectation.

Attention and pain

Attention is a mechanism by which sensory events including nociceptive information are selected and enter awareness. Two modes of attention selection are conceptualized in a neurocognitive model: "top-down" and "bottom up" selections [Legrain et al., 2009]. Top-down selection is an intentional and goal-directed process that prioritizes information relevant for current action. This is achieved by modifying the sensitivity of the relevant signals relative to the noise. The signal can be enhanced by amplifying the activity of neurons that respond to the relevant stimuli. The noise represented by the irrelevant stimuli, on the other hand, can be dampened by inhibiting the activity of the neurons that respond to it. Simply put, this refers to the concentration and staving focus despite distraction. Bottom-up selection corresponds to an unintentional, stimulus-driven capture of attention by the events themselves. Various symptoms associated with cancer, such as pain, nausea or fear, are good examples of unintentional stimuli, which can act as a source of distraction [Legrain et al., 2009]. Clinically, these concepts help one explore the possibility for an individual to exercise executive control over nociceptive interference, either improving the top-down or bottom-up selection, through training with mind-body interaction exercise such as Tai Chi [Peng et al., 2012].

Expectation and pain

Expectation is a complex function of the human brain which allows us to anticipate a multitude of future scenarios, including upcoming pain and discomfort. Expectation invokes coping strategies such as behaviors to avoid pain and/or an activation of the different inhibitory mechanisms for pain relief [Diederich and Goetz, 2008; Ingvar, 2009]. Activation of the descending pain control system through the anticipation of pain relief is well exemplified by the placebo response. The descending inhibitory network involves a constellation of areas in the higher centers such as the rostral anterior cingulate cortex, the periaqueductal gray and the rostral ventromedial medulla. The network influences the ascending nociceptive input through endogenous opioids and non-opioids pathways [Zubieta and Stohler, 2009; Pollo and Benedetti, 2011]. This concept helps one to understand the possibility for an individual to exercise executive control over nociceptive input, by anticipating the forthcoming pain and utilizing imagery techniques and meditation to cope [Buhle, 2010; Goffaus *et al.*, 2007; Menzies and Taylor, 2004].

Tai Chi improves mind body control

Tai Chi is an excellent exercise for training the mind body interaction. The traditional and fundamental teaching of Tai Chi-"the mind moves the gi and the gi moves the body" -helps people optimize their coping mechanisms [Wile, 1996; Yang, 1990]. Each style involves movement of the whole body in fluidity and harmony. Without concentration, focus and attention, directed either to the body or the environment, the movement will be disorganized and it will not be Tai Chi [Wayne and Kaptchuk, 2008a]. Besides, the styles and movements of Tai Chi are full of metaphors, such as 'white crane spreads its wing' and 'grasp the bird's tail'. The practitioner is required to feel the qi or internal energy flowing like water across the body. Concentration and mindfulness meditation itself may modulate multiple aspects of health including mood, pain, and functions of the immune and peripheral autonomic nervous systems [Vitetta et al., 2005; Davidson et al., 2003]. Encouraging control through the use of visual imagery and managing beliefs and expectations can also influence our physiology and health [Kaptchuk, 2002; Peng, 2012].

Meditation/breathing effects on psychological well-being

Tai Chi improves psychological well-being

Meditation, breathing and visual imagery are essential components of Tai Chi and help control mood and are associated with improvements in psychological wellbeing, including reduced stress, anxiety, depression and mood disturbance, as well as increased self-esteem [Peng, 2012]. Tai Chi is an excellent modality for mindfulness stress reduction because of the relatively low cost, the low physical and emotional risk involved, and because of the way it encourages patients to take a more active role in their treatment.

The improvement in psychological well-being can be associated with the 'mind' or physical components of Tai Chi. As discussed earlier; practitioners of Tai Chi depend on the mind to direct the inner energy. Furthermore, the practitioner coordinates the movement with breathing or movement of qi. In doing so, they must keep their mind peaceful and placid. Internal peace of mind and coordinated breathing are the important components of mindfulness stress reduction [Kabat-Zinn, 2003]. Physical activity/ exercise itself has been shown associated with better psychological health [Mishra *et al.*, 2012; Conn *et al.*, 2006].

Evidence for the effects in psychological well-being

The effectiveness of Tai Chi in psychological well-being was recently examined in two systematic reviews [Wang et al., 2009; Wang et al., 2010]. One review [Wang et al., 2010] included 40 studies (17 randomized controlled trials, 16 non-randomized comparison studies, and seven observational studies) with approximately 3,800 patients or healthy individuals from six countries. The conclusion was that Tai Chi was associated with favorable effects on mood, improved stress levels and self-esteem, and reduction in anxiety and depression. The effects on stress, anxiety and depression were of moderate effect sizes using bias-corrected Hedges'g score. Despite the fact that the conclusions were limited by variation in designs, comparisons, heterogeneous outcomes and inadequate controls, similar conclusions were drawn by another review around the same time [Wang et al., 2009].

Whereas exercise itself has been shown associated with better psychological health in cancer patient [Mishra *et al.*, 2012; Conn *et al.*, 2006], a randomized study examining the effects of Tai Chi in cancer survivors confirmed the improvement in self-esteem [Mustian *et al.*, 2004].

Evidence of benefits of Tai Chi in cancer patient

Whereas the literature supporting the health benefits of Tai Chi in chronic non-cancer pain patients such as those with osteoarthritis and fibromyalgia is strong, the research of Tai Chi in cancer patients is limited. A search of the literature examining the benefits of Tai Chi in cancer patient revealed very few vigorous scientific trials. There are three systematic reviews [Lee *et al.*, 2007; Lee *et al.*, 2010; Mansky *et al.*, 2006], four randomized controlled trials [Mustian *et al.*, 2004; Mustian *et al.*, 2006; Galantino *et al.*, 2003, Rausch, 2007], four prospective controlled trials [Eom, 2007; Seoung, 2008; Kim, 2009; Hwang and Kwak, 2009] and one prospective case series [Hui *et al.*, 2008]. Of the four randomized clinical trials, one is a thesis which was never published in any peer reviewed journal [Rausch, 2007] and two trials reported on the same population

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First autho	or/ Cancer group	Number of patients	Intervention	Outcome	Jadad Score/AC/	
year	patient	randomized or analyzed			blinded assessor	
Galantino	Stage II-IV	11 patients randomized:	Yang-style	No significant difference	2/0/0	
<i>et al.</i> , 2003	3 breast cancer	Tai Chi-6, Walking-5	(38 movements) or	between the 2 groups in fatigue		
	patients with		walking; 1 h ×3/week	score, functional assessment,		
	CRF		for 6 weeks	BMI, 6-min walking distance and		
				HRQoL		
Mustian	Breast cancer	31 patients randomized,	Yang-style	Tai Chi improved self-esteem but	2/0/0	
<i>et al.</i> , 2004	4* patients post	21 completed the study:	(15-move short-form)	not HRQoL at 12 weeks		
	treatment	Tai Chi-11, Psychosocial	or PST; 1 h ×3/week			
		support therapy-10	for 12 weeks			
Mustian	Breast cancer	31 patients randomized,	Yang-style	Tai Chi improved hand grip	3/0/0	
<i>et al.</i> , 2006	6* patients post	21 completed the study:	(15-move short-form)	strength but not 6-min walking		
	treatment	Tai Chi-11, Psychosocial	or PST; 1 h ×3/week	distance and shoulder flexibility		
		support therapy-10	for 12 weeks			

Abbreviations: CRF, cancer-related fatigue; HRQoL, health related quality of life; PST, psychosocial support therapy; BMI, body mass index; AC, allocation concealment; *, The study populations in both Mustian studies were identical. However, method of randomization was mentioned in one study [Mustian *et al.*, 2006]. Therefore, the Jadad score of two studies were different.

based on their description of demographics [Mustian *et al.*, 2004; Mustian *et al.*, 2006]. The three systematic reviews, therefore, included randomized trials based on two populations (*Table 1*).

Table 1 Published randomized controlled trials for Tai Chi intervention in cancer patient

Those randomized trials examined the effect of Tai Chi on breast cancer patients. The sample sizes were very small, with a total number of 11 and 21 patients analyzed in Galantino and Mustian trials respectively. Galantino et al. examined the effectiveness of Tai Chi (n=6) on fatigue and body mass index compared with the walking exercise (control n=5). They found no inter-group differences. Mustian et al. compared Tai Chi exercise with psychological support therapy and found a significant improvement in self-esteem and muscle strength (hand grip) at 12 weeks. With their very limited sample size, they did not demonstrate an intergroup difference in improvement in HRQoL, shoulder flexibility, and aerobic capacity (6-minute walking distance). However, it is important to note that the HRQoL and aerobic capacity in the Tai Chi group at 12 weeks assessment were significantly improved compared with baseline while the psychological support group reported decreases in both outcomes at 12 weeks and only the Tai Chi group demonstrated improvements in flexibility at 12 weeks compared with baseline [Mustian et al., 2004; Mustian et al., 2006].

In the non-randomized controlled trials and prospective

case study, all showed improved in various outcomes: physical strength and flexibility, HRQoL measures, psychosocial parameters and pain. Unfortunately, one was a master thesis [Seoung, 2008], one was a PhD dissertation [Kim, 2009], one was published in Korean language [Eom, 2007], and one did not publish the data for the control group [Hwang and Kwak, 2009]. The prospective case series was published in the letter to editor [Hui *et al.*, 2008].

In summary, more vigorous trials are in need for examining the benefit of Tai Chi in cancer patients. The existing literature neither proves nor refutes the notion that Tai Chi is beneficial in cancer patients.

Limitation of study of Tai Chi in palliative care population

Tai Chi is not only a physical exercise; it is a complex intervention involving physical, cognitive and ritualistic components [Peng, 2012]. Therefore, there are a number of intrinsic limitations in designing studies to evaluate this mind-body therapy. The challenges and difficulties in designing studies for Tai Chi were well summarized elsewhere [Wayne and Kaptchuck, 2008a; Wayne and Kaptchuck, 2008b; Peng, 2012]. First, it is basically impractical to use a double-blinded design since the patients will be aware whether they are performing Tai Chi or not. Second, Tai Chi is a mind-body therapy with many components contributing to the therapeutic effects. It is a major challenge to design a sham mind-body intervention when one attempts to separate the various mind and body components. Third, there are different families or styles of Tai Chi with different philosophy and training. Instructors or masters of different experience can affect the size of the therapeutic effect. This can contribute to the heterogeneity of the treatment effects. Finally, there is heterogeneity of the "dose". Different studies may choose different intensity of training, such as 1 hour per week for 6 weeks versus 3 hours a week for 3 months. This can contribute to different effect size and difficulty in comparing the results between studies.

Summary

In summary, Tai Chi is an ancient martial and health art involving gentle flowing circular movement of the upper limbs, constant weight shifting of lower limbs, meditation, breathing, moving of gi (the internal energy in Chinese belief) and various techniques to train mind-body control. It is a mild to moderate aerobic exercise and the constant shifting of body weight helps the practitioners to improve the balance and minimize the risk of fall. Because the movements are slow and gentle, cancer patients can pace according to their physical fitness. Tai Chi helps individual to focus and improve their body-mind control. The role of higher centers in pain modulation is well supported by an abundance of literature and practicing Tai Chi potentially helps cancer survivors optimize their coping mechanisms. Meditation, breathing and visual imagery are essential components of Tai Chi. Tai Chi is associated with improvements in psychological well-being including reduced stress, anxiety, depression and mood disturbance, and increased self-esteem. Literature specifically examining the effects of Tai Chi in cancer population is limited and more research is required to understand the full effects of Tai Chi in the cancer population.

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The role of rehabilitation

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Introduction

In individuals with life altering diseases, palliative care allows the opportunity for patients to function with the support of trained professionals at the highest level possible until death [WHO, 1990]. The entire practice of rehabilitation medicine addresses function as it relates to the disease process and the impact on the individual. Both medical specialties are geared toward addressing function, modifying the disease process, as possible, and treating symptoms. A palliative specialist should have a basic understanding of the scope of rehabilitation medicine and how these services can benefit the palliative patient. The purpose of this chapter is to define rehabilitation in the palliative patient, describe its components and services, and, by the use of two cases, help the palliative specialist in providing care [Tookman *et al.*, 2005].

Palliative rehabilitation

Palliative rehabilitation must begin with a full assessment of an individual's physical, cognitive, and functional attributes and/or deficits. This is usually addressed by a team of professionals developing a rehabilitation plan. This team (*Table 1*) works together as a multidisciplinary team, gathering information and data individually. They also work as an interdisciplinary team, sharing information to modify or revise a specific problem or rehabilitation plan. This plan may be used or adapted for cancer or non-cancer diagnoses.

The rehabilitation plan

The plan begins with the history and physical examination. While this is basic to all medicine, from a rehabilitation standpoint, there are two important additions. Of special interest is the evaluation and function of the musculoskeletal and neurologic systems.

For the musculoskeletal system this includes:

- Musculoskeletal structure and symmetry;
- Joint function and rage of motion;
- Muscle strength [Ganter et al., 2005] (Table 2).
- For the neurologic system, the evaluation includes:
- Mental status and cognitive evaluation;
- Speech and language function;
- Classic neurologic assessment of cranial nerves, reflexes and sensory examination [Ganter *et al.*, 2005].

While this information by itself is important, the impact of the physical or cognitive deficits on the individual's function must be assessed. To do this, one must perform a functional assessment.

The functional assessment is performed by each individual therapist, within their area of expertise: physical therapy for mobility, occupational therapy for self care and activities of daily living (ADLs), and speech therapy for cognition and swallowing. These evaluations can take place in an acute care setting, outpatient clinic, or at the patient's home. The information obtained from these evaluations is used with the physical exam to guide the development of the rehabilitation plan and determine goals. The palliative specialist is familiar with the use of functional assessment tools such as the Karnofsky performance status (KPS) and the palliative performance scale (PPS) [Glare and Christakis, 2004]; whereas these tools have as their basis the functional assessments as performed by the rehabilitation team members.

Physical therapy assesses mobility including bed mobility to evaluate the ability to move side to side, ability to lift off the bed, and move from supine (flat back) to sit and reverse.

Table 1 Palliative team

(I) The patient and their family

(II) Physiatrist-medical specialist trained in physical medicine and rehabilitation and is responsible for the rehabilitation management

(III) Physical therapist (P.T.) – specialist in addressing musculoskeletal and neurologic dysfunction and their impact on function of movement (bed mobility, transfers, and ambulation)

(IV) Occupational therapist (O.T.) - specialist in addressing dysfunction and function as it relates to activities of daily living (ADLs) and cognition

(V) Speech and language therapist-specialist in addressing dysfunctional/function in communication, swallowing and cognitive abilities

(VI) Other, as needed-psychology, respiratory therapy, dietician, chaplain, recreational therapist, social worker

Table 2 Motor strength				
Grade	Performance			
5-normal	Full ROM and full resistance			
4-good	Full ROM and partial resistance			
3-fair	Full ROM against gravity, no resistance			
2-poor	Full ROM with gravity eliminated			
1-trace	Minimal contraction			

More advanced mobility includes transfer skills of moving from bed to chair or from one level to another. Ambulation must be assessed for the need of assistance of another person, or the use of an assistive device (cane, walker). ADLs are evaluated by occupational therapy. This includes grooming tasks (brushing teeth, washing face, combing hair). Bathing involves the activities of the whole body and requires the use of muscles, joint range of motion, and the need for assistance or adaptive equipment. Speech, language, and swallowing evaluations are performed by speech therapy and determines the ability to understand verbal or written language, the ability of the individual to express themselves, and if there is a swallowing deficit, to address swallowing reeducation and diet and/or liquid consistency and modification. The functional assessments not only note the existence of what type or where a deficit occurs, but also grade the deficit so that the team can compare findings and track progress. The patient's function and the amount, type, and need for assistance can also be defined (Table 3).

Using the information from the history, physical examination, and functional assessment, allows each discipline to determine the patient's current deficits both physically and functionally, and to determine what reasonable goal setting can be performed with an interest in maximizing function.

Table 3 Levels of function				
Assistance	Effort required			
Total assistance	Patient expends <25% effort			
Maximal assistance	Patient expends 25-49% effort			
Moderate assistance	Patient expends 50-74% effort			
Minimal assistance	Patient expends at least 75% effort			
Supervision	Requires set up, cues, stand-by assist			
Independent	Can perform task without help or			
	assistance of any kind			

Goal setting

In rehabilitation, goals must be realistic and measurable for all team members (Table 1). The rehabilitation course of treatment must not only assess the functional status and the type of assistance, but must consider the severity of the disease process and the probability of improvement or progression of the disease [Tookman et al., 2005]. The patient is a vital member of the team and many times it is difficult for the individual to agree with certain goals. However, it is important to remember that goals must be interdisciplinary and include the patient [McGrath, 1992]. This requires that all parties, heath care professionals, patient and patient's family are truthful and forthcoming in order to form legitimate goals while the patient and family develop appropriate life planning. An example of an inappropriate goal: "I want to walk better." An appropriate goal is one that can be measured. An example of an appropriate goal: "The patient will increase their ambulation by 100 feet and improve from moderate to minimal assist."

Using the information from the history and physical examination, the evaluations by the therapeutic disciplines, the functional assessments, and the goals, the rehabilitation team can arrive at a plan.

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Case examples

Two cases will be presented as examples of the assessment process, development of the rehabilitation plan and modification of the plan based on the patient's medical, physical, and functional status.

First case

Patient A is a 54-year-old male originally presented to the emergency department with new onset of right sided weakness, slurring of speech and expressive language deficits. Workups revealed a left, frontal mass of 3 cm by 5 cm in size with associated edema. Biopsy revealed pathologic findings of a Glioblastoma Multiforme. Patient A underwent a craniotomy with subtotal resection of the tumor, followed by external beam radiation. He now presents to you for continued palliative treatment, but wants to maintain his function for as long as possible.

Findings for this patient include: right upper extremity plegia; right lower extremity paresis; expressive aphasia; and some swallowing difficulties. The PPS was 50%. The patient was able to sit with moderate assistance, and was unable to perform any work. His cognition was full, but required considerable assistance with ADLS.

The physical and functional state of the patient was evaluated, and the following goals were advanced: maintain range of motion of joints for comfort, increase mobility from moderate to minimal assistance, utilize ambulation aide to improve stability/balance to minimal level assist, and increase PPS to 60% with the patient's right side weaknesses and language deficits. Occupational therapy would address the ADL deficits and range of motion with the following goals: maintain range of motion for comfort, increase/improve transfers to minimal assistance, increase improve ADLs to moderate assistance, and increase PPS to 60%. Finally, speech therapy goals include that the patient be able to safely express his needs and swallowing would be safe for diet consistency and liquid type.

Precautions should be noted for the therapists to include right sided weakness and language deficits, as both may interfere with therapy. The preceding was an example of an initial therapy prescription. Once the therapy specialist has the opportunity to evaluate the patient, their findings may, and probably will result in modifications to plan of treatment, goals, and even precautions. The initial goal was to increase the patient's function so this PPS went from 50% to 60%. While this is not a great increase, it would give the patient greater function and the treatment by the therapist would allow both he and his family to adjust as changes occur.

Once the patient's status declined to the point that he was bedfast (PPS of 30%), therapy could instruct him on therapeutic activities to be performed in bed. The family could be instructed on proper positioning, and if oral intake were possible, instruction could be given for compensatory techniques and comfort feeds. A separate discussion concerning the palliative/rehabilitative function of enteral feeding is held elsewhere in this book (see chapter on Nutrition and Hydration).

Second case

Patient B is a 65-year-old male with a three year history of progressive weakness. The patient was diagnosed two years ago with amyotrophic lateral sclerosis (ALS). He has recently moved to your city and requests care. The patient has decided he does not want enteral feeds, tracheostomy, or a ventilator. Associated complaints are contractures, dyspnea on exertion, fatigue, and weight loss of 30 pounds in the last year. Physical examination reveals: 65-year-old male with definite muscle wasting, contractures of hips and knees (due to sitting in a wheelchair), diffuse muscle weakness of grade 2 (poor)-3 (fair) throughout; and decubitus ulcer on sacrum.

ALS affects approximately 1.4 individuals per 100,000 annually, and affects men 1.5 times as often as women (below the age of 65) and has a peak incidence between the ages of 55 and 75 years [Milonas, 1998]. It is a progressive neurologic disorder characterized by the loss of motor neurons in the spinal cord and brain. It is, of course, ultimately fatal and can progress slowly or rapidly but is a "perfect match" for palliation and rehabilitation [McCluskey, 2007]. Designing a program for this diagnosis is clinically challenging, the course is increasingly one of decline, and is ever changing [McCluskey, 2007]. Because of the clinical course, both Palliative Medicine and Rehabilitation Medicine should and must work together in designing and modifying the patient's rehabilitation program.

Rehabilitation medicine can anticipate functional decline and address the patient's needs so that the functional status may be maximized. This allows the patient greater independence and the need for less assistance by others. This reinforces the patient's wellbeing as well as their own self worth. In the event of decline, rehabilitation can address caregiver needs so that safe mobility and care of the patient occurs and training and equipment can be obtained so that the safety of the patient and caregivers may be met. Goals must be clear and well defined. In the development of a rehabilitation prescription, these goals should available to all parties so that additions, corrections, or modifications may occur as needed. The following is an example.

Maintain/increase the range of motion so that the patient may both safely sit in a wheelchair and recline in bed. A properly fitted wheelchair is required for support of the head, neck, trunk, and extremities [Trail *et al.*, 2001]. This includes a proper wheel chair cushion. Patient and family education on swallowing, diet modification, and compensatory techniques to prevent aspiration must be a goal [Carter and Miller, 1998]. Also, the education should include a range of motion program utilizing both gentle and progressive strengthening techniques, and education on respiratory care [Yorkston, 2004].

The goals for ADLS are grooming of minimal to moderate assist; moderate assist for transfers, and nutritional education to slow weight loss and wasting [Kasarskis *et al.*, 1996].

The goal of physical therapy is to maintain strength and function, especially as it relates to mobility [Chen *et al.*, 2008]. Strengthening should be resistive, but done in such a way as not to overly fatigue the patient. Flexibility can maintain muscle and joint function and can prevent unwanted contractures and other deformities [Kinser and Colby, 2007].

Precautions for this patient should monitor the manual muscle test, taking care to observe the fatigue the patient [Longstreth *et al.*, 1998], monitor respiratory function, immediately notify physician for a forced vital capacity (FVC) of 50% or less [Miller *et al.*, 1999], and weigh patient weekly reporting any serious weight loss [Kasarskis, 1996]. An appropriate wheelchair with head, lateral trunk, and arm supports will help maintain the patient in an upright position, help prevent deformities, and allow for ease of respiratory effort and swallowing with the goal of decreased episodes of aspiration pneumonia.

It is important to remember, that no wheelchair cushion can prevent a decubitus ulcer, and that only appropriate pressure relief every 15-20 minutes when sitting or every 2-4 hours when sleeping can decrease the risk. This applies to both of the above cases, and the palliative specialist must keep this in mind as function declines. Complications with bowel and bladder should also be monitored as they can increase the risk of skin breakdown.

Physical therapy can perform an initial assessment, evaluate and grade motor strength, with frequent rechecks, mobility evaluation and education for bed mobility, transfers, and wheelchair function, a range of motion program, and seating, with wheelchair support and cushion. Finally, the use of specialized equipment may be needed for transfer such as a Hoyer lift requiring education for safe use by family and caregivers. Occupational therapy concerns those tasks that we take for granted. Just the simple act of shaving, bathing, toileting, and dressing allow an individual to function at a higher level. The longer one can function at the higher level can directly impact the level of assistance one needs, and the location that the care takes place. The goal of occupational therapy is to maintain strength and range of motion so that the patient can perform ADLs with the least amount of assistance and with the "greatest of ease." This might include special adaptive equipment to assist with grooming, bathing, hygiene, or dressing. To perform a task "with ease" may require adaptive techniques and a simpler way of doing things so that less energy is consumed. The occupational therapy assessment should include: motor strength, range of motion, functional status, and cognitive evaluations as well as ADLs, the need for adaptive equipment, tasks simplification, energy conservation, and equipment needs.

From a speech standpoint, it only makes sense that the ability to communicate be an important task. However, swallowing is a paramount issue, as it must be done safely and efficiently to prevent aspiration and to maintain a nutritional status. This includes the swallowing evaluation, diet and liquid modification, and compensatory strategies: sitting upright, chin tuck, head turning and tiling and modified diet and liquids. Respiratory dysfunction is of primary concern with the ALS patient. While there is no direct pathology to the lung by the disease process, the impact on the muscles of the mouth, throat, inspiration and expiration result in the declining respiratory status and increased risk of aspiration, pneumonia, and death [Benditt and Boitano, 2008]. Respiratory therapy can follow the FVC, instruct the patient and care givers in breathing, exercises and energy conservation, institute supplemental oxygen starting with a nasal cannula, and progressing to non-invasive posture pressure ventilation (NPPV) as clinically indicated with education in airway maintenance.

Supplemental oxygen should be made available with frequent checks of the FVC. Once the FVC is less than 50%, noninvasive positive pressure ventilation should be considered for the patient [Miller *et al.*, 1999]. One should obtain a baseline FVC and every three months document the patient's status [Czaplinski *et al.*, 2006]. However, a change in functional status or report of respiratory decline should warrant an immediate reevaluation. Patients with ALS lose weight because of continuous motor activity, work effort, and declining nutritional status. With continued

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muscle wasting and weight loss, a nutritionist should provide education for diet modification and dietary supplements.

Summary

The goals of caring for patients with life limiting diseases can only be met by the continued efforts of many health care professionals. As can be seen in the two previous cases, the rehabilitation of patients, in conjunction with their palliative needs, requires a multidisciplinary and interdisciplinary plan that is not unknown or uncommon to palliative medicine. The interface of these two specialties is a common one, the patient, and their goals are similar. Both are concerned with function as well as symptoms. In palliative medicine, this might be the effect of pain on mobility, and decreasing pain so one could stay more functional. In rehabilitation, the concern is the physical capability on mobility and addressing the patient's capabilities to maximize function. What may be clearer now is the extent of work, information, and effort that goes into caring for these patients, developing a treatment plan and building in the flexibility to meet the patient's needs or function. Palliative and rehabilitation may cross paths daily without acknowledging or knowing about the other. It is important for each of these specialties to search out the other in their hospital or community so that communication and understanding can result in better care for many challenging patients.

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Dyspnea

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Introduction

Dyspnea is a highly unpleasant to severely distressing subjective perception of difficulty breathing. Its evolutionary purpose is to condition behavior that will ensure continuous oxygen availability and gas exchange. Dyspnea is the most common severe symptom in the dying patient. Its prevalence exceeds 80% in the last year of life in patients suffering from chronic lung disease and lung cancer. Dyspnea is often underdiagnosed and undertreated. Its management is challenging. Adverse effects may set limits to the aggressive use of anti-dyspnea medications. Opioids are the most effective agents and constitute the main stage of dyspnea management. Sedative and neuroleptic medications are not effective. The use of these agents should be limited to treatment of anxiety and delirium respectively. A multi-disciplinary approach to dyspnea that includes pharmacotherapy, counseling, breathing and relaxation techniques as well as involvement of the patient's family is an effective strategy. High doses of opioids, sedatives and neuroleptics may be necessary in the dving patient. The risk of hastening death is acceptable if the goal is control of severe distress and an aggressive symptom management is not considered euthanasia.

Definition and evolutionary purpose of dyspnea

The homeostasis of the human body and the vast majority of multicellular organisms is highly dependent on continuous availability of oxygen. Upon complete cessation of oxygen delivery, the central nervous system will suffer metabolic derangements that will result in loss of consciousness within several minutes. Shortly after, irreversible injury to the brain neurons and myocardial cells will ensue causing brain death and subsequently biological death (suffocation, asphyxiation). This remarkable vulnerability of animal organisms to compromised gas exchange has evolutionary led to behavior that places high priority on avoiding situations that could potentially lead to impaired oxygen delivery and suffocation. The negative feedback that reinforces this self-protective behavior is a highly unpleasant to severely distressing subjective experience known as "breathlessness", "shortness of breath" or "air hunger", also referred to as "dyspnea" in the medical community. "Dyspnea" ($\delta \upsilon \sigma \pi \upsilon \upsilon \omega$) is of Greek origin and is derived from "dys"-difficult, impaired and "-pnoia"breathing. The evolutionary value of dyspnea is similar to that of pain. As pain conditions individuals to avoid selfdestructive and risky behavior that could result in tissue injury, so does dyspnea, reinforcing avoidance of situations and behavior potentially leading to hypoxia.

The term "dyspnea" is generally reserved for pathological situations but exercise-related breathlessness is not qualitatively different from dyspnea. Along with the feeling of muscle exhaustion, it too serves a protective role preventing the individual from over-exercising by setting physiological limits to exertion. Without this feedback mechanism, one could escalate their physical activity to levels, at which severe brain, heart and other tissue hypoxia and acidosis would set in with devastating consequences.

Dyspnea plays a role in maintaining carbon dioxide levels and acid-base homeostasis as well. Severe hypercapnia without hypoxemia does not occur under ordinary circumstances, i.e., without the use of supplemental oxygen. Therefore, from evolutionary standpoint, the hypercapnia controlling mechanisms cannot be viewed separately from those controlling hypoxemia. Metabolic acidosis without hypoxemia does occur however and it clearly increases ventilatory requirements and contributes to dyspnea.

Dyspnea severity is difficult to quantify. Objective evidence of respiratory distress as well as the patient's account

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of her breathing should be taken into consideration. Similar to pain, the perception of breathlessness is very subjective. Lack of objective findings suggestive of difficulty breathing such as tachypnea (rapid breathing), hyperpnea (increased tidal volume) and accessory respiratory muscle use does not rule out dyspnea. Even though this is not common, it is important for clinicians in palliative care settings not to disregard complaints of dyspnea not supported by objective distress. For the most part, dyspnea is easy to identify and tends to be very distressing to the patient.

Mechanism of dyspnea

The controller regulating ventilation is located in the medullar and pontine area of the brain stem. The neurons in these respiratory centers control the rhythmicity and frequency of the action potential of the motor neurons innervating the respiratory muscles [Hall, 2011]. The purpose of this controller system is to maintain blood gases and pH homeostasis. The primary afferent components of this feedback mechanism are chemoreceptors in the medulla and peripherally as well as stretch receptors in the lungs. It would be intuitive to assume that higher integration of the afferent signals obtained by those chemoreceptors reflecting hypoxemia and acidosis constitutes the basis of dyspnea. However, even though the pathway of breathlessness is closely intertwined with the control of breathing, dyspnea does not simply reflect the afferent feedback from the chemoreceptors. The mechanism of dyspnea remains elusive and controversial despite decades of intense discussions and research. The primary purpose of dyspnea is believed to be maintenance of tissue oxygen homeostasis, yet low blood oxygen content (hypoxemia) or low tissue oxygen concentration (hypoxia) are not the only or even the primary triggers of dyspnea. From evolutionary point of view, developing dyspnea as a behavior-modifying, protective mechanism would require an earlier, more complex afferent signal, which precedes actual compromised oxygen delivery. Indeed, lowering oxygen content in the inhaled air to as low as 15% and the resulting hypoxemia do not cause significant dyspnea as long as ventilation is not impaired. This level of hypoxemia is generally well tolerated for short periods of time and is commonly artificially created within the scope of the high altitude simulation test (HAST) and corresponds to hypoxemia normally seen at altitudes of 8,000 ft [Dine and Kreider, 2008]. On the other hand, holding one's breath or complete obstruction of the airway will result in severe dyspnea within seconds without measurable hypoxemia or hypercapnia. Preexisting hypoxemia or hyperoxemia do have an impact on one's breathholding ability, which indicates that oxygen delivery is still a factor in this process [Klocke and Rahn, 1959]. It is clear though that the mechanism of severe dyspnea during breath holding goes beyond hypoxemia. It is quite difficult for an average untrained individual to hold her breath long enough for the peripheral oxyhemoglobin saturation to fall below 90%a level considered completely safe in general [Klocke amd Rahn, 1959]. Rebreathing of gas mixture containing as low as 8% O₂ and as high as 7.5% CO₂ relieves dyspnea after breath holding [Flume et al., 1994]. During exercise [Lane et al., 1990], the level of perceived dyspnea correlates fairly well with the workload and minute ventilation and artificially causing hypoxemia or hypercapnia doesn't result in more severe dyspnea for the same level of minute ventilation. Patients who suffer from severe emphysema (pink puffers) tend to be quite dyspneic even with normal oxygen and carbon dioxide levels [Dornhorst, 1955]. The receptors and afferent pathways responsible for dyspnea in the setting of normal blood gas levels remain unclear. The sensors primarily responsible for maintaining blood gas homeostasis-carotid and aortic body receptors (sensitive mostly to hypoxemia) and the medullar respiratory centers (sensitive mostly to acidosis and hypercapnia) appear to be involved in the sensation of dyspnea but their role may be indirect through causing increased minute ventilation. Stretch receptors in the lungs, as well as muscle and tendon receptors, have been implicated as the afferent component of the dyspnea pathway. According to the theory of "lengthtension inappropriateness" [Campbell and Howell, 1963], dyspnea is the perception of inappropriate change of muscle length and lung volume to the tension generated by the respiratory muscles. This theory can explain shortness of breath during breath holding and in conditions that affect lung mechanics but cause no measurable gas exchange abnormalities.

Skin and upper airway receptors may also play a role in the mechanism of shortness of breath. Many dyspneic patients choose to sit next to an open window or a fan, which provides some relief of their breathlessness.

In summary, dyspnea is a complex process, which is triggered by various peripheral and central receptors. Pathologic conditions resulting in "breathlessness" affect either the afferent part of the "dyspnea pathway" (organic causes) or the integration and interpretation of the afferent impulses in the central nervous system (panic attack, psychogenic dyspnea).

Dyspnea in palliative care

Dyspnea, along with pain, is one of the two most dreaded symptoms patients suffering from a terminal condition have to endure and a common reason for palliative care referrals [Elsayem *et al.*, 2004]. It is the most common source of distress in advanced lung cancer [Muers and Round, 1993]. More than 90% of patients suffering from a chronic lung disease and close to 80% of lung cancer patients experience shortness of breath in the last year of their life [Edmonds *et al.*, 2001]. Other chest malignancies including metastatic disease, heart failure, pneumonia, pulmonary embolism, chemotherapy-related lung injury, and radiation pneumonitis are some other conditions commonly causing dyspnea in the palliative patient population.

Unfortunately, dyspnea tends to be more difficult to treat than pain. As death nears, the prevalence of shortness of breath in cancer patients increases and it often becomes the patients' main complaint as therapy can be ineffective [Higginson and McCarthy, 1989]. Dyspnea is the most distressing symptom in the dying patient [Steinmetz *et al.*, 1993]. On the other hand, in less severe cases, shortness of breath is often underreported and can therefore be overlooked and insufficiently treated by health care providers. According to some reports, more than half of patients with advanced cancer who experience dyspnea do not receive treatment for it [Roberts *et al.*, 1993].

Measuring dyspnea

Scales measuring dyspnea are available but are less commonly used than pain scales. The use of numerical or visual rating instruments should be encouraged in order to avoid under diagnosis and insufficient therapy. Patients may view their shortness of breath as an unavoidable and untreatable part of their disease and may not be forthcoming reporting it. Clinicians often rely on physical signs of respiratory distress but those may not be always apparent. Tachypnea may be absent in some cases of dyspnea and vice versa-patients may have rapid breathing without experiencing dyspnea. As previously discussed, the correlation between hypoxemia and dyspnea is poor. For this reason, health care providers should proactively inquire about dyspnea and the routine use of grading scales can standardize this process. Various quality-improvement agencies recommend that a measure of dyspnea is included in routine palliative care assessment [Mularski et al., 2010].

Numerous scales have been designed and used for measuring dyspnea. The type of scale used is less important—its systematic use is. The typical scale is a Likert numerical scale that reflects self-reported dyspnea severity. Visual analog scales may be preferable in some cases, especially in children. One of the oldest dyspnea scales—the Borg dyspnea scale and its modifications—have been traditionally geared towards grading exercise-induced dyspnea and can be used in ambulatory patients [Borg, 1982]. Other scales are more appropriate in terminally ill patients. Cancer dyspnea scale [Tanaka *et al.*, 2000] and Dyspnea-12 [Yorke *et al.*, 2010] are some examples.

Once the patient is unable to participate in grading her symptoms, clinicians have to rely on physical signs of distress. Observer-reported scales are available for those cases, e.g., the Respiratory distress observation scale [Campbell *et al.*, 2010]. The superiority of these scales over a routine physical examination is questionable.

Treatment

If possible, treatment of dyspnea should primarily be focused on the underlying pathological condition. Bronchodilators should be used in obstructive lung conditions. Management of pleural effusions should be considered. Severe anemia may need to be corrected. Pulmonary embolism should be treated with anticoagulation and, in selected cases, inferior vena cava filters can be placed. Specific treatment for different respiratory disorders is beyond the scope of this chapter and we will focus on symptomatic treatment of dyspnea.

Not having a well-defined physiological target makes managing dyspnea challenging. Altering the central perception of dyspnea remains the main stage of its treatment. Available therapeutic modalities are mostly based on empiric experience. Agents used to treat dyspnea are medications developed and primarily used for a different purpose, which were incidentally found to have dyspnea alleviating properties. The complex and unclear mechanism of dyspnea has been a major obstacle in the development of specific "anti-dyspnea" agents. At the same time, treating respiratory distress is a major focus of palliative medicine and a very common challenge for palliative care professionals facing a terminally ill patient.

Oxygen

Oxygen is frequently used in the management of dyspnea, especially if the patient shows evidence of hypoxemia. The efficacy of oxygen therapy is often limited but its lack of any significant adverse effects if appropriately used, and

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relatively modest cost make it an indispensable part of the management of the terminally ill dyspneic patient. Oxygen can cause worsening hypercapnia in patients prone to carbon dioxide retention. Although the mechanism behind this phenomenon is controversial, its clinical significance is not [Gelb et al., 1977]. Severe respiratory acidosis and carbon dioxide narcosis can occur if chronic and severe hypoxemia is completely and rapidly reversed. For this reason, it is recommended that hypoxemia is slowly and only partially corrected in the patient population predisposed to carbon dioxide retention (e.g., end-stage COPD, obesity hypoventilation syndrome). However, decreased ventilatory drive caused by oxygen therapy may be, at least in part, responsible for dyspnea relief and thus more liberal oxygen use is justified in palliative settings. Humidification is recommended to avoid discomfort caused by dry mucous membranes. The role of oxygen therapy in non-hypoxemic patients is limited. Multiple studies have shown that oxygen would not improve dyspnea if appropriate blood oxygen levels are present [Ben-Aharon et al., 2008; Mahler et al., 2010]. However, the individual response to oxygen therapy is variable. In view of its benign nature, use of oxygen in non-hypoxemic patients is acceptable if subjective dyspnea relief is reported.

Opioids

Opioids have long been known as the most effective agents in the management of dyspnea. Before the advent of the modern CHF therapy, morphine and digitalis were the only agents available for the treatment of respiratory distress in heart failure [Bramwell, 1937]. Opioids remain the main tool in the management of dyspnea in the terminally ill today. Multiple studies have confirmed their efficacy in cancer and chronic lung disease [Ben-Aharon et al., 2008; Jennings et al., 2002]. The highly effective analgesic properties of opioids in addition to the antidyspneic effects make these agents invaluable in palliative care. Opioids exert direct suppression on the central and peripheral chemoreceptors and can cause hypoventilation in higher doses. However, hypoventilation is not required to achieve an antidyspneic effect. Despite common fears among health care professionals, opioids can be safely used for this purpose and severe carbon dioxide retention is uncommon [Clemens et al., 2008]. Decreased respiratory rate and work of breathing further improves breathlessness in addition to the central effects of opioids. Additionally, opioids can cause diffuse CNS suppression and decrease the level of alertness, which contributes to the treatment of respiratory distress. This process can be further augmented by developing of hypercapnia and CO₂ narcosis. There is no physiologic ceiling to the effects of opioids. Overdosing can lead to deep coma. The effects and side-effects of opioids are synergistically enhanced by benzodiazepines and vice versa. The therapeutic window of opioids can be narrow and, when higher therapeutic effect is needed in severe cases of dyspnea, it may not exist at all. When dealing with an unstable, dying patient, palliative care professionals often have to walk a fine line ensuring comfort and reasonable control of shortness of breath without prematurely causing death. This is not always possible when death is impending. In those cases, patient comfort takes priority. It is important to understand that the medications needed to provide symptom control in the dying patient can and often will contribute to death. This fact is almost always accepted by the patient's family with a great deal of understanding as preventing the suffering of their dying loved one is their main priority too. In an agonizing patient, especially after withdrawal of mechanical ventilation, high doses of opioid, sedative and neuroleptic agents are often needed. Death is frequently hastened by these aggressive comfort measures. As the goal of this therapy is symptom control, this is not considered euthanasia.

The respiratory effects of opioids are mediated by mureceptors, mostly mu₂. Mu-receptor knockout mice don't exhibit changes in their ventilation when treated with morphine [Mogil and Grisel, 1998]. Morphine has been for the most part the agent of choice due to experience, price and availability but other potent mu-agonist (fentanyl, meperidine, hydromorphone) are likely as effective [Clemens and Klaschik, 2008]. The therapy can be tailored to the particular patient based on personal preferences, the patient's previous experience, side effects and allergy profile. Oral, subcutaneous or intravenous route can be elected depending on the acuity and the patient's ability to take oral agents. Weaker agonists (codein, hydrocodone) are not adequate for treatment of dyspnea but in mild cases. Dihydrocodeine was found to have some benefit in treating ambulatory COPD patients. Codeine can cause hypoventilation but is ineffective in the treatment of dyspnea [Rice et al., 1987]. Dextromethorphan has been similarly found to be ineffective [Giron et al., 1991]. A detailed discussion of different opioids, side effects and pharmacokinetics can be found elsewhere in this book.

Partial agonists and mixed opioid agonists-antagonist (buprenorphine, pentazocine, butorphanol) are rarely used for dyspnea control. The experience with those agents is limited. It is important to know that the therapeutic ceiling these agents have with regards to analgesia may also become apparent in the treatment of dyspnea [Hoskin and Hanks, 1991]. This fact limits their titrating potential. For these reasons and because of questionable benefits over pure agonists, the use of these agents cannot be recommended in the terminally ill.

Inhaled opioids

Opioid receptors have been found in the bronchial mucosa [Belvisi *et al.*, 1992]. Those findings have triggered an understandable interest in the potential utility of inhaled opioids in the treatment of dyspnea. The nebulized delivery route could theoretically achieve effective dyspnea relief while minimizing side effects. The evidence for the use of inhaled opioids in chronic lung disease is contradictory. Some small studies have suggested that nebulized morphine and hydromorphone may be as effective as parenteral administration of these agents [Bruera *et al.*, 2005; Charles *et al.*, 2008]. Unfortunately, multiple subsequent trials have failed to show consistent benefit of inhaled morphine [Viola *et al.*, 2008].

Inhaled fentanyl on the other hand is clearly an effective agent in the management of dyspnea [Coyne *et al.*, 2002]. However, nebulized fentanyl also appears to be an effective analgesic not inferior to fentanyl administered intravenously [Coyne *et al.*, 2002]. Therefore, the dyspnea-alleviating properties of fentanyl are very likely to be related to systemic absorption and probably to its high lipophilicity.

In summary, inhaled opioid therapy may have a role in selected cases but it can't be recommended for routine use in palliative care.

Sedatives

Sedatives, mainly benzodiazepines, are widely used in palliative care. The main drawbacks of these agentsaddictive potential and tolerance- are less relevant in the care of the terminally ill. Benzodiazepines are very effective in controlling anxiety, including anxiety and panic attacks related to shortness of breath. Benzodiazepines act synergistically with opioids but when used alone, these agents have a less established role in dyspnea control. A Cochrane review concluded that there was no evidence those agents were effective in the relief of breathlessness in advanced cancer and COPD [Simon *et al.*, 2010]. Benzodiazepines do have opioid sparing properties. Adding midazolam to morphine has proven to be more effective than morphine alone in severe-cancer related respiratory distress [Navigante *et al.*, 2006]. The mutual potentiation between benzodiazepines and opioids is apparent in both the desired and adverse effects. The risk of over-dosing and severe respiratory depression is increased when they are used simultaneously. Traditionally, diazepam, lorazepam and midazolam have been the agents most commonly used in palliative care but the benefits and side-effects of benzodiazepines are a class effect and the choice of an agent should be based on pharmacokinetics and individual needs.

Buspirone is a non-benzodiazepine anxiolytic, which is considered to have no addiction or dependence potential [Murphy *et al.*, 1989]. It does not cause respiratory depression and may be helpful in the treatment of anxiety in patients with chronic lung disease. Some small early studies suggested that buspirone may have a role in the treatment of dyspnea in COPD. However, a more recent large doubleblind, placebo-controlled study concluded that buspirone is largely ineffective as an anti-dyspneic agent [Bushunow *et al.*, 2011]. Currently, in palliative care settings, the use of this agent should be limited to management of anxiety.

Neuroleptics

In order to avoid potentially fatal respiratory depression, neuroleptics are occasionally preferred by some providers in the treatment of dyspnea. In this context, their use remains controversial. While less sedating, promethazine was found to be superior to diazepam in ambulatory COPD patients in relieving exercise-induced dyspnea and improving exercise tolerance [Woodcock *et al.*, 1981]. Diazepam actually decreased exercise tolerance. In dying lung cancer patients, promethazine was found to provide clinical relief from dyspnea and restlessness but no comparison has been done to other agents in this population [McIver *et al.*, 1994]. Other studies have found promethazine largely ineffective [Rice *et al.*, 1987].

Haloperidol is often used to treat delirium in the terminally ill. For this purpose it is very effective and is generally considered the drug of choice because of its long track record and low cost. Haloperidol may also be useful as an antiemetic [Buttner *et al.*, 2004]. Evidence of its effectiveness as an anti-dyspnea agent is lacking and haloperidol cannot be recommended for that purpose.

Therefore, the role of neuroleptics in the management of respiratory distress should be mainly adjunctive and aimed

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at agitation and delirium. It is important to keep in mind that neuroleptic agents can cause extrapyramidal symptoms including the rare neuroleptic-induced acute laryngeal dystonia, which can compromise the airway and cause dyspnea and respiratory distress on its own [Medarov and Rossoff, 2006].

Other agents

Anecdotal evidence exists that inhaled furosemide may provide lasting control of dyspnea in terminally ill cancer patients [Shimoyama and Shimoyama, 2002]. Its effectiveness has not been confirmed in controlled studies. The potential mechanism is unclear. The small dose used (20 mg) makes systemic diuretic effect unlikely. Furosemide may have bronchodilator properties and it has been used and studied more extensively in bronchial asthma [Sestini *et al.*, 1994; Newton *et al.*, 2008]. Its value in the management of dyspnea remains questionable and inhaled furosemide cannot be recommended for routine use.

Non pharmacological management of dyspnea

Some patients find open windows and fans helpful providing some breathlessness relief [Burgess and Whitelaw, 1988]. This effect is believed to be mediated by the trigeminal nerve. Facial cooling in the areas innervated by the maxillary and mandibular branches of the trigeminal nerve can reduce dyspnea [Schwartzstein *et al.*, 1987]. Using a simple fan is easy to do; it is cheap and, more importantly, patients can operate it independently, which gives them back some much needed sense of control [Booth and Wade, 2003]. Dyspneic patients often have high minute ventilation, which may lead to dry mucous membranes and additional discomfort. Maintaining humidity is important especially if high-flow oxygen is used.

Sitting position provides a more optimal diaphragm position and can be very helpful in alleviating dyspnea at rest. This is especially relevant in cardiac failure patients who may be completely unable to assume a recumbent position, which would result in increased venous return and heightened sense of shortness of breath (orthopnea).

The multidisciplinary nature of palliative medicine should be kept in mind in the management of dyspnea too. The psychological and social aspects of the management of the terminally ill dyspneic patient need to be routinely addressed. Weekly sessions focusing on counseling, breathing re-training, relaxation and teaching coping and adaptation strategies was shown to decrease distress from breathlessness by more than 50% [Corner *et al.*, 1996]. Nutritional deficiencies need to be addressed if appropriate as malnutrition can affect the respiratory muscles. However, evidence-based data are lacking and the role of nutrition in management of dyspnea, though intuitive, remains unclear.

Dyspnea at rest is not only very distressing for the patient to endure but also for her loved ones to witness. The importance of involving the family in the management and educating them cannot be emphasized enough. The patient's family often concentrates on the vital signs and especially oxygen saturation. Not surprisingly, low oxygen is often equated with shortness of breath and vice versa. Frequent counseling can be very helpful in eliciting and addressing their concerns. The goals of any therapy need to be discussed with the patient and the family in detail.

Anxiety and depression are not uncommon in the terminally ill. Inability to breathe, not surprisingly, can be a source of severe anxiety and panic attacks. Vice versa, panic disorder can be a trigger of paroxysmal episodes of severe dyspnea and choking sensation. In a patient who suffers from dyspnea at base line, a superimposed panic attack can be catastrophic. Management of mood disorders and especially anxiety is an integral part of palliative care. More detailed discussion on their management can be found elsewhere in this book.

Although some small studies have suggested that acupuncture and acupressure may improve dyspnea on exertion in COPD [Suzuki *et al.*, 2012; Wu *et al.*, 2004], there is no consistent evidence supporting the use of these techniques. Acupuncture proved ineffective in the management of cancer-related dyspnea [Vickers *et al.*, 2005]. The routine use of these modalities in the palliative care of dyspneic patients cannot be recommended.

Gas mixture containing 72% helium and 28% oxygen has been shown to improve breathlessness in lung cancer patients [Ahmedzai *et al.*, 2004]. Airflow limitation is very common in this patient population due to various degree of smoking related obstructive lung disease. The benefit of helium in patients without an underlying airway disease is unclear and its routine use cannot be recommended.

Summary

Dyspnea is a leading source of distress in the terminally ill and often becomes the primary stressor for the patient when death is impending. At the same time, it is often underreported and undertreated, especially in the

Table 1 Ireatment of dyspnea				
Agent/intervention	Effectiveness	Remarks		
Oxygen	+/+++	Can be effective in hypoxemia. Its utility without hypoxemia is very limited		
Systemic opioids	++++	The most effective anti-dyspnea agents		
Inhaled opioids	++	Inhaled fentanyl may be as effective as parenteral fentanyl due to systemic absorption. No evidence to support topical effect		
Sedatives	+	May be helpful in the management of dyspnea-related anxiety. Ineffective for treatment of dyspnea per se.		
Neuroleptics	+	May be helpful in the management of dyspnea-related and agonal delirium. Ineffective for treatment of dyspnea per se.		
Inhaled furosemide	+	Limited utility in bronchospasm. Not recommended for routine use in palliative care		
Fans and other means of air movement	++	Easy and cheap to use. No adverse effects		
Counseling, breathing re-training, relaxation	+++	Weekly counseling sessions have been shown to significantly improve dyspnea		
Maintaining sitting position	++	Improves respiratory mechanics. Particularly effective in congestive heart failure		
Acupuncture, acupressure	+	No consistent evidence of efficacy		
Helium	++	May be helpful if airflow obstruction is present		

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early stages of the disease. Dyspnea can and should be aggressively treated in the palliative population. Concerns about hastening death should not prevent palliative care providers from the liberal use of opioids and other pharmacological agents. This risk is considered acceptable in the dying patient. In less advanced cases, aggressive treatment of dyspnea may actually improve survival [Azoulay et al., 2008].

There are multiple pharmacological and nonpharmacological tools available to the palliative care provider that provide various options to ensure comfort and control of the highly distressing sensation of shortness of breath in the terminally ill (Table 1).

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Nausea and vomiting

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Introduction

Nausea has been considered a uniquely unpleasant discomfort that defies precise definition [Melzack *et al.*, 1985]. Although this statement may be reasonably accurate, it has little clinical utility.

Smith has defined nausea as an unpleasant sensory and emotional experience which may be described in terms of a "sick" feeling with or without a sense of impending vomiting/retching; often associated with a perception of epigastric or upper abdominal unpleasantness or awareness [Smith, 2005]. Retching consists of spasmodic inspiratory movements with the glottis closed and abdominal muscle contractions such that the pressure generated by the abdominal musculature is opposed by negative intrathoracic pressure (the gastric antrum contracts-while fundus and cardiac relax). Vomiting is the forceful expulsion of the gastric contents out of the mouth from a coordinated contraction of predominantly abdominal muscles and diaphragm while the gastric cardia is open and elevated with contracted pylorous [Donnerer, 2003]. The perception of nausea and/or the act of vomiting or retching may be extremely unpleasant and quite severe. Severe nausea, vomiting, or retching can be among the most disabling of symptoms. The patient may suffer an intensely unpleasant and/or distressing experience and some patients may actually choose to live with pain rather than to take a pill that can alleviate their pain if that pill also results in severe nausea. Furthermore, severe nausea, vomiting, and/or retching may lead to significant adverse effects including: dehydration, electrolyte imbalances, malnutrition, and significant deterioration in quality of life (QOL).

Pathophysiology of nausea/vomiting

Borison and Wang postulated the existence of a discrete vomiting center located in the medulla [Borison and Wang, 1949; Wang and Borison, 1951]; however, Miller and Wilson [Miller and Wilson, 1983] [via stimulation of the nucleus tractus solitarius or nucleus of the solitary tract (NTS) and reticular formation] could not identify any discrete locus and concluded that the neural circuitry involved in emetic responses is diffusely distributed in and around the region described by Borison and Wang [Borison and Wang, 1949; Wang and Borison, 1951].

There is no well-defined discrete vomiting center. The terminology "vomiting center" should be replaced with the term "emetic complex" (EC)—to refer to groups of loosely organized neurons distributed throughout the medulla which are sequentially activated by a central pattern generator (CPG) and play a role in emesis.

The EC is composed of the prodromal-sign center (PSC) (located in the reticular area dorsally adjacent to the semi compact part of the nucleus ambiguous) and the central pattern generator center (CPGC) [located dorsomedial to the retrofacial nucleus (RFN)]. The PSC predominantly consists of CPG-driving neurons and prodromal-sign neurons. The CPGC (for vomiting) appears to have afferent areas driving expulsion and retching [Donnerer, 2003].

The emetic reflex (ER) is considered a defense mechanism (with significant autonomic nervous system involvement) in order to rid toxins/noxious agents from the gastrointestinal (GI) system prior to absorption [Donnerer, 2003]. Rather than a vomiting center located in a specific location, the ER arc consists of essentially five major parts which contribute to and/or coordinate the ER and are distributed through the medullary and brainstem areas. The five major parts of the ER are: the vestibular nuclei and cerebellum (VN/C); the higher central nervous system (CNS) centers [including cerebral cortex and limbic system (CC/LS)]; the nucleus of the solitary tract or NTS; the chemoreceptor trigger zone/ area postrema (CTZ/AP); and the EC. The VN/C, CC/LS, NTS, and CTZ/AP are thought to all eventually "feed into" the final common pathway—the EC (*Figure 1*).

There are three major lines of defense that humans have



Figure 1 Locations of receptors that may contribute to nausea and vomiting

against toxin or noxious agent gaining enteral access to the internal milieu of the body. The first line of defense is aimed at preventing the ingestion of toxins/noxious agents into the GI system and entails sight, task, smell, hearing, anxiety/ memory, and vestibular labyrinth mostly from VN/C and CC/LS parts [Donnerer, 2003]. The second line of defense is aimed at preventing the absorption of toxins/ noxious agents and entails the NTS which is the sensory nucleus of the vagus nerve and glossopharyngeus nerve. The vagus nerve receives afferent signals from almost all parts of the upper digestive organs and is located posterior to the EC [Donnerer, 2003].

The third line of defense is aimed at sensing toxins/ noxious agents in the circulation and entails the CTZ/AP. The CTZ/AP located on the floor of the fourth ventricle has a dual detection function. Chemoreceptors facing the ventricle are directly exposed to toxins/noxious agents in the cerebrospinal fluid (CSF) [Donnerer, 2003]. Also, there exists a dense vascular network of fenestrated capillaries which allow detection of circulating irritants which would not pass through the blood-brain barrier [Donnerer, 2003]. Chemoreceptors are additionally present in the area postrema which are outside the blood brain barrier and sensitive to toxins/noxious agents.

Vagal afferent fibers possess a variety of receptors which can facilitate (e.g., 5-HT3, CCK1, TRPV1, NK1) or diminish (e.g., ghrelin, leptin, KOR, GABA-B) neural activity [Andrews and Sanger, 2002]. A complex intricate network of signals affect human appetite/satiety/food intake. It is conceivable that certain peptides/hormones that affect appetite may contribute to the perception of nausea in some circumstances. Many of these peptides/hormones are released from the gut (e.g., oxyntomodulin and GLP-1 [which both bind to the GLP-1 receptor (GLP-1R)], peptide YY, ghrelin (which binds to the GHSR) particularly in the postprandial period) [Cohen *et al.*, 2003].

Ghrelin, a gastric peptide, which possesses orexigenic effects, is the endogenous ligand for the growth hormone secretagogue receptor (GHSR) with stimulating effects on growth hormone and GI motility [Gaskin *et al.*, 2003]. Gaskin and colleagues demonstrated that a sub-threshold dose (12.5 mg/kg; SC) of N(omega)-nitro-L-arginine methyl ester (L-NAME) [a nitric oxide snythase (NOS) inhibitor] significantly blocked the ghrelin-induced increase in food intake [Gaskin *et al.*, 2003]. The administration of ghrelin increased NOS levels in the hypothalamus-

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supporting the hypothesis that ghrelin's effects are nitric oxide dependent [Gaskin *et al.*, 2003].

Hermann and colleagues hypothesized that tumor necrosis factor alpha (TNF α), acting on the neural circuitry of the medullary dorsal vagal complex (DVC), may lead to altered gastric function with possible gastric stasis, anorexia, nausea, and vomiting [Hermann *et al.*, 2003]. Microinjections of TNFR:Fc (TNFR:Fc; TNF-receptor linked to the Fc portion of the human immunoglobulin Ig G1—which neutralizes the suppressive effects of endogenous TNFalpha), an adsorbent construct in the CNS, suppressed induction of NTS cFos immunoreactivity normally evoked by TNF α [Hermann *et al.*, 2003]. The transmission of emetic signals between visceral vagal afferent neurons and the second-order neurons of the NTS may be mediated by glutamate binding to non-N-methy1-D-aspartate (NMDA) receptors in dogs [Furukawa *et al.*, 1998].

The caudal nucleus of the NTS processes preproglucagon to glucagons-like peptides (GLP)-1 and-2 which inhibit food intake when given intracerebroventricularly [Vrang *et al.*, 2003]. GLP-1/2-containing neuronal circuitry seems to con- stimulates these neurons, and LiCl-induced suppression of food intake is blocked by the GLP-1 receptor antagonist exendin-9 [Vrang *et al.*, 2003]. Vrang *et al.* demonstrated that gastric distention (via balloon in non anesthetized freely moving rats) produced significant increases in c-Fos-expressing NTS neurons [Vrang *et al.*, 2003]. Fundus and corpus distention increased the percentage of c-Fos-activated GLP-1 neurons to 21%±9% and 32%±5% compared with 1%±1% with sham distention (P<0.01) [Vrang *et al.*, 2003].

The precise role of the neurokinin (NK) 1 receptor and NK1 receptor antagonists in emesis and its treatment remains uncertain. HSP-117, an NK1 receptor antagonist with antiemetic activity, inhibited the substance P-induced discharge of action potentials of single NTS neuron recorded in slices of ferret brainstem [Saito et al., 1998], suggesting that the site of action of NK1 receptor antagonists may be the NTS. However, this site is more likely where NTS second-order neurons activate the prodomal-sign center for vomiting (located in the reticular area dorsally adjacent to the semi compact part of the nucleus ambiguous) via NK1 receptors [Fukuda et al., 2003]. Although the major site of action for the effects of many antiemetics appears to be central, it is conceivable that peripheral actions may contribute to antiemetic effects as well. Gastric dopamine (D2) receptors are involved in inhibiting gastric motility during nausea/vomiting and

represent a potential peripheral target for dopamine (D2) receptor antagonists [Donnerer, 2003] (*Figure 2*).

Serotonin, 5-HT, is found throughout the gut and CNS. In the gut, 5-HT is found in the mucosal enterochromaffin cells which are the sensory transducers which release 5-HT to activate intrinsic (via 5-HT4 and 5HT1P receptors) and extrinsic (via 5HT-3 receptors) primary afferent nerves.

Approximately 80% of total body serotonin is found in the GI tract, the remainder being divided between the platelets, which avidly take up free serotonin, and the CNS. Ninety five percent of GI 5-HT is found within the granules of the enteroendocrine cells (ECs) secretory located mainly at the base of the crypts [Spiller, 2002]. Factors which may lead to 5-HT exocytosis include: mechanical stimuli such as luminal pressure or mucosal stroking, bacterial toxins (e.g., cholera toxin), and cytotoxic drugs which nonspecifically damage the cells, (e.g., cisplatinum) [Schworer et al., 1991]. There is also classical receptor mediated stimulation via β-adrenergic, purinergic $A_{2A/B}$ and muscarinic receptors, together with inhibitory α_2 -adrenergic, histamine type 3 receptors and purinergic A₁ receptors. These probably act through modulating intracellular Ca++, a surge in which is associated with 5-HT release [Spiller, 2002]. Serotonin can stimulate 5-HT3 receptors with resultant inhibit gastric secretions, and stimulate ions of migrating motor complex (MMCs) [Coleman et al., 2001b] [with enhancement of intestinal secretions thereby accelerating small bowel transit [Coleman et al., 2001a]. They also stimulate antral contractions and vagal afferents inducing nausea [Coleman et al., 2001b]. 5-HT3 antagonists inhibit splanchnic afferent nerve response to painful distension and inhibit vagal responses to chemotherapy induced 5-HT release. They also inhibit discharge of secreto-motor nerves, which act via vasoative intestinal peptide (VIP), and nitric oxide (NO) [Spiller, 2002].

5-HT3 receptor antagonists, although having a major action on the CTZ, also may dampen the ER afferent input and transmission by inhibiting presynaptic vagal 5-HT3 receptors, blocking 5-HT enterochromaffin cell autoreceptors (thereby inhibiting 5-HT release), and impeding transmission of emetic afferent input in vagus nerve nuclei [Hesketh and Hesketh, 1991; Freeman *et al.*, 1992; Donnerer and Beubler, 2003].

Additionally, although the anti-emetic actions of NK1 receptor antagonists appear to be largely (if not entirely) central—it is *theoretically* conceivable that the inhibition of NK1 receptors of vagal motor neurons [which inhibit fundic relaxation (a prodomal event before vomiting)] may contribute as well [Fukuda *et al.*, 2003].



Figure 2 Neural mechanisms controlling nausea and vomiting.

Brain circuitry of nausea/vomiting

Napadow and colleagues utilized functional magnetic resonance imaging (fMRI) approach evaluated brain activity contributing to and arising from increasing motion sickness [Napadow et al., 2012]. They evaluated parametrically increasing brain activity (I) precipitating increasing nausea and (II) following transition to stronger nausea. All subjects demonstrated visual stimulus-associated activation (P<0.01) in primary and extrastriate visual cortices. In subjects experiencing motion sickness, increasing phasic activity preceding nausea was found in the amygdala, putamen, and dorsal pons/locus ceruleus. Increasing sustained responses following increased nausea were found in a broader network including insular, anterior cingulate, orbitofrontal, somatosensory and prefrontal cortices. Sustained anterior insula activation to strong nausea was correlated with midcingulate activation (r=0.87), suggesting a closer linkage between these specific regions within the brain circuitry

subserving nausea perception. It appears phasic activation in fear conditioning and noradrenergic brainstem regions may precipitate transition to strong nausea, sustained activation, however, following this transition a broader interoceptive activation of brain regions may occur involving limbic, somatosensory, and cognitive networks, reflecting the multiple dimensions of this aversive commonly occurring symptom [Napadow *et al.*, 2012]. A correlation analysis across all brain regions specifically found that subjects who showed greater anterior insula activation following transition to strong nausea also demonstrated greater activation in midcingulate cortex, suggestion a closer linkage between these specific regions [Napadow *et al.*, 2012].

Etiologies of nausea/vomiting

There are numerous etiologies for nausea and/or vomiting. Metabolic causes include: uremia, uncontrolled diabetes

Highly emetogenic (>90%)CisplatinCyclophosphamide (>1.5 g/m²)MechlorethamineStreptozocinModerately ematogenicCarboplatin(30-90%)Cytarabine (>1 g/m²)DaunorubicinDoxorubicinEpirubicinIdarubicinIdarubicinIfosfamideIronotecanOxaliplatinLow risk (10-30%)BortezomibCetuximabCytarabine (<100 mg/m²)DocetaxilEtoposideGemcitabine
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Mitomycin
Mitoxantrone
Paclitaxel
Pemetrexed
Trastuzumab
5-fluorouracil
Minimal risk (<10%) Bevacizumab
Bleomycin
Busulfan
Cladribine
Fludarabine
Vinblastine
Vincristine
Vinorelbine

mellitus, electrolyte imbalance (e.g., sodium, potassium), hormonal imbalance (e.g., hyperemesis gravidarum), altered GI tract motility, hyperthyroidism, addison's disease, and porphyria. Inflammation/irritation/infection of the airway, posterior pharynx, abdomen (including liver, pancreas, and biliary tree), GI tract, kidneys, bladder, ureter, and testes or cervix may lead to stimulate afferent pathways leading

 Table 2 Recommended treatment regimens for prevention of chemotherapy induced nausea and vomiting

 Emetic risk category
 Antiemetic regimen

 Highly emetogenic
 Dexamethasone

 SHT₃ receptor antagonist
 Aprepitant

 Moderately emetogenic
 Dexamethasone

 SHT₃ receptor antagonist
 Dexamethasone

 Low risk
 Dexamethasone

No routine prophylaxis recommended

to nausea and/or vomiting. Additionally, nausea and/or vomiting can result from increased intracranial pressure, chemotherapy, medications/opioids, radiation, movement of endolymph in the semicircular canals-stimulating cranial nerve VIII, hypovolemia/hypotension, pain/anxiety, headaches (e.g., migraine), and unpleasant memories [Kovac, 2003]. Major causes for nausea/vomiting associated with terminal conditions and the treatment of these conditions include chemotherapy-induced nausea/vomiting (CINV) (*Tables 1,2*), opioid-induced emesis (OIE), postopertative nausea/vomiting (PONV) (*Table 3*) and radiation-induced emesis (RIE).

Hwang *et al.* studying the dopamine agonist (-)-N-11Cpropyl-norapomorphine (11C-NPA) in nonhuman primates concluded that 11C-NPA is a suitable (positron emission tomography) PET radiotracer to image/quantify highaffinity sites of dopamine D2-like receptors [Hwang *et al.*, 2004]. The high-affinity sites (D2 high) are G protein coupled [Hwang *et al.*, 2004]. With the use of these and other techniques (e.g., PET imaging of the CNS utilizing novel radiotracers), it is hoped that insight may be gained into the importance/contribution of the actions of various receptors in facilitating nausea/vomiting in an individual patient. In the future, armed with this knowledge, clinicians may be able to design optimal antiemetic "cocktails" for individual patients.

Nausea assessment

Minimal risk

Wood and colleagues reviewed various instruments available for the assessment of cancer-related nausea, vomiting, and retching [Wood *et al.*, 2011]. Twenty-four tools evaluating nausea were identified that met their inclusion criteria. Thirteen tools measured vomiting as a separate experience.

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Table 3 Assessment/recommendations for prevention and management of PONV					
Risk factors	Number of risk factors	PONV incidence	Prophylaxis strategy		
	0	9%	None		
Female gender	1	20%	4 mg dexamethasone		
			± 2nd antiemetic		
Nonsmoker	2	39%	Avoid inhalation agents if possible		
			+4 mg dexamethasone		
			± 2 nd antiemetic		
History of PONV or	3	60%	Avoid inhalation agents if possible		
motion sickness			+4 mg dexamethasone		
			+ another prophylactic antiemetic (e.g., scopolamine patch)		
Use of opioids >100 mcg	4	78%	Avoid inhalation agents if possible		
fentanyl or equivalent			+4 mg dexamethasone		
			+ NK-1 Receptor Antagonist		
			± another prophylactic antiemetic (e.g., scopolamine patch)		
Rescue strategy: antiemetic not used for prophylaxis, e.g., ondansetron1mg IV.					
[Adapted from Apfel et al., 2002]. PONV, postopertative nausea/vomiting.					

Only 3 tools included a separate assessment of retching. The number of CINVR-related questions in each tool ranged from 2 to 17 [Wood *et al.*, 2011].

Of the 24 tools that addressed nausea in the oncology population, many were designed to focus on the patient's more broad functional status or quality-of-life issues. One commonly used tool, the Morrow Assessment of Nausea and Emesis [Morrow, 1984], specifically asked questions regarding pretreatment nausea. Another tool, the MASCC Antiemesis Tool [MASCC, 2012], individually addressed both acute and delayed nausea and vomiting.

Rhodes and McDaniel [1999] developed the Index of Nausea, Vomiting, and Retching (INVR) and demonstrated the tool's ability to be used in both paper and computerized charting [Rhodes and McDaniel, 1999]. The INVR has questions regarding the number of retching episodes in the previous 12 hours and the distress felt by these episodes. The INVR utilizes a 5-point Likert-type scale; although this has not been shown to be as sensitive to early changes as the VAS, it has been found to be clinically useful and easy for patients to understand [Wood *et al.*, 2011]. There have been various versions of this tool published [Wood *et al.*, 2011]. The INVR revised in 1996 addresses the frequency and distress associated with all 3 symptoms: nausea, vomiting, and retching [Rhodes and McDaniel, 1999].

In 1997, Hesketh et al. classified the acute emetogic potential of individual chemotherapeutic agents (often referred to as the Hesketh score [Hesketh *et al.*, 1997]. In this system, agents are classified according to proportion of patients expected to experience emesis with each agent in the absence of effective antiemetic prophylaxis as follows: level 1, <10% of patients; level 2, 10-30% of patients; level 3, 30-60% of patients; level 4, 60-90% of patients; and level 5, >90% of patients [Hesketh *et al.*, 1997].

Nausea and vomiting do appear to become more common as death approaches, so it is not surprising that nausea has been found to be a predictor of a shortened survival in one study [Chang *et al.*, 2004]. In patients admitted to specialist palliative care programs, nausea has been reported by 36% patients at the first contact with the service [Ventafridda *et al.*, 1990; Donnelly *et al.*, 1995; Vaino and Auvinen, 1996], 62% at 1-2 months before death [Reuben and Mor, 1986; Coyle *et al.*, 1990], and 71% in the final week of life [Fainsinger *et al.*, 1991; Conill *et al.*, 1997].

Glare and colleagues have categorized nausea etiology in palliative medicine into 4 groups: due to the primary disease, due to a side effect of therapy, secondary to debilitation, and caused by an unrelated comorbid condition for nonmedical conditions in palliative medicine associated with nausea mat include significant advanced cardiac obstructive pulmonary disease, end-stage renal disease, and advanced dementia [Glare *et al.*, 2011]. In elderly palliative care patients, conditions such as mesenteric ischemia, subacute
Table 4 Non-pharmacological management of PONV

Practical tips for managing preventing nausea and vomiting

- Keep dry crackers near the bed for morning nausea
- Try chamomile, peppermint, catnip, or ginger tea, and fresh, dried, or candied ginger
- Sniff a cut lemon
- Eat salty foods such as pretzels; carry a small packet of salt when going out
- Avoid trigger foods known to cause nausea
- Avoid strong odors
- Avoid stomach irritants (e.g., tobacco, aspirin)
- If there is a pattern to nausea, eat more during periods with less nausea
- Do not eat and drink at the same time; drink liquids an hour before or after eating
- Eat meals sitting up rather than lying down
- Avoid lying down for at least an hour after eating; rest with your head higher than your feet
- Keep the room temperature cool
- Avoid eating in a room that is hot, stuffy, or filled with cooking odors

Dietary measures for relieving nausea, vomiting, and diarrhea

- Drink clear beverages such as fruit juices, broth, ginger ale, energy drinks, or herbal teas
- Eat small amounts of food every few hours rather than 2-3 large meals per day
- Eat slowly and sip beverages slowly
- Suck on popsicles or frozen fruit juice
- Try the BRAT diet: bananas, white rice, applesauce, and white bread toast
- Eat bland, soft foods (e.g., pasta, mashed potatoes, jello)
- Eat dry foods like unbuttered toast, saltine crackers, and dry cereal without milk
- Avoid greasy foods, fried foods, margarine, butter, and oils
- Avoid spicy foods
- Avoid dairy products
- Avoid caffeine (in coffee, tea, soft drinks, chocolate, some pain medications)
- Avoid alcoholic beverages
- Avoid acidic foods and juices (e.g., citrus fruits, tomatoes)
- Eat foods high in soluble fiber
- Avoid foods high in insoluble fiber

cholangitis, Meniere's disease, myocardial infarction, drug toxicity, constipation, and urinary tract infection need to be high on the differential diagnosis of nausea and vomiting [Glare *et al.*, 2011].

Treatment of nausea/vomiting

The treatment of nausea/vomiting typically starts with

general measures aimed at ameliorating nausea and/ or vomiting. Avoidance of environmental stimuli, such as sights, sounds, or smells that may initiate nausea are recommended [Rhodes and McDaniel, 2001]. Fatty, spicy, and highly salted food should be avoided (*Table 4*); however, in most cases the treatment of nausea/vomiting should target the predominant factor(s) contributing to these symptoms.

Nonpharmacologic treatment strategies for nausea/ vomiting

Gastric electrical stimulation (GES) has been introduced for treating gastric motility disorders. GES with long pulses or dual pulses, but not short pulses, are able to alter (enhance or inhibit) such parameters of gastric motility as gastric slow waves and gastric emptying. Synchronized GES has been reported to improve antral contractions. A special method of GES using high frequency-short pulses, called Enterra[®] Therapy, has been clinically applied to treat nausea and vomiting in patients with gastroparesis [Yin *et al.*, 2012]. Although the mechanisms of GES remain uncertain, improved gastric accommodation, direct enteric nervous system effects, enhanced vagal activity, and activation of central neurons are believed to be the underlying mechanisms involved in the antiemetic effect of Enterra[®] therapy [Yin *et al.*, 2012].

Although the literature is scant and results have been mixed, behavioral approaches such as relaxation and distraction, relaxation training utilizing muscle relaxation and guided imagery. Massage has been reported to be effective for nausea and pain in bone marrow transplant patients [Ahles *et al.*, 1999]. Foot massage was shown to reduce nausea significantly in hospitalized cancer patients [Grealish *et al.*, 2000]. A systematic review of complementary and alternative medicine for symptom management at the end of life was unable to identify any large-scale trials in terminally ill patients for nausea and vomiting.

Acupuncture has been fairly well established in the prevention of PONV [Lee and Fan, 2009]. It consists of stimulating the so-called P6 wrist point (located on the ventral surface of the forearm approximately 3 fingerwidths proximal to the wrist joint) by using acupuncture, acupressure, and other techniques [Chernyak *et al.*, 2005]. Acupuncture and ginger have been shown to be effective for chemotherapy-induced emesis and anticipatory nausea [Ezzo *et al.*, 2006; Hickok *et al.*, 2007], but have not been evaluated in the nausea of far advanced disease.

Pharmacologic treatment of nausea/vomiting

Ideally, the agents utilized for the treatment of nausea/ vomiting should target the receptors that are predominantly involved in contributing to nausea/vomiting in an individual patient (*Table 5*). Clinicians should be aware of adverse events and/or drug-drug interactions of various medications that may contribute to nausea/vomiting.

Dopamine receptor antagonists (DRAs)

Dopamine receptor antagonists (DRAs) are by far the most commonly used antiemetic agents, especially in palliative medicine. Although the reasons why DRAs are so popular are not entirely certain, it is likely that the two major reasons are: (I) DRAs are relatively inexpensive and (II) DRAs are the oldest antiemetic agents, and so they have the "longest track record" and also the highest number patient years, of usage as well as being the most familiar agents to clinicians.

DRAs may be the most popular class among the antiemetic agents; however, they probably should not be at the top of the popularity list of antiemetics since they may be one of the least effective (especially at the usual doses employed), as well as the antiemetic class with the most frequent adverse effects and most significant adverse effects. Furthermore, it is unfortunate that clinicians may resort to switch from one DRA that was ineffective to another DRA rather than adding a second antiemetic agent from a totally different class (e.g., 5-HT3 receptor antagonists, NK-1 receptor antagonists).

Butyrophenones

Droperidol (Inapsine) and haloperidol (Haldol) are butyrophenones and two DRAs that are used in palliative medicine quite frequently for treatment of nausea and vomiting. The pharmacokinetics and pharmacodynamics of haloperidol administration by different routes is an important consideration as the side effects are determined by its route of administration. Haloperidol is extensively metabolized by hepatic enzymes, partially by the CYP450 family, and there are active, inactive and toxic metabolites. Only 1% is excreted unchanged in the urine. Its metabolism is complex. Haloperidol's metabolism consists of glucuronidation to an inactive metabolite (50-60%), reduction (and back oxidation) to reduced-haloperidol (an active metabolite) (23%) and N-dealkylation to a pyridium metabolite (a toxic metabolite) (20-30%). As a result of haloperidol's variable metabolism, haloperidol has a variable half-life (12-35 hours). Reduced-haloperidol is not detected after intravenous administration for even longer than after oral administration which suggests that first pass metabolism is responsible for increased reduced-haloperidol concentrations.

Due to its strong antidopaminergic action, it is classified as a highly potent neuroleptic. The peripheral antidopaminergic effects at the CTZ, accounts for its strong antiemetic activity. The peripheral effects also lead to the relaxation of the gastric sphrincter muscle.

Nausea and vomiting

nts to various receptors	IV V VI VII VIII IX X XI XII XIII XIV XV XVI								+++ ++	++++	++++		++++	++++		+ + + + ++ +	+++ +++ +++	++++ ++		++ ++ ++ + +++	++++	soniet: III. M. antroconiet: N/ E. HT2A. antroconiet: V/ E. HT3A. antroconiet: V/ E. HT3B. antroconiet: V/I. E. HT3C. antroconiet:
×														++++	++++	+						8A antagonist; \ Iulator; XIII, 5-F
×							-						; + + +	+								st; V, 5-HT3 5-HT1 mod
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Droperidol is a short-acting butyrophenone derivative with minimal side effects when compared to haloperidol. It has minimal effects on the respiratory system and has sedative properties that last from 2 to 6 hours. It has minimal anticholinergic properties. It can be used only parenterally, unlike haloperidol which can be used orally, SC, IV or IM. Droperidol was widely believed to be more effective against nausea than vomiting, but the analysis of IMPACT data and reanalysis of a previous meta-analysis suggested that droperidol was equally effective in reducing both nausea and vomiting [Apfel *et al.*, 2009].

Although there is a black box warning for droperidol, as with haloperidol, due to prolongation of the QTc interval, prolongation is felt to be dose dependent. ECG changes not accompanied by dysrhythmias, does not seem to be a reason to avoid the use of this drug [Lischke *et al.*, 1994]. Patients with preexisting conduction defects or prolongation of QTc interval may be at risk to develop dysrhythmias after droperidol administration because disposition dysrhythmias has been reported to increase after administration of a QTc interval-prolonging drug.

Metoclopramide (Reglan)

Metoclopramide is a dopamine antagonist with a short-life and is one of the most frequently used dopamine antagonists. However, due to the extrapyramidal symptoms (EPS) that emerged during its use at high doses for the prevention of chemotherapy induced nausea and vomiting (e.g., 200 mg every 4-6 h), clinicians wound up shying away from relatively high doses [George et al., 2010]. A 10 mg dose of metoclopramide has become the most commonly used dose [Grallla et al., 1981; Henzi et al., 1999]. A systematic review showed this conservative 10mg dose to have no clinically relevant antiemetic effect [Henzi et al., 1999] and this dose is the most commonly used antiemetic dose. A dose-response study of metoclopramide by Wallenborn et al. [Wallenbron et al., 2006] found that doses of metoclopramide higher than 10 mg (e.g., 25-50 mg) were as effective as other antiemetics.

Metoclopramide, a benzamide prokinetic antiemetic, is not only used for nausea and vomiting, but also may be utilized as a prokinetic agent, or for hiccups, or gastroesophageal reflux. A "black box" warning has been issued by the Food and Drug Administration in relation to tardive dyskinesia to limit use to 12 weeks. Currow and colleagues studied a consecutive cohort of patients from 12 participating centers in two countries who were having metoclopramide initiated had data collected at three time points--baseline, 2 days (clinical benefit), and day 7 (clinical harm) [Currow *et al.*, 2012]. Of the 53 people included in the cohort, 23 (43%) reported benefit at 48 hours, but only 18 (34%) of these people were still using it one week after commencing it. For the other 5, the medication was ceased due to harms. The most frequent harms were akathisia (n=4), headache (n=4), and abdominal pain (n=4). Nine people (17%) had no clinical benefit and experienced harms. Thus, one in three people gained net clinical benefit at one week [Currow *et al.*, 2012].

In addition to the EPS, metoclopramide has also been associated with adverse events related to the cardiovascular system, including one patient experiencing multiple cardiac arrests after repetitive metoclopramide administrations [Bentsen and Stubhaug, 2002]. The dosage forms of metoclopramide include: Injection, solution [preservative free]: 5 mg/mL (2 mL) [Reglan[®]: 5 mg/mL (2, 10, 30 mL)], Solution, oral: 5 mg/5 mL (0.9, 10, 473 mL), Tablet, oral: 5 mg, 10 mg [Reglan[®]: 5 mg, 10 mg (scored)], Tablet, orally disintegrating, oral: [MetozolvTM ODT: 5 mg, 10 mg (mint flavor)].

Metoclopramide has a rapid absorption after oral administration (Bioavailability: Oral: Range, 65% to 95%) and an onset of action of 30-60 minutes after oral administration; 1-3 minutes after intravenous administration; 10-15 minutes after intravenous administration. The time to peak after administration is 102 hours and therapeutic duration of action of 1-2 hours, regardless of route. Its protein binding is about 30%. The half-life elimination in patients with normal renal function is children: ~4 hours; and adults: 5-6 hours (may be dose dependent), Roughly about 85% of metoclopramide is excreted in the urine.

Metoclopramide oral disintegrating tablets for PONV prophylaxis: I.M., I.V. Metozolv[™] ODT; Reglan[®] (unlabeled route): 10-20 mg near end of surgery. Note: Guidelines discourage use of 10 mg metoclopramide (as well as standard clinical doses of ginger root or cannabinoids) as being ineffective for PONV [Gan et al., 2007]; however, a comparative study indicates that higher doses (e.g., 20 mg) may be efficacious [Quaynor and Raeder, 2002]. Orally-disintegrating tablets may be administered on an empty stomach at least 30 minutes prior to food, and they should not be removed from packaging until time of administration. If tablet breaks or crumbles while handling, discard and remove new tablet. Using dry hands, patients should place tablet on tongue and allow to dissolve. I.M. or I.V. routes of administration are alternatives but generally suboptimal. The dosing in renal impairment with a creatinine clearance (Cl_{cr}) <40 mL/minute is to administer 50% of normal dose.

Nausea and vomiting

Contraindications to the administration of metoclopramide include: hypersensitivity to metoclopramide or any component of the formulation; GI obstruction, perforation or hemorrhage; pheochromocytoma; history of seizures or concomitant use of other agents likely to increase extrapyramidal reactions, depression, EPS, neuroleptic malignant syndrome (NMS), and Tardive dyskinesia. Metoclopramide has a U.S. Boxed Warning: May cause tardive dyskinesia, which is often irreversible; duration of treatment and total cumulative dose are associated with an increased risk.

Prochlorperazine (Compazine)

Prochlorperazine is a piperazine phenothiazine antipsychotic which block postsynaptic mesolimbic dopaminergic receptors in the brain and has antiemetic effects by its antagonist actions in the D2 dopamine receptors in the chemoreceptor trigger zone. It also exhibits alpha-adrenergic blocking effect on α 1 receptros and may depress the release of hypothalamic and hypophyseal hormones.

Prochlorperazine is utilized for the management of severe nausea and vomiting of various etiologies (e.g., postoperative, acute migraine, toxins, radiation, or cytotoxic drugs). Nausea and vomiting treatment with prochlorperazine may be via various routes: Oral: usually, 5 or 10 mg 3 or 4 times daily (Dosages >40 mg daily should be used only in resistant cases); Rectal: 25 mg suppository prochlorperazine twice daily, and IV: 2.5-10 mg. For control of severe nausea and vomiting during surgery: 5-10 mg IV given 15-30 minutes before induction of anesthesia. If necessary, repeat initial dose once before surgery. Geriatric patients with dementia-related psychosis treated with antipsychotic agents are at an increased risk of death. Analyses of 17 placebo-controlled trials in geriatric patients mainly receiving atypical antipsychotic agents revealed an approximate 1.6- to 1.7-fold increase in mortality compared with that in patients receiving placebo.

The onset of prochlorperazine generally takes 30-40 minutes (conventional tablet), 60 minutes (rectal suppository), or 10-20 minutes (IM administration), and the antiemetic effects roughly have a duration of 3-4 hours (conventional tablet, rectal suppository, or IM administration). Prochlorperazine exhibits weak anticholinergic effects, moderate sedative effects, strong extrapyramidal effects, and strong antiemetic effects. It also has peripheral and/or central antagonistic activity against α -adrenergic, serotonergic, histaminergic H₁, and muscarinic receptors.

To control acute symptoms during or after surgery, usually 5-10 mg IV, repeated once, if necessary; single

IV doses of the drug should not exceed 10 mg. If prochlorperazine is administered intramuscularly the initial dose should be 5-10 mg; if necessary, initial dose may be repeated every 3 or 4 hours, but total dosage should not exceed 40 mg daily. For control of severe nausea and vomiting during surgery: 5-10 mg IM given 1-2 hours before induction of anesthesia. If necessary, dose may be repeated once, 30 minutes after the initial dose. To control acute symptoms during or after surgery: 5-10 mg IM, repeated once in 30 minutes, if necessary. Contraindications to prochlorperazine administration include: Comatose states or in the presence of large amounts of CNS depressants (e.g., alcohol, barbiturates, opiates), pediatric surgery, children <2 years of age or <9 kg, children with conditions for which dosage has not been established, and known hypersensitivity to prochlorperazine or other phenothiazines.

Perphenazine (Trilafon)

Perphenazine is a relatively high potency phenothiazine that blocks dopamine 2 (D2) receptors predominantly but also may possess antagonist actions at histamine 1 (H_1) and cholinergic M1 and alpha 1 adrenergic receptors in the vomiting center leading to reduced nausea and vomiting. It has less risk of sedation and orthostatic hypotension but greater risks of EPS than with low potency phenothiazines. The potency of its antiemetic effects are intermediate. It is available as an oral tablet in strengths 2, 4, 8, and 18 mg as well as in an injectable formulation-5 mg/mL. After intramuscular injection the initial effect may be seen after 10 minutes, with peak effects occurring after 1-2 hours. Perphenazine is well absorbed after oral administration. The time to peak after oral administration is 1-3 hours with the time to peak of the metabolite 7-hydroxyperphenzaine 2-3 hours. Perphenazine has a half-life elimination of 9-12 hours and its metabolite 7-hydroxyperphenazine of 10-19 hours.

Perphenazine is extensively hepatic to metabolites via sulfoxidation, hydroxylation, dealkylation, and glucuronidation; primarily metabolized by CYP2D6 to N-dealkylated perphenazine, perphenazine sulfoxide, and 7-hydroxyperphenazine (active metabolite with 70% of the activity of perphenazine) and excreted in the urine and feces. Contraindications to the use of perphenazine include: Hypersensitivity to perphenazine or any component of the formulation (cross-reactivity between phenothiazines may occur); severe CNS depression (comatose or patients receiving large doses of CNS depressants); subcortical brain damage (with or without hypothalamic damage); bone marrow suppression; blood dyscrasias; and liver damage. The prevalence rate of tardive dyskinesia may be 40% in elderly; development of the syndrome and the irreversible nature are proportional to duration and total cumulative dose over time. Extrapyramidal reactions are more common in elderly with up to 50% developing these reactions after 60 years of age. Drug-induced Parkinson's syndrome occurs often; akathisia is the most common extrapyramidal reaction in elderly.

Promethazine (Phenergan)

Promethazine is a phenothiazine derivative which is also a potent histamine receptor H_1 antagonist and an antiemetic. Its mechanisms of action include: blocking postsynaptic mesolimbic dopaminergic receptors in the brain; strong alpha-adrenergic blocking effects decreasing the release of hypothalamic and hypophyseal hormones; competing with histamine for the H_1 -receptor; muscarinic-blocking effects, and reducing stimuli to the brainstem reticular system.

The antiemetic dose of promethazine is 12.5-25 mg every 4-6 hours as needed. Promethazine is available as the hydrochloride in multiple formulations including: injectable solution, suppositories, tablets, and syrup (6.25 mg/5 mL). The oral route is generally the preferred route of administration, however, if the oral or rectal routes are unavailable; there may be circumstances in which the parenteral route of administration is a very reasonable therapeutic option. Intramuscular (I.M.) Administration is the preferred parenteral route of administration (although parenteral administration is not ideal). If promethazine is administered intramuscularly, it should be administered into a deep muscle.

Intravenous (I.V.) administration is not the preferred route as severe tissue damage may occur. The solution for injection should be administered in a maximum concentration of 25 mg/mL (however, more dilute solutions are recommended). If administered I.V., it should be administered via a running I.V. line at the port farthest from the patient's vein, or through a large bore vein (not hand or wrist). Clinicians should consider administering it over 10-15 minutes (maximum: 25 mg/minute) and discontinuing immediately if burning or pain occurs with administration. Promethazine has a U.S. Boxed Warning- Promethazine injection can cause severe tissue injury (including gangrene) regardless of the route of administration. Tissue irritation and damage may result from perivascular extravasation, unintentional intra-arterial administration, and intraneuronal or perineuronal infiltration. In addition to gangrene, adverse events reported include tissue necrosis,

abscesses, burning, pain, erythema, edema, paralysis, severe spasm of distal vessels, phlebitis, thrombophlebitis, venous thrombosis, sensory loss, paralysis, and palsies. Surgical intervention including fasciotomy, skin graft, and/or amputation has been necessary in some cases. The preferred route of administration is by deep I.M. injection. Subcutaneous administration is contraindicated. Discontinue intravenous injection immediately with onset of burning and/or pain and evaluate for arterial injection or perivascular extravasation. Although there is no proven successful management of unintentional intra-arterial injection or perivascular extravasation, sympathetic block and heparinization have been used in the acute management of unintentional intra-arterial injection based on results from animal studies. Furthermore, the injectable solution may contain sodium metabisulfite; which may cause allergic reactions.

There is also a Pediatric U.S. Boxed Warning-Respiratory fatalities have been reported in children <2 years of age. Use contraindicated in children <2 years. In children ≥ 2 years, use the lowest possible dose; other drugs with respiratory depressant effects should be avoided. Avoid use in children who may have Reyes' syndrome or hepatic disease as adverse reactions caused by promethazine may be confused with signs of primary disease.

Promethazine has an onset of action of about 20 minutes if administered orally or intramuscularly and about 5 minutes if administered intravenously. Its duration of action is usually 4-6 hours (but can be up to 12 hours). The oral absorption of promethazine is rapid and complete. There is a large first pass effect limiting systemic oral bioavailability [Sharma and Hamelin, 2003] which is about 25%. The time to maximum serum concentration is 6.7-8.6 hours after suppositories and 4.4 hours after syrup.¹¹Hepatic metabolism of promethazine is predominantly by hydroxylation via CYP2D6 and N-demethylation via CYP2B6 [Sharma and Hamelin, 2003]. The half-life elimination for I.M. administration is about 10 hours; 9-16 hours for I.V. administration; and 16-19 hours (range, 4-34 hours) for suppositories or syrup [Strenkoski et al., 2000] with urinary excretion.

Contraindications to the use of promethazine include: allergy or hypersensitivity to promethazine, any H_1 antihistamine, and/or any phenothiazine (cross-reactivity between phenothiazines may occur) or any component of the formulation; coma; treatment of lower respiratory tract symptoms (e.g., asthma); children <2 years of age; intraarterial or subcutaneous administration. Concerns related



Figure 3 Timeline of 5-HT3 receptor antagonists (5-HT3RAs).

to adverse effects include: altered cardiac conduction, anticholinergic effects, EPS, NMS, orthostatic hypotension, photosensitivity, sedation, impaired core body temperature regulation, lowered seizure threshold, cholestatic juandice, tardive dyskinsesia (especially in patients with Parkinson's disease), and the potential for serious skin injury if administered parenterally.

Trimethobenzamide (Tigan)

Trimethobenzamide is a (non-phenothiazine) benzamide antiemetic that acts centrally to block D2 receptors, thereby inhibiting the medullary chemoreceptor trigger zone by blocking emetic impulses to the vomiting center.

Trimethobenzamide is available as: Capsules, oral, as hydrochloride: 300 mg [Tigan[®]: 300 mg], Injection, solution, as hydrochloride [Tigan[®]: 100 mg/mL (20 mL)], or Injection, solution, as hydrochloride (preservative free) [Tigan[®]: 100 mg/mL (2 mL)].

The dose for nausea/vomiting is Oral: 300 mg 3-4 times/day, or I.M.: 200 mg 3-4 times/day, and for PONV is I.M.: 200 mg, followed 1 hour later by a second 200 mg dose. The oral bioavailability of trimethobenzamide is 60% to 100%. The time to peak is about 45 minutes after oral administration and; I.M. about 30 minutes after intramuscular administration. The onset action of trimethobenzamide for antiemetic effects is 10-40 minutes after oral administration and; 15-35 minutes after intramuscular administration is 3-4 hours. The half-life elimination is 7-9 hours. Metabolism is via oxidation with the formation of the metabolite trimethobenzamide N-oxide. Excretion is via the urine (30% to 50%, as unchanged drug within 48-72 hours). Contraindications to trimethobenzamide are

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hypersensitivity to trimethobenzamide or any component of the formulation. Also, injection is contraindicated in children.

5-HT3 receptor antagonists (5-HT3RAs)

The chemical structures of the first generation 5-HT3 receptor antagonists have been categorized into three major classes [Ho and Gan, 2006]: (I) Carbazole derivatives (ondansetron); (II) Indazoles (granisetron); and (III) Indoles (dolasetron). Palonosetron is a highly selective second generation 5-HT3 receptor antagonist that has two stereogenic centers and may exist as four steroisomers [Tian *et al.*, 2006]. Palonosetron has a longer half-life (40 h) and greater receptor binding affinity (>30 fold) versus first generation 5-HT3RAs (*Figure 3*).

It is 62% bound to plasma proteins [Siddiqui and Scott, 2004]. The liver metabolizes approximately 50% of palonosetron. The two primary metabolites, N-oxide-palonosetron and 6-(S)-hydroxypalonosetron, are essentially inactive [Ho and Gan 2006; Siddiqui and Scott, 2004].

The second generation palonoestron has a much longer half life than the first generation 5-HT3 antagonists and a greater than 30 fold 5-HT3 receptor binding affinity. Although all the 5-HT3 antagonists share much of the same mechanisms of action, they have different chemical structures, binding affinities, dose responses and duration of effects and they are metabolized differently via different components of the cytochrome P450 system (*Table 6*).

A correlation exists between the number of active CYP 2D6 alleles and number of vomiting episodes a patient may have, that is, the more active alleles a patient has the more likely they will be unresponsive to the antiemetic and vice versa.

Table 6 5-H15 receptor antagonists								
Agent	Trade name	T1/2 (h)	Dose	Metabolism	Metabolism	Receptor subtypes		
, igent		= ()	2000	(primary pathway)	(secondary pathway)			
Ondonsetron	Zofran	3.9	0.15 mg/kg	CYP3A4	CYP1A2	5-HT3B		
					CYP2D6	5-HT1B, 5-HT-1C, α-1, MOR		
					CYP2E1			
Granisetron	Kytril	9-11.6	10 mcg/kg	CYP3A4		5-HT3A, 5-HT3B, 5-HT3C		
Dolasetron	Anzemet	7-9	0.6-3 mg/kg	Hydrodolasetron	Hydrodolasetron	5-HT3B		
				CYP2D6	CYP3A			
Palonosetron	Aloxi	40	0.75 mg	CYP2D6	CYP3A	5-HT3A		
					CYP1A1/2			

with glucocorticoid steroids such as dexamethasone in chemotherapy induced nausea and vomiting. Some studies advocate for intravenously administered 5-HT3 antagonists, others argue for oral administration. The concomitant use of aprepitant, an NK1 receptor antagonist, significantly increases the efficacy of the 5-HT3 antagonist in acute or delayed chemotherapy induced nausea and vomiting.

5-HT3 receptor antagonists are often used in conjunction

In a study which was a meta-analysis of randomized control trials comparing 5-HT3 receptor antagonists and non-5-HT3 antagonists in post-op breast surgery patients, the 5-HT3 antagonists were found superior to placebo or active controls in the prevention of post-op nausea and vomiting [Singhal *et al.*, 2012]. 5-HT3 antagonists were also superior to placebo in preventing nausea alone and were effective in reducing post op vomiting and the use of rescue antiemetics. 5-HT3 antagonists did not cause a significantly higher incidence of adverse events as compared to placebo.

Several studies comparing ganisetron alone versus in combination with dexamethasone or droperidol found that the combination showed greater efficacy than ganisetron alone in post op nausea and vomiting [Dua *et al.*, 2004; Gan *et al.*, 2004; Reihner *et al.*, 2000]. However, in the absence of large randomized trials, no single agent has emerged as the standard of care for preventing post op nausea and vomiting in women undergoing breast surgery [Singhal *et al.*, 2012].

The intravenous administration of 5-HT3 receptor antagonists is followed by rapid distribution within the body. Dolasetron is rapidly eliminated ($t_{1/2\beta}$ <10 min) and metabolized to the active form, hydrodolasetron. A ubiquitous enzyme, carbonyl reductase, mediates the reduction of dolasetron to hydrodolasetron [Anzemet, 2005]. Hydrodolasetron is 70% bound to plasma protein and has a t1/2 β of approximately 7 h. It is predominantly metabolized by cytochrome P450 (CYP) CYP2D6 in the liver. Fifty-three percent of an administered intravenous dose of dolasetron is excreted unchanged in the urine [Anzemet, 2005; Ho and Gan, 2006].

The recommended adult dosage for oral Granisetron (Kytril) is 2 mg once daily or 1 mg twice daily in emetogenic chemotherapy and radiation. In the 2-mg once-daily regimen, two 1-mg tablets or 10 mL of granisetron oral solution (2 teaspoonfuls, equivalent to 2 mg) is given 1 hour before chemotherapy. In the 1 mg twice-daily regimen, the first1-mg tablet or 1 teaspoonful (5 mL) of granisetron oral solution is given 1 hour before chemotherapy, and the second tablet or second teaspoonful (5 mL) of oral solution, 12 hours after the first [Hsu, 2010]. Granisetron is also available in a transdermal delivery system. As with ondansetron, QT prolongation has been reported with Granisetron [Hsu, 2010]. Agents such as ondansetron and dolasetron that block sodium channels may produce QRS widening, and blocking potassium channels may lead to QT prolongation. Ondansetron and dolasetron may prolong QT intervals by up to about 5% [Boike et al., 1997]. Yavas and colleagues conducted a prospective study in efforts to determine acute effects of palonosetron on electrocardiographic (ECG) parameters in cancer patients [Yavas et al., 2011]. Although median QT min value was higher after palonosetron administration than before palonosetron administration, the difference was not statistically significant (p: 0.6) [Yavas et al., 2011].

Thus, if clinicians were concerned about initiating a 5-HT3RA in a patient with pre-existing cardiac issues, a QT interval near the upper limit of normal, and the

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risk of arrhythmogenic potential; then palonosetron may be the 5-HT3RA of choice coupled with cautious dosing, close and frequent clinical follow-up, and frequent electrocardiographic monitoring.

Granisetron is metabolized by the liver through N-demethylation, aromatic ring oxidation, followed by conjugation [Kytril, 2006]. The elimination half-life of granisetron is between 5 and 8 h. Unlike the other 5-HT3 receptor antagonists, granisetron's major route of metabolism is mediated by the P450 CYP3A isoenzyme [Ho and Gan, 2006]. Clearance is predominantly by hepatic metabolism. In normal volunteers, 11% of the oral dose is eliminated unchanged in urine, 48% as metabolites in urine, and 38% as metabolites in feces in 48 hours [Hsu, 2010].

Ondansetron has a short $t1/2\beta$ of approximately 3 to 5 h [Zofran, 2006]. Seventy to seventy-six percent of ondansetron is protein bound. It is extensively metabolized via CYP3A4 in the liver by the hydroxylation of the indole ring followed by glucuronide or sulfate conjugation [Ho and Gan, 2006; Zofran 2006].

5-HT3RA agents not available in the US include tropisetron, ramosetron, and for irritable bowel disease where diarrhea is the dominant symptom---cilansetron and alsoetron (alosetron was withdrawn from U.S. market in 2000 due to adverse effects) [e.g., ischemic colitis], and is only available through a restrictive Risk Evaluation and Mitigation Strategies (REMS) program to patients meeting certain requirements.

It is conceivable that simultaneous multiple routes of administration of 5-HTRAs may be beneficial under certain circumstances. Ryu and colleagues conducted a prospective, randomized, double-blind study was to compare the efficacy and tolerability of intravenous, oral, and the combination of oral and intravenous ramosetron for PONV prophylaxis in patients undergoing laparoscopic cholecystectomy [Ryu et al., 2011]. Patients scheduled for laparoscopic cholecystectomy were double-randomly allocated to 1 of 3 groups. Patients were randomly allocated to receive either 0.3 mg of intravenous ramosetron (group A), 0.1 mg of oral ramosetron (group B), or the combination of 0.1 mg of oral ramosetron and 0.3 mg of intravenous ramosetron (group C). All patients received standardized balanced anesthesia with desflurane and remifentanil. Postoperative nausea, retching, vomiting, pain, and adverse effects were assessed at 0 to 2, 2 to 24, and 24 to 48 hours after surgery. They found that the combination of 0.1-mg oral and 0.3-mg intravenous ramosetron was more effective than either 0.3-mg intravenous ramosetron or 0.1-mg oral

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ramosetron alone for the prophylaxis of nausea and vomiting after laparoscopic cholecystectomy during the first 24 hours after surgery [Ryu *et al.*, 2011].

Non-5-HT3RA agents may also have antagonist effects at 5-HT3 receptor. Metoclopramide possesses some weak antagonist effects at the 5-HT3R. Mirtazapine and olanzapine have significant 5-HT3RA properties. Galanolactone, a diterpenoid found in ginger, is a 5-HT3A and felt to be at least partially responsible for the antiemetic mechanisms of ginger [Huang *et al.*, 1991].

Genetic polymorphism in the cytochrome P450 monooxygenase system, drug efflux transporter adenosine triphosphate-binding cassette subfamily B member 1 and 5-hydroxytryptamine type 3 receptor subunits with differences in 5-HT3RAs interacting with different 5-HT3 receptor subtypes, also contribute to the interindividual variation in response to different 5-hydroxytryptamine type 3 receptor antagonists [Ho and Gan, 2006].

Kaiser *et al.* showed that patients who were ultrarapid metabolizers experienced more vomiting compared with extensive or poor metabolizers when given ondansetron and tropisetron in the treatment of chemotherapy-induced nausea and vomiting [Kaiser *et al.*, 2002]. This difference was predictably more pronounced for tropisetron than ondansetron, because tropisetron was primarily dependent on the CYP2D6 isoenzyme for metabolism [Ho and Gan, 2006].

The adenosine triphosphate-binding cassette subfamily B member 1 (ABCB1) drug transporter (also known as P-glycoprotein or MDR-1) is a transmembrane efflux pump in many tissues including the blood-brain barrier [Marzolini *et al.*, 2004]. Patients who were homozygous for the ABCB1 3435T allele responded better to antiemetic therapy compared with individuals who were heterozygous or homozygous for the ABCB1 3435C allele. This difference reached statistical significance in the granisetron-treated group [Babaoglu *et al.*, 2005].

Nausea and vomiting is among the most distressing symptoms to many patients. The release of serotonin may occur in a variety of medical conditions/interventions. Serotonin may contribute to nausea and vomiting via binding to the 5-HT3 receptor and in those states where this is a predominant factor, 5-HT3 receptor antagonists (5-HT3RAs) may be particularly effective as antiemetic agents.

Anticholinergic antiemetics (transdermal scopolamine)

The transdermal scopolamine delivery system (patch) was

designed to deliver a sustained, constant rate of delivery (steady-state flux) of scopolamine through intact skin [Transdermal scopolamine, 2006]. The scopoderm patches are circular (2.5 cm²) and 0.2 mm thick. They contain a 1.5-mg reservoir of scopolamine base plus a priming dose of 140 µg of scopolamine to accelerate the attainment of steadystate blood concentration [Pergolizzi et al., 2012]. The patch is designed for zeroorder delivery for a total release of 1.0 mg of scopolamine over a period of three days. The system consists of 4 layers. The first is an adhesive layer that sticks to the skin and contains the priming dose. There is an intermediate microporous polypropylene (rate-determining) membrane layer. The third layer is the scopolamine reservoir. The fourth layer is a backing of impermeable aluminized polyester film [Pergolizzi et al., 2012].

Scopolamine moves into and through the adhesive layers by passive diffusion at a rate determined by the characteristics of the intermediate membrane [Pergolizzi *et al.*, 2012]. Permeation is highest in the postauricular area (behind the ear), but there is large interindividual variation [Pergolizzi *et al.*, 2012]. Circulating plasma levels of scopolamine are detected within 4 hours of postauricular patch application with peak levels at about 24 hours [Pergolizzi *et al.*, 2012]. When the patch is removed, scopolamine plasma levels decline in exponential fashion, with a half-life of about 9.5 hours [Pergolizzi *et al.*, 2012].

Apfel and colleagues performed a systematic review and meta-analysis, and found transdermal scopolamine was associated with significant reductions in PONV with both early and late patch application during the first 24 hours after the start of anesthesia [Apfel *et al.*, 2010], and it appears that application of the patch may still diminish PONV even if applied 2 hours prior to surgery.

NK-1 receptor antagonists

Aprepitant, an oral NK-1 antagonist, is made of a morpholine core with two substituents (trifluromethylated phenylethanol and flurophenyl groups) attached to adjacent ring carbons, and one substituent (triazolinone) joined to the morpholine ring nitrogen [Hale *et al.*, 1998]. Its bioavailability is about 60-65% and it is primarily metabolized by CYP3A4 with minor metabolism by CYP1A2 and CYP2C19. Roughly 55% of metabolites are excreted in the urine and 45% of metabolites are excreted in the feces.

NK-1 receptor antagonists have to penetrate the bloodbrain barrier to access central NK-1 receptors in the brainstem emetic centers in order to be effective in preclinical models. Potent NK-1 receptor antagonists that did not cross into the brain were ineffective as antiemetics [Tattersall *et al.*, 2000]. NK₁-RAs competitively inhibit Substance P and are believed to curb nausea and vomiting centrally by halting neurotransmission within the CPG for vomiting [Saito *et al.*, 2003]. Substance P acting at central NK-1 receptors is likely one of the final common mechanisms involved in activation and coordination of the vomiting reflex [Hornby, 2001].

Apfel *et al.* [Apfel *et al.*, 2008] found that aprepitant reduced the incidence of postoperative vomiting in a pooled analysis of clinical trials comparing aprepitant to commonly utilized antiemetics. Darmani *et al.*, in preclinical models, demonstrated synergistic antiemetic interactions between serotonergic 5-HT3 and tachykininergic NK1-receptor antagonists [Darmani *et al.*, 2011]. NK-1 receptor antagonists can be utilized as part of a multimodal strategy to reduce nausea and/or vomiting in a variety of clinical settings.

In August 2010, a single-dose formulation of fosaprepitant (NK 1 Receptor antagonist) a prodrug of aprepitant for IV administration was approved in the European Union for use instead of the 3-day oral regimen of aprepitant, together with a 5-HT3 receptor antagonist and a corticosteroid. Additionally, in November 2010, the FDA approved a single-dose formulation, EMEND for Injection 150 mg, for patients receiving highly emetic chemotherapy. Other NK-1 antagonists that are in various stages of development include: casopitant [Ruhlmann and Herrsetedt, 2009], rolapitant [Gan *et al.*, 2011], netupitant [Stathis *et al.*, 2012], and vestipitant [Sabbatini *et al.*, 2010].

Summary

Nausea, vomiting and retching are among the worst of symptoms that patients may experience. Despite the existence of evaluation and management guidelines as well as many antiemetic agents, the clinical results of the treatment of nausea, vomiting and retching remain suboptimal. A greater appreciation of the neurotransmitters/ mediators that may contribute to nausea, vomiting, and retching in an individual patient, as well as the specific receptors/receptor subtypes where they act, will hopefully lead to improved patient outcomes.

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Dysphagia

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Introduction

Dysphagia in the palliative care setting is a particularly distressing symptom contributing to poor quality of life, malnutrition, possible aspiration and can ultimately shorten an already grim prognosis. Etiologies for dysphagia for palliative care patients include advanced neurologic and myogenic disorders, head and neck cancers causing oropharyngeal dysphagia and esophageal cancer. This chapter outlines the common causes of malignant dysphagia and appropriate patient assessment to guide palliation. Current palliation techniques for esophageal dysphagia are discussed however the optimal management remains complex and controversial with a lack of consensus on an ideal approach. Ultimately, the course of palliation must be individualized to the patient's medical condition, tumor characteristics and institutional expertise.

Overview

Definition and prevalence

Dysphagia is defined as the difficulty encountered in swallowing liquids or solids. This inability to appropriately transfer food can occur at the level of the oropharynx or the esophagus. An estimated 40% of institutionalized patients suffer from dysphagia [Brady, 2008]. Half of patients with head and neck cancers will report swallowing difficulties. Dysphagia remains the most common symptom for patients with esophageal cancer, increasing in severity with more advanced cancer stage. Patients with advanced neurological conditions such as Parkinson's disease, multiple sclerosis and stroke can have a prevalence of dysphagia ranging from 30-60% [Daniels, 2006]. In the palliative care setting treatment goals include alleviation of symptoms, prevention of recurrent aspiration, and maintenance of nutrition status.

Physiology

Swallowing phases are divided into the (I) oral preparatory phase; (II) oral swallowing phase; (III) pharyngeal phase and (IV) esophageal phase. The oral phases are voluntary and consist of food mastication, mixing with saliva and formation of an appropriately prepared food bolus. The food bolus is transferred from the oral cavity to the oropharynx by contraction of the tongue against the hard palate. Weakness of the tongue can cause spillage of bolus out of oral cavity or into the pharynx, posing an aspiration risk [Goyal and Mashimo, 2006]. The entry of the bolus in the oropharynx initiates the pharyngeal phase. Elevation and forward motion of the larynx prevents aspiration, the food bolus enters the upper esophageal sphincter (UES) with relaxation of the lower esophageal sphincter (LES) as well. Primary peristalsis propels the food bolus through the esophagus, and local esophageal distention triggers secondary peristalsis that begins at the point of distention and extends distally [Hirano and Kahrilas, 2012]. Transfer of bolus through the pharynx is typically completed in less than 1 sec and through the esophagus in 5-6 secs at a velocity of 3 to 4 cm/sec [Goyal and Mashimo, 2006].

Etiology of dysphagia in palliative care

Oropharyngeal dysphagia

Oropharyngeal dysphagia results from poor food bolus

Table 1 Dysphagia severity scales						
Name	Scale description	References				
Likert scale based on	5-point ordinal scale-this is a simple yet effective scale and is our preference in	Bergquist et al., 2005				
tolerance of different	characterizing esophageal dysphagia. 0, no dysphagia; 1, dysphagia to solids; 2,					
food consistencies	dysphagia to semi-solids; 3, dysphagia to liquids; 4, dysphagia to own saliva					
Mann assessment	24 skills related to motor and sensory components of swallowing are evaluated on	González-Fernández				
of swallowing ability	a 5- or 10-point scale. A total score over 200 is obtained	<i>et al.</i> , 2011				
(MASA)	In addition aspiration is clinically evaluated and rated					
Australian therapy	Evaluates the impact of dysphagia on a 5-point scale spanning three domains	Skeat and Perry, 2005				
outcomes measures	including (I) activity restriction (II) participation limitation and (III) distress well being					
(AusTOMs)						
Dysphagia outcome	Uses a 7-point scale to objectively characterize the functional severity of	O'Neil <i>et al</i> ., 1999				
and severity scale	dysphagia					

formation, deficiencies in mastication mechanisms, and/or inefficient transferring of the bolus to the oropharynx. Oropharyngeal dysphagia in the palliative setting may be a result of non-degenerative conditions (stroke, traumatic brain injury), degenerative neurogenic diseases (Parkinson's disease, multiple sclerosis, dementia) or myogenic disorders such as amyotrophic lateral sclerosis (ALS). Such patients require multidisciplinary management with the close involvement of speech therapists for rehabilitation, the neurologist for disease specific management and the palliative care physician. Patient assessment for oropharyngeal dysphagia and nutritional supplementation is discussed below however detailed therapeutic management is beyond the scope of this chapter.

Structural causes of oropharyngeal dysphagia include head and neck cancers. In addition to the symptoms induced by the primary tumor, therapeutic management of these conditions may further complicate the situation, as both radiation and surgery frequently result in significant dysphagia.

Esophageal dysphagia and esophageal cancer

Esophageal dysphagia occurs due to mechanical obstruction or abnormal motility. In the palliative care setting, the most common etiology of esophageal dysphagia is esophageal cancer.

Squamous cell carcinomas or adenocarcinomas of the esophagus account for 95% of malignant esophageal tumors [Daly et al., 1996]. Squamous cell carcinomas are generally located in the proximal or mid-esophagus, and are the primary histologic type in Asia with smoking and alcohol as the primary risk factors. Adenocarcinomas are more prominent in North America with a rapidly increasing incidence observed in the past several decades. These tumors

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are located distally near the gastroesophageal junction and associated with risk factors including gastroesophageal reflux disease (GERD), alcohol and smoking.

The aggressive nature of the cancer and vague symptomology results in almost one in two patients presenting with inoperable disease with an average life expectancy of 5-6 months [Siegel et al., 2012]. Rapid and optimal palliation of the resultant dysphagia becomes of key importance in this patient population in order to preserve quality of life and nutritional status.

Patient assessment

History

A complete patient history should reveal severity of dysphagia, the nature of the pathology (obstructive vs. nonobstructive), type of dysphagia, presence of accompanying symptoms and evidence of aspiration.

Use of a standardized scoring classification greatly aids in the management of patients with dysphagia, as response to treatment can be assessed objectively. Multiple dysphagia scales are featured in the literature with the most commonly applied bedside tools described in Table 1. Use of different scoring systems varies with institutional preference, healthcare provider type (physician, speech therapist), required ease of applicability (bedside, online, in conjunction with radiological imaging) and underlying disease (stroke vs. malignancy). We find most useful a simple 5-point likert scale; 0, no dysphagia; 1, dysphagia to solids; 2, dysphagia to semi-solids; 3, dysphagia to liquids; 4, dysphagia to own saliva [Bergquist et al., 2005]. Obstructive

Dysphagia

pathology results in dysphagia to solids in the initial stages with progression of disease resulting in dysphagia to liquids as well. This is in contrast with advanced neurogenic or myogenic disorders that result in equal dysphagia for liquids and solids generally.

Distinguishing between oropharygeal and esophageal dysphagia guides palliation however they are not mutually exclusive and components of both may be present in some cases. Patients with oropharyngeal dysphagia report difficulty with the initiation of swallowing with associated symptoms such as coughing, choking, and regurgitation. In contrast patients with esophageal dysphagia report a sensation of an impacted food bolus and can often localize the lesion with good accuracy and must be questioned about the anatomical site [Logemann, 1983].

A complete history also includes enquiries about anorexia, weight loss, chest pain, odynophagia and bone pain, all of which are ominous for an advanced oncologic process. Tumor invasion into the recurrent laryngeal nerve can cause hoarseness and vocal cord paralysis [Maish, 2012]. Symptoms of aspiration (coughing upon food/liquid intake) and sequelae (episodes of pneumonia) of aspiration must also be further investigated although aspiration episodes may also be silent [Smith, 2008]. Details of completed treatments for the underlying pathology such as chemotherapy, radiotherapy and surgeries will also guide appropriate palliation of dysphagia.

Physical exam

Physical exam for patients suffering from dysphagia aims to differentiate between oropharygeal and esophageal dysphagia, to evaluate the risk of aspiration, and to determine the nutritional status of the patient. The need for further detailed assessment by a speech language therapist must also be considered.

Examination includes inspection of the oropharyngeal cavity for masses, presence of candidiasis, saliva secretion and status of dentition. Oral pharyngeal and/or esophageal candidiasis are encountered in patients receiving antibiotics, chemotherapy, radiation therapy to the head and neck and contribute to dysphagia, odynophagia and poor nutrition [Epstein *et al.*, 1993]. Cranial nerve examinations should assess strength of facial muscles for mastication and strength of tongue movements. Up to 35% of head and neck cancer patients can develop trismus due to inflammation and fibrosis of the mastication muscles after radiotherapy [Sciubba and Goldenberg, 2006]. Important lymph node basins to be examined include both cervical and supraclavicular nodes which may be enlarged in head and neck and esophageal cancers.

Evaluation of aspiration can be performed with a speech and language therapist through a formal test with liquids and solids of different consistencies. Bedside evaluation with 10 mL of fluid ingestion while assessing for cough and monitoring pulse oximetry for desaturations has also been reported for preliminary screening [Smith *et al.*, 2000]. Another potential investigation utilizes swallowing of liquids or solids labeled with radiopharmaceuticals and imaging with a gamma camera.

Nutritional status as ascertained by general appearance, weight and BMI should be documented in order to establish the patient's baseline and assess progress with palliative treatment.

Investigation

For esophageal dysphagia the diagnosis of an advanced esophageal malignancy will likely already be established in the palliative care setting. Initial diagnosis and histologic confirmation is obtained through upper endoscopy, however repeat endoscopy is frequently required in order to plan and perform other therapeutic maneuvers discussed below. Even in the case of a known metastatic esophageal malignancy in which staging investigations may have previously been performed, progressive symptoms of dysphagia may require additional investigations including repeating the CT scan, barium contrast studies, or endoscopy in order to best assess the optimal mode of palliation. For patients with upper esophageal obstruction, a bronchoscopy is frequently warranted to evaluate the status of tracheal involvement which may complicate the use of radiotherapy as a palliative modality [Riedel et al., 1998].

Patients with metastatic and locally advanced inoperable esophageal tumors and those whose overall medical status precludes surgery are the core population referred to palliation of their dysphagia [Edge *et al.*, 2010].

Management

Nutritional support

The decision to provide additional nutritional support is a careful consideration. The priorities for patients with a very short prognosis (e.g., few days) are to maximize comfort and control pain. Dehydration and feeding do not contribute



Figure 1 Self-expanding metal stent (SEMS) insertion for an obstructing esophageal cancer. (A) Obstructing esophageal tumor; (B) Luminal patency obtained after SEMS insertion; (C) Tumor overgrowth at distal end of stent.

to distress in the final moments of end of life care and discussion with the family is essential for the understanding of this difficult issue [McCann *et al.*, 1994; Parkash and Burge, 1997].

For patients requiring nutritional support as a bridge to palliation of dysphagia, feasible options include nasogastric feeding, and gastrostomy tube insertion. Jejunostomy tubes are uncommon in the palliative setting due to their higher complication rate and the lack of indication for post-pyloric feeding. Parenteral nutrition is also not routinely employed due to the associated complications and the presence of a functioning gut.

Nasogastric feeding is an inexpensive, easily performed temporizing method for nutritional supplementation over a short course. Enteric feeding tubes of finer bores (3.5-12 F) are more comfortable and can be used longer than the standard bore nasogastric tube (16-18 F). Postpyloric placement of feeding tubes is preferred to decrease the risk of aspiration. Depending on tumor bulk, some patients with esophageal cancer may have near complete obstruction preventing insertion of even small bore tubes. In such instances, either endoscopic placement or other supplementation options must be explored.

Gastrostomy tube insertion can be performed under conscious sedation and local anesthetic as an outpatient procedure. Tube insertion is completed under radiologic or endoscopic guidance. In patients with near complete obstruction, radiologically guided tube insertions are preferable. The use of percutaneous endoscopic gastrostomy (PEG) tubes are complicated given the difficulty of passing the large caliber gastrostomy tube though an obstructed esophagus with an increased risk of perforation. Minor complications of gastrostomy tubes include local wound infection, tube leakage and tube clogging. Major complications include accidental gastrostomy removal (if newly inserted PEG tubes may lead to free gastric perforation), iatrogenic esophageal or gastric perforation, necrotizing fasciitis (rare), and buried bumper syndrome [DeLegge, 2012; Keung *et al.*, 2012; Margolis *et al.*, 2003].

Esophageal dilation and stenting

Simple esophageal dilation is popular for benign esophageal disease such as strictures but rarely employed for malignant dysphagia due to its short-lived relief of days to weeks, requirement for repeated dilations, and high risk of perforation [Papachristou and Baron, 2007]. Currently self-expanding metal stents (SEMS) are the most commonly used for esophageal stenting and have replaced their predecessor—the fixed diameter plastic intubation stents which was associated with high rates of perforation and haemorrhage [DePalma, 1996]. Self-expanding plastic stents are currently available but have considerably high migration rates compared with SEMS and therefore not popular for palliation purposes [Verschuur *et al.*, 2008].

SEMS are available in a variety of lengths, diameters and alloys and can be fully covered, partially covered or uncovered (*Figure 1*). Fully covered stents have higher rates of stent migration however are most resistant to tumor ingrowth and subsequent repeated obstruction as compared with their uncovered counterpart; as such, their use is primarily for benign indications such as esophageal perforation or benign strictures. Partially covered stents have uncovered ends therefore are less likely to migrate but



Figure 2 Progression of DS over time in the various treatment groups. Rapid relief of dysphagia is noted within two weeks of treatment initiation, whereby 85% of patients were able to achieve a DS =0 or 1. In Brachytherapy or EBRT, an initial lag period of 6-8 weeks is observed before effective relief of dysphagia is noted. However, the percentage of patients who have achieved a DS ≤ 1 at 10-week follow-up is higher in brachytherapy (85%) and EBRT (90%), than in endoluminal stent group (72%). Reprinted with permission from Hanna *et al.*, 2012.

still resistant to ingrowth of tumor [Kim and Yang, 2012]. Partially covered self-expanding metallic stents are thus preferred for the palliation of malignant dysphagia.

Esophageal stenting can provide rapid and effective (85-100%) relief from dysphagia for esophageal tumors and can also be used for closing malignant fistulas. In addition to improving overall quality of life, stenting has been associated with an increase in appetite and overall wellbeing [Madhusudhan *et al.*, 2009]. However the results rarely last beyond 5-6 months and tumor ingrowth causes recurrent obstruction and dysphagia and stent migration in approximately 30% of cases [Hanna *et al.*, 2012]. Other reported complications of stent placement include perforation, bleeding and aspiration [Siersema *et al.*, 2001]. In an effort to capture the rapidity of symptom relief from stent insertion yet acquire a longer relief period, combined modality treatments have emerged and are discussed further below.

There are some caveats to stent insertion, and they cannot be employed in all patients. A certain amount of tumor burden is required in order to secure the stent in place. Thus some patients with early, yet symptomatic, dysphagia may not be suitable for stent insertion due to the high risk of migration. Furthermore, stent insertion for extreme proximal, or distal, tumors is frequently not feasible. Stent insertion for dysphagia due to cervical esophageal tumors, is complicated by the close proximity of the cricopharynx and the mucosal sensitivity of this area. Most patients are unable to tolerate a stent with the proximel end in the cricopharynx due to a constant gaging reflex. Similarly, dysphagia due to gastric cardia or sub-cardia tumors extending proximally into the esopahgus are difficult to manage with endoscopically placed stents. The stent, when placed across the esophagogastric junction, may assume a diagnonal or transverse orientation abutting against the greater curvature and thus further exacerbating obstruction as well as representing a risk for both bleeding and perforation. Furthermore, stents placed in this location may induce significant acid reflux. Attempts to alleviate this issue with valved stents has been met with only moderate success.

Radiation therapy

Radiation therapy for palliation of esophageal dysphagia consists of external beam radiation therapy (EBRT) or endoluminal brachytherapy and can provide longer sustaining symptom relief as compared with stenting (*Figure 2*). Multifractionated EBRT is not often used in isolation for inoperable esophageal cancer because if chemotherapy can be tolerated, the combination yields longer progression free survival [Herskovic *et al.*, 1992]. This multimodality treatment is discussed later in the chapter. Nevertheless, hypofractionated EBRT alone has been demonstrated to relieve dysphagia effectively [Caspers *et al.*, 1988] but its administration still requires multiple treatments, frequently between 2 and 10 fractions, and significant commitment, a challenge for palliative care patients.

Brachytherapy enables the delivery of high dose of radiation to a localized area via a trans-oral catheter while

minimizing exposure to surrounding unaffected tissues. High dose intraluminal brachytherapy delivers significant radiation in short application time (minutes) and can be completed in 1 or 2 fractions. Low dose brachytherapy delivers radiation slower over a period of 24-48 hrs and therefore requires more catheter insertions. Single dose brachytherapy is preferred for palliation due to convenience and effectiveness [Sur et al., 2002]. Randomized controlled trials comparing SEMS and brachytherapy have demonstrated a superior score for stenting in the first month, with equalization of both therapies at one month. By 150 days post-treatment start, brachytherapy provided better relief and quality of life as compared with stents [Homs et al., 2004]. Therefore, brachytherapy affords convenience and longer duration of palliation. A major drawback remains a greater delay to the start of treatment compared with stenting and a long time lag between implementation of treatment and relief of symptoms [Hanna et al., 2012]. Complications of radiation therapy are encountered in 10-40% of the cases and include esophagitis, stricture formation and trachea-esophageal fistula.

Multimodal therapy

Definitive chemoradiation therapy is currently the standard of treatment for non-operable esophageal cancer following the results of the landmark RTOG 85-01 trial. The two arms of this trial consisted of 5-FU and cisplatin chemotherapy in addition to radiotherapy or radiotherapy alone. The chemoradiotherapy arm had better median survival at 14 months and a 27% 5-year survival vs. 9 months and no patients alive at five years for the radiotherapy group alone (al-Sarraf et al., 1997). In addition to survival benefits, patients with significant dysphagia also received adequate relief of symptoms with this combined modality approach. Reported median time to observe any improvement is two weeks with maximal improvement occurring in an average of two weeks [Coia et al., 1993]. A major limitation for definitive chemoradiation includes the patient's ability to tolerate the chemotherapy regimens. The second limitation includes the prolonged time to dysphagia relief, which may be unacceptable in patients with very short prognoses or severe malnutrition, warranting therapies with more rapid relief of symptoms.

An alternative multimodality therapy for patients seeking rapid and long lasting dysphagia relief without chemotherapy is the combination of stent placement and brachytherapy, however this protocol is still in the experimental stages. A recent pilot study demonstrated stent and brachytherapy to be a safe and feasible combination with only minor complications [Bergquist *et al.*, 2012]. However further trials are required to compare this multimodal regimen with outcomes derived from stent alone and brachytherapy alone in order to definitely evaluate its effectiveness.

Trials have also explored the combination of EBRT and brachytherapy with preliminary results indicating an absolute increase of 18% in dysphagia relief experience, no difference in toxicities as compared with brachytherapy arm alone and no survival advantage [Rosenblatt *et al.*, 2010].

Other endoscopic methods

In addition to stenting, a variety of other endoscopic approaches have been developed for patients that are not candidates for chemoradiation. No one approach is superior and utilization should be tailored to patient and tumor characteristics. In general, these additional therapies have fallen out of favor in light of the effectiveness and ease of insertion of the newer generation stents.

Photodynamic therapy (PDT)

Although PDT is best described for Barretts esophagus with high-grade dysplasia, this modality has been described for inoperable carcinoma and as salvage therapy after stent blockage. The first step in the process is intravenous injection of a photosensitizing agent (Profimer sodium), which selectively accumulates in the tumor bed. At 48 hrs after injection, endoscopy is performed with exposure to laser light (monochrome light of 630 nm) over a 20-30 min session resulting in ablation of the targeted malignant cells through tissue necrosis. A repeat endoscopy is performed after 2-3 days to debride necrotic tissue and for a second light application with relief of symptoms observed within 5-7 days [Christie et al., 2005]. In comparison with laser Nd:YAG, PDT may offer marginally better relief of dysphagia especially for proximally located obstructions [Lightdale et al., 1995]. The use of PDT has been limited by the fact that patients need to avoid sunlight for one month after treatment or risk having severe cutaneous burns. Other complications include perforation and transient worsening of dysphagia due to inflammation [Marcon, 1993; Prosst et al., 2003]. Particular caution must be exercised in patients with previous radiation exposure as an increase in complication severity such as trachea-esophageal fistulas and hemorrhage have

Dysphagia

been observed [Sanfilippo et al., 2001].

Laser

Neodymium-yttrium-aluminum-garnet (Nd-YAG) laser treatments are delivered through flexible endoscopy in an average of 3-4 treatments every 24-48 hrs in order to complete fulguration of tumor [Haddad and Fleischer, 1994]. Relief of dysphagia is achieved in over 70% of patients however since it is short lasting in duration multiple repeat treatments may be required. Exophytic tumors, short lesion length (<5 cm) and lack of tortuous segments are positive predictors of success with this technique [Schembre, 2001]. The major complications reported are esophageal perforation and tracheoesophageal fistula occurring in approximately 5% of cases [Dallal *et al.*, 2001].

Argon plasma coagulation (APC)

APC is a technique initially used widely in open surgery and currently gaining popularity in endoscopy. Its hemostatic and tissue ablative properties make it particularly suitable for bleeding obstructive esophageal tumors causing dysphagia. Ionization of argon gas is achieved through a high voltage current and applied to the tumor with a notouch technique using a flexible endoscopic probe resulting in tissue coagulation and necrosis. Because this debulking procedure has a short symptom relief period it has been studied in combination with other procedures such as brachytherapy and PDT resulting in longer alleviation of symptoms. A randomized control trial demonstrated the first dysphagia recurrence was observed at a median time of 88 days for APC + brachytherapy group, 59 days for the APC+PDT group and 35 days for the APC group [Rupinski et al., 2011]. The major complication associated with APC remains esophageal perforation with a risk of up to 8% in some studies [Heindorff et al., 1998].

Other endoscopic interventions

Absolute alcohol injection into the tumor is an inexpensive ablative technique performed under endoscopy. It can also be utilized in treating stent obstruction due to tumor overgrowth [Ozdil *et al.*, 2010]. Its widespread use is limited due to its short duration of action, need for multiple treatments and complications such as fistulas, perforation and mediastinitis [Chung *et al.*, 1994]. Chemotherapy injection into the tumor bed in the form of cisplatin/ epinephrine gel is another investigative technique currently underway [Harbord *et al.*, 2002], but as with the other ablative therapies, it is unlikely to offer a long-term benefit.

Medications

There is no single medication that can be administered to relieve symptoms from malignant dysphagia. Oropharygeal and esophageal candidiasis can develop in the palliative care setting worsening underlying dysphagia by adding a component of odynophagia. For fungal infection restricted to the mouth, nystatin swish and swallow at a dose of 400,000 to 600,000 units four times daily is a first line treatment. However, either the patient's inability or fungal resistance may require oral fluconazole (1st dose of 200 mg, 100-200 mg daily) with 90% effectiveness [Finlay *et al.*, 1996]. Esophageal candidiasis requires systemic therapy with either oral fluconazole, or in the presence of resistance, other azoles such as voriconazole, posaconazole or itraconazole although the side effect profile for these medications is higher.

Chemotherapy or radiation induced mucositis of the mouth is a self-limited side-effect of these treatments for head and neck cancer patients. In addition to meticulous oral hygiene, cocktails of topical anti-inflammatories and analgesics are used to relieve symptoms and aid in dysphagia. These cocktails often referred to as "magic or miracle" mouthwashes can consists of lidocaine, diphenhydramine, maalox, dexamethasone or antibiotics and vary with institution [Galloway and Robert, 2012]. These formulae can be effective in addressing the odynophagia associated with treatment related mucositis, but clearly do little to aid in the mechanical obstruction and dysphagia.

Summary

Dysphagia for the palliative care patient is a source of distress and agony that compromises nutrition and quality of life and possibly shortens survival. Etiologies for oropharnygeal dysphagia range from advanced neurologic and myogenic disorders to head and neck cancers. Advanced inoperable esophageal cancer is the most common cause of esophageal dysphagia in the palliative setting. Management of dysphagia is a multidisciplinary initiative beginning with a complete patient assessment delineating extent and type of dysphagia, associated symptoms, presence of aspiration and expected course of disease and expectations. The optimal palliation of esophageal dysphagia is complex lacking consensus. However, at present, given the technical ease of insertion, esophageal stenting provides the most rapid relief of dysphagia, however recurrence of dysphagia does occur in a significant proportion of patients. Furthermore,

in certain situations (extreme proximal or distal esophageal tumors, low burden tumors) stent placement is not feasible or less desirable. In these circumstances, external beam radiotherapy or brachytherapy, although less rapidly effective, are ideal and provide longer symptom relief. Multimodality treatments such as combination of stenting and brachytherapy are still in investigative phases but hold promise. Other endoscopic palliative techniques including alcohol injection, APC, laser Nd-YAG and PDT have fallen out of favor given the rapidly effective resolution of dysphagia imparted by the newer generation self expanding metallic stents. As with all aspects in the management of this complex patient population, the optimal palliation procedure for each patient will be influenced by patient characteristics, tumor properties, institutional facilities and physician expertise.

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Hiccups

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Introduction

Hiccups are caused by an abrupt, involuntary spasm of the diaphragm and intercostal muscles followed by sudden closure of the glottis. This produces the characteristic "hic" sound. Hiccups are usually self limited and benign in nature, and they occur both in the adult and pediatric population. They are considered persistent if they last more than 48 hours, and intractable if they last more than two months [Souagjian and Cain, 1968]. In the latter case, they can be a source of significant patient discomfort, dehydration, anxiety, pain, insomnia, exhaustion and even death [Howard, 1992; Marinella, 2009].

Pathophysiology

The pathophysiology of hiccups remains complex and not very well understood. Historically, they were initially attributed to phrenic nerve irritation by Shortt in 1833 [Reddy et al., 2007]. Currently, it is believed that the pathophysiology involves an arc reflex with three components: the afferent pathway is mediated by the vagus, the phrenic nerves and the sympathetic chain, which convey somatic and visceral sensory signals. The central hiccup center involves the brain stem respiratory center, the reticular activating system in the medulla oblongata, the hypothalamus, and the temporal lobes [Marinella, 2009; Becker, 2010]. Both dopamine and gammaaminobutyric acid (GABA) seem to be the neurotransmitters that are centrally implicated in the hiccup process [Becker, 2010]. The efferent pathway travels within the phrenic nerve to the diaphragm and accessory nerves to the intercostals muscles. Interestingly, hiccups involve unilateral contraction of the left hemidiaphragm in approximately 80% of cases, which has important therapeutic implications as we discuss later [Tegeler and Baumrucker, 2008; Samuels, 1952]. The

frequency of hiccups ranges from 4-60/minute, with some intraindividual variability [Samuels, 1952; Souajian and Cain, 1968]. Even though intractable hiccups affect both genders, there seems to be a slight male predominance, especially in in the cancer population [Takiguchi *et al.*, 2002].

Etiology

Hiccups can be elicited by any inflammatory, infectious or neoplastic process that affects one of the three arc reflex components, and can originate from central or peripheral pathways. Etiologies of hiccups are quite extensive and include benign entities such as stomach distention, sarcoidosis or cerebrovascular accidents, especially in the medulla. Hiccups can also be iatrogenic and occur after surgical interventions such as coronary bypass grafting or pericardial window for drainage of effusion. Cancer patients can have hiccups due to their underlying malignancy, whether it consists of a malignant effusion or a tumor infiltrating the diaphragm, the vagus or phrenic nerves. They can also experience hiccups from associated metabolic derangements, ongoing chemotherapy, or treatment related infections. A list of common etiologies for hiccups is presented in Table 1.

Evaluation of the patient

All patients require a thorough history and physical examination in attempts to identify the onset, duration, severity, effect on quality of life, and ultimately the etiology of the hiccups. The clinician must also differentiate between acute, persistent, and intractable hiccups since this will influence the type and urgency of treatment. The patient should be questioned regarding the variability in

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Table 1 Etiologies of hiccups.	Table 1 (continued)
Malignancy	latrogenic
Esophagogastric cancer	Surgical procedures (coronary bypass, thoracic or upper
Lung cancer	abdominal procedures/pericardial window, diaphragm
Lymphoma	surgery, foregut surgery)
Pancreatic cancer	Epidural injections with local anesthetics
Renal cancer	Medications: dexamethasone, diazepam, opioids,
Liver metastasis	antibiotics, barbiturates, chemotherapy
Hepatoma	Psychogenic
Colon cancer	CNS, central nervous system.
Leukemia	
Metabolic disorders	symptoms with position, recumbency, respiratory cycle
Hyponatremia, hypokalemia, hypocalcemia	and relationship to eating. A history of malignancy and
Renal failure	or chemotherapy is often encountered, and constitutional
Uremia	symptoms including weight loss, fatigue, fevers, and night
Uncontrolled diabetes mellitus	sweats should be investigated. It is also important to inquire

Hypoadrenalism

CNS pathology

Brain tumors
Stroke
Hematoma/cerebral hemorrhage
Encephalitis/meningitis
Brain abscess
Cardiovascular disorders
Myocardial ischemia/infarction
Pericardial effusion/pericarditis
Thoracic/pulmonary disorders
Pneumonia
Pleural effusion/pleuritis
Thoracic herpes zoster
Mechanical ventilation
Mediastinal lymphadenopathy or other tumor
Gastrointestinal disorders
Erosive esophagitis
Infectious esophagitis (e.g., herpes simplex, cand species)
Peptic ulcer disease
Gastric distention from food, liquid, air, endoscop
Gastric outlet or small bowel obstruction
Pancreatitis
Ascites
Cholecystitis
Subdiaphragmatic abscess

symptoms with position, recumbency, respiratory cycle and relationship to eating. A history of malignancy and/ or chemotherapy is often encountered, and constitutional symptoms including weight loss, fatigue, fevers, and night sweats should be investigated. It is also important to inquire whether the patient can sense the hiccups predominately occurring on one side or the other, or if one side is felt to be more involved. This is particularly important when considering an interventional procedure. The severity of the symptoms is paramount to assess, since even short duration hiccups can have a devastating effect on quality of life. In fact, severity is frequently exacerbated by large amplitude hiccups, higher frequency and a continuous pattern. Patients with severe symptoms may justify urgent evaluation in the hospital setting.

All patients who present with hiccups require routine blood tests and at least a chest X-ray to rule out a thoracic mass. Computed tomography (CT-SCAN) of the neck, chest and upper abdomen is often warranted, especially in the case of severe and/or persistent hiccups, or in the presence of constitutional symptoms. CT-SCAN is particularly useful to investigate the presence of pleural effusion, ascites, mediastinal disease possibly involving the phrenic nerves, tumor invasion of the diaphragm, etc. In our experience, fluoroscopy can also help assess the symmetry or asymmetry of the hiccups and the differential involvement of each hemidiaphragm. This can allow treating the originating side first, if there is any. An upper endoscopy may be warranted if esophagitis is suspected, and a bronchoscopy in patients with respiratory symptoms or evidence of pulmonary lesions on imaging studies. An electrocardiogram is warranted to rule out an underlying myocardial ischemia.

Treatment

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Transient hiccups are usually self limited and do not need

Table 1 (continued)

Hiccups

a specific treatment. Management of chronic and/or debilitating hiccups should be first directed at identifying and treating the underlying cause (i.e., cerebrovascular ischemia, diaphragmatic tumor, stopping the offending medication). Many pharmaceutical and non-pharmaceutical therapeutic options are proposed in the literature with variable efficacy and will be discussed next. However, no strong recommendation can be drawn due to the lack of compelling scientific evidence and the overall paucity of data.

Non pharmacologic remedies

Many of these remedies would have already been used by patients prior to presentation to a clinician and include breath holding, drinking of cold water, re-breathing in paper bag, swallowing granulated sugar, etc. Less frequently known techniques outside of health professionals include vagal maneuvers, carotid massage, and gentle orbital pressure. While these approaches may be successful in acute hiccups they are generally ineffective in persistent or chronic hiccups. Therefore, initial treatment by clinicians is typically pharmacologic and is discussed further below.

The most studied non pharmacologic treatment for persistent and chronic hiccups is the use of acupuncture. A recent review article by the Cochrane Collaboration [Moretto et al., 2013] evaluated four randomized controlled studies of acupuncture in the treatment of persistent and chronic hiccups [Bao et al., 2003; Han, 2006; Jiang et al., 2002; Wang, 2011]. Each study demonstrated a reduction in hiccups, but the authors noted that all four of them had a high risk of bias, did not compare the intervention with placebo, and failed to report side effects or adverse events for either the treatment or control groups. Their conclusion was that acupuncture may be effective but the results need to be viewed with caution. Furthermore, it should be noted that all four publications were performed in regions of the world where acupuncture is a frequently employed tool with wide availability and expertise.

Pharmacologic treatment

While there are many case reports or case series of successful treatment of prolonged hiccups with medications, few if any randomized study evaluating pharmacologic treatments exists. Chlorpromazine is to date the only Food and Drug Administration approved medication to treat chronic or persistent hiccups. It continues to be the drug of choice for the treatment of hiccups in emergency room settings. Its side effects are quite numerous though and include sedation, extrapyramidal symptoms, confusion and hypotension [Friedman, 1996]. Gabapentin is an antiepileptic drug that blocks neural calcium channels increasing the release of GABA, which may modulate diaphragmatic excitability [Porzio et al., 2003; Tegeler and Baumrucker, 2008]. It was reported successfully in the treatment of persistent hiccups with very few side effects [Porzio et al., 2003; Alonso-Navarro et al., 2007]. Its pain modulating effects makes it even more attractive in the management of cancer or terminally ill patients with neuropathic pain. Another GABA derivative, baclofen, has also been reported to successfully treat hiccups in a doubleblind randomized placebo controlled trial [Ramirez and Graham, 1992]. In this study Ramirez and Graham showed that baclofen increased the hiccup free period by 69% at a dose of 15 mg/day and by 120% at 30 mg/day, even if it did not completely eliminate them compared to the placebo. Baclofen was also shown to effectively treat hiccups due to CNS tumors [Tay and Yadav, 2010]. However, significant side effects of baclofen include nephrotoxicity and renal failure, especially in older patients [Chou et al., 2006]. Other categories of drugs include beta blockers, such as carvedilol, a potent non cardioselective agent which suppressed a 2-year bout of hiccups in a patient with tardive dyskinesia [Stueber and Swartz, 2006]. A potential mechanism of action is antagonism of the sympathetic component of the afferent hiccup arc. A serotonin (five hydroxytryptophan) agonist, tandospirone, showed promising results in the treatment of stroke related hiccup, through inhibition of central phrenic nerve activity [Takahashi et al., 2004]. Even though benzodiazepines such as valium can cause hiccups, midazolam was successfully used to treat intractable hiccups [Moro et al., 2005; Wilcock and Twycross, 1996]. Prokinetic agents were traditionally used to treat hiccups by avoiding or improving stomach distension, a known predisposing factor. Other miscellaneous drugs that have been successfully used to treat hiccups include calcium channel blockers, antidepressants and lidocaine [Alderfer and Arciniegas, 2006; Wilcox et al., 2009; Dunst et al., 1993]. The latter can decrease neuronal excitability by blocking sodium channels and stabilizing the cell membrane [Landers et al., 2008; Cohen et al., 2001]. General anesthesia has also been used in the treatment of persistent hiccups; Lierz et al. reported a case of persistent hiccups which was successfully treated with general anesthesia where the patient was given paralytic agents and positive pressure ventilation via face mask for 15 minutes [Lierz and Felleiter, 2002].

Interventional treatment

Procedural based intervention is indicated when symptoms are severe and other modalities have failed. The treatment can focus on the underlying cause, if any is found. This may include resection of an intrathoracic mass (schwannoma, goiter), treatment of underlying lymphoma, drainage of pleural effusion or ascites.

Cervical blockade can be used as an adjunct to surgical intervention in the above cases or if no identifiable cause is found. Ultrasound guided blockade of phrenic nerve has been reported in the treatment of chronic hiccups. Calvo and colleagues administered 4 cc of 1% lidocaine plus 40 mg of triamcinolone solution via ultrasonographic guidance to the cervical phrenic nerve to five cancer patients with intractable hiccups and reported persistent resolution in three of them, without any adverse effects [Calvo et al., 2002]. Two patients recurred and were retreated leading to persistent resolution in one patient and reduction in severity in the fifth and last patient. Many other case reports or case series of varying techniques for cervical phrenic approaches have been described with good success [Michálek and Kautznerová, 2002; Kang et al., 2010; Bertini et al., 2012]. Transesophageal pacing of the diaphragm has also been described [Andres, 2005]. These procedures should be done unilaterally to avoid the risk of bilateral phrenic injury or malfunction.

In the rare cases when the above approaches have failed or when symptoms recur, other surgical approaches have been described including surgical transection, clipping or direct injection of the phrenic nerves. These procedures can be performed through a transcervical approach at the level of the scalene muscle, or a transthoracic one using thoracoscopy [Morgan *et al.*, 2003; Kim *et al.*, 2013].

Summary

Persistent and/or chronic hiccups is a serious condition that can dramatically affect quality of life and be debilitating. When patients seek medical assistance, the clinician must conduct a thorough evaluation in attempts to assess the physiologic impact of hiccups, identify the cause and rule out a specific underlying pathology. Initial management should be directed at symptom control and treatment of the underlying cause, which in certain cases could be as simple as discontinuation of the offending medication. Although there is no strong data to support any single approach or algorithm to treat these patients, it is reasonable to start with the lowest risk procedures. Once simple nonpharmacologic attempts have failed, pharmacologic agents should be employed and these typically include chlorpromazine, baclofen or gabapentin, used separately or in combination, based on patients' co-morbidities. Acupuncture may be of value, but its efficacy is not very well established. If the hiccups persist, based on limited data, injection of the phrenic nerve at the level of the scalene muscle is appropriate, simple, and safe. Ultrasound guidance is typically used and an anesthesiologist/pain specialist is the most qualified to perform these procedures. Ultimately, in the rare situations when all else has failed, surgical intervention may be used to interrupt the phrenic nerve either temporarily or permanently.

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Constipation/diarrhea

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Introduction

Constipation and diarrhea are common symptoms in palliative medicine that could have a significantly negative impact on the quality of life of patients suffering from serious and chronic illnesses. A common risk factor for constipation in the setting of palliative care is the use of opioid analgesics [Caraceni et al., 2012; Pergolizzi et al., 2008; Prommer, 2011; Thomas et al., 2008a]. Opioid-induced constipation (OIC) and narcotic bowel syndrome (NBS) are two preventable conditions caused by opioids that should be considered when evaluating patients with constipation in this setting. Diarrhea, although less common than constipation, is seen in about 10% of patients, and can lead to serious fluid and electrolyte disturbances, and nutrient deficiencies [Fallon and O'Neill, 1997]. The most common causes of diarrhea in palliative care are laxative use, side effects of medications, radiotherapy, and specific disease processes, including AIDS/HIV infection, enteric infection, pancreatic and biliary conditions, inflammatory bowel disease, and celiac disease. This chapter provides an overview of drug-related risk factors, frequency and clinical characteristics, and therapeutic options for the management of constipation as well as diarrhea in the context of palliative medicine.

Risk factors for constipation

Opioid effects in the colon result in reduced motility and decreased propulsive migrating contractions, and an increased risk of constipation, acute abdomen, paralytic ileus, and obstruction. OIC is a direct consequence of drug binding to peripheral *mu* receptors located in the enteric nervous system (ENS) [Kurz and Sessler, 2003]. The ENS coordinates normal gastrointestinal (GI) function and is

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composed of the myenteric plexus, which coordinates motor function, and the submucosal plexus, which is responsible for secretory and absorptive functions. Opioids augment GI function through several mechanisms within the ENS and colon: (I) inhibition of acetylcholine release decreases longitudinal smooth muscle contractions, which decreases peristalsis and forward movement of stool, and an increased segmental contraction leads to stasis; (II) inhibition of vasoactive intestinal polypeptide (VIP) and prostaglandin E1 release; combined with (III) enhanced norepinephrine and serotonin release, decreases secretions and desiccates the stool; and (IV) decreases in intestinal stasis enhance passive absorption of water and electrolytes.

The severity of OIC is influenced by several characteristics of exposure, including opioid dose (based on equivalent daily doses of oral morphine), route of administration, and presence of concomitant causes of constipation (Table 1). High-potency opioids (i.e., morphine, oxycodone, and fentanyl) at higher equivalent daily doses of oral morphine may cause OIC more often than low- or medium-potency agents (i.e., tramadol and codeine) at lower equivalent daily doses of oral morphine [Maguire et al., 1981]. However, patient factors such as immobility, may contribute heavily to the risk of constipation, and therefore, opioid dose should not be considered independently of other factors [Bennett and Cresswell, 2003]. In terms of the method of administration, transdermal fentanyl causes less OIC than morphine [Tassinari et al., 2008], and may be a preferred agent in patients whose opioid requirements are stable. In contrast, evidence supporting an effect of switching from oral to a parenteral route of administration is inconclusive [Daeninck and Bruera, 1999; Mancini et al., 2000; Mazumdar et al., 2008].

Constipation

Opioid therapy for treatment of pain

Concomitant treatment with drugs that independently increase the risk of constipation [anticholinergics, antihypertensives (calcium channel blockers, diuretics), aluminum-containing antacids, calcium, and iron supplements]

Age >65 years

Low fiber diet

Female sex

Lack of physical activity

Endocrine or neuromuscular disorder

History of constipation in childhood

History of abuse

Depression or anxiety

Family history of cancer

History of pelvic surgery

Diarrhea

Laxative therapy for prevention or treatment of constipation Chemotherapy (5-fluorouracil, irinotecan, capecitabine, and docetaxel, in particular)

Targeted cancer therapies (erlotinib, gefitinib, and sorafenib)

Concomitant medications that independently increase the risk of diarrhea [antibiotics, promotility drugs, proton pumps inhibitors, magnesium-containing antacids, misoprostol, digoxin, anti-arrhythmic agents, oral hypoglycemic drugs (biguanides, alpha-galactocidase inhibitors)]

Radiotherapy

Carcinoid tumor

AIDS/HIV infection

Clostridium difficile associated diarrhea

Comorbid conditions in the elderly (inflammatory bowel disease, pancreatic or biliary disease, celiac disease)

Frequency and characterization of opioidinduced constipation

In a survey, performed in the United States and Europe (PROBE 1) [Bell *et al.*, 2009], of 322 patients taking daily oral opioids and laxatives, 45% of respondents reported fewer than three bowel movements per week, 81% reported constipation, and 58% reported straining. Symptoms were most often reported as severe, and had at least a moderate negative

Unlike other opioid-induced adverse effects (i.e., respiratory depression, nausea, sedation), tolerance to constipation will rarely develop and is often cited as the most common dose-limiting adverse effect that may prevent adequate pain control. Clinically, OIC is a constellation of symptoms, including hard/dry stools, straining, feeling of incomplete evacuation, bloating and abdominal distention. These symptoms are similar to those seen in chronic constipation, but patients with OIC may also experience decreased appetite, dyspepsia/heartburn, and gastroesophageal reflux. Uncontrolled OIC can lead to complications, including fecal impaction with overflow diarrhea, pseudo-obstruction of the bowel causing anorexia, nausea, vomiting, inadequate absorption of oral medications, urinary retention and incontinence, and confusion.

In a meta-analysis of 11 randomized studies of opioid therapy for nonmalignant pain, constipation affected an average of 41% of patients taking opioids for eight weeks [Kalso *et al.*, 2004]. In terms of the burden of symptoms in advanced illness, OIC can rival the distress caused by pain. Since tolerance to this side effect does not develop, constipation is unlikely to improve over time, and therefore must be anticipated, monitored, and addressed throughout the opioid treatment course.

Therapeutic options for management of constipation

Nonpharmacologic management of constipation

A variety of nonpharmacologic options are available for the general management of chronic constipation. Lifestyle measures such as increasing fluids, increasing dietary fiber intake, or initiating an exercise regimen are often the firstline approach, but studies evaluating the effects of these measures have yielded mixed results, and patients have likely already tried many of these measures prior to reporting symptoms to their clinicians.

Although a diet low in fiber can lead to constipation, a high-fiber diet will not necessarily benefit all patients with constipation, especially patients with an underlying motility disorder. The American Gastroenterological Association does, however, recommend a gradual increase in fiber intake in either dietary or supplement form as a first-line approach to management of chronic constipation [Bharucha *et al.*, 2013]. Supplemental fiber should be introduced gradually to avoid significant bloating and cramps, and patients

	gones	
Agent	Examples	Description
Bulking agents	Methylcellulose, psyllium	Absorbs liquids in the intestines and swells to form a soft,
		DUIKY SLOOI
Osmotic laxatives	Lactulose, sorbitol, polyethylene glycol (PEG),	Draws water into the bowel from surrounding body tissues
	magnesium citrate, magnesium hydroxide	providing a soft stool mass
Stimulants/irritants	Bisacodyl, senna	Encourage bowel movements by acting on the intestinal wall
Lubricants	Mineral oil	Coats the bowel and the stool mass with a waterproof film
		so stool remains soft
Stool softeners	Docusate sodium	Helps liquids mix into the stool and prevent dry, hard stool
		masses
Chloride channel	Lubiprostone, linaclotide	Increases fluid secretion in the intestine, which increases
activators		intestinal muscle movement
Combinations	Various products	Combinations containing more than 1 type of laxative

should be advised that they may experience an increase in gaseousness.

Exercise has not been shown to be an effective standalone therapy for chronic constipation, but may help to improve bowel function as part of a broader rehabilitation program for elderly patients with constipation [Benton *et al.*, 1997]. If nonpharmacologic approaches prove insufficient, laxative therapy is typically the next step. Commonly used products include bulking agents, stool softeners, osmotic laxatives, and stimulant laxatives (*Table 2*). Use of combination products containing two or more laxatives is generally not advised except in refractory patients, as combination products may cause more side effects.

Management of opioid-induced constipation

When routine prophylactic laxatives are insufficient [Ishihara *et al.*, 2012; van der Spoel *et al.*, 2007], treatment with subcutaneous methylnaltrexone should be considered. Methylnaltrexone is a quaternary N-methyl derivative of the opioid antagonist naltrexone, an opioid antagonist similar to naloxone, but is less lipid soluble so it is less likely to cross the blood brain barrier and reverse the palliative effects of opioids or cause withdrawal reactions. The efficacy of methylnaltrexone was evaluated in a study of 134 patients with advanced illness receiving opioids for ≥ 2 weeks and laxatives for ≥ 3 days without relief of OIC who were randomized to methylnaltrexone 0.15 mg/kg *vs.* placebo subcutaneously every other day for two weeks [Thomas *et al.*, 2008b]. When comparing methylnaltrexone *vs.* placebo, bowel movement without laxative occurred more

often within four hours of the first dose in 48% vs. 15% (P<0.001, NNT 3). The range of response with individual doses of methylnaltrexone was 37-48% vs. 7-15% with placebo. More patients treated with methylnaltrexone had three or more laxative-free bowel movements per week in 68% vs. 45% (P=0.009, NNT 5). There were no significant differences in scores of withdrawal or changes in pain. A similar response rate persisted in the three-month open-label extension trial. Adverse effects were more common with methylnaltrexone vs. placebo (*Table 3*).

While opioid side effects such as constipation and nausea are common and anticipated during palliative care, other less common adverse events may occur that may not be attributed to opioid therapy, even though opioids are the root cause. This is the case for NBS, which has several unique characteristics that differentiate it from OIC and warrant a much different approach to treatment.

NBS is characterized by chronic recurring abdominal pain that worsens with continued or escalating doses of narcotics [Grover *et al.*, 2012]. Other symptoms of NBS include: intermittent vomiting, weight loss and occasional ileus-like symptoms. The recurrence or persistence of painful NBS symptoms leads to additional use of narcotics. After a short period of relief, pain typically recurs, despite narcotics, and is stronger. These symptoms lead to additional narcotics, yet again. Until it is recognized, NBS symptoms will persist and continue to worsen. Treatment of NBS involves early diagnosis, and gradual withdrawal of narcotics [Grunkemeier *et al.*, 2007]. Benzodiazepines and clonidine are useful in the management of withdrawal symptoms as the patient is titrated off the narcotic.

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Table 3 Methylnaltrexone-related adverse effects						
	Percent	Percent in	Number needed			
Adverse effect	in treated	placebo	to treat to cause			
	group (%)	group (%)	harm (NNH)			
Abdominal pain	17	13	25			
Flatulence	13	7	16			
Diarrhea	6	4	50			
Nausea	11	7	25			
Increased body	8	3	20			
temperature						
Dizziness	8	3	20			
[Thomas et al., 2008b]						

Risk factors for diarrhea

The next section reviews risk factors for diarrhea in palliative medicine (*Table 1*), with an emphasis on drug-related causes. Subsequent sections cover frequency and characterization, and therapeutic options for the management of diarrhea.

Drug-induced diarrhea is the most common cause of diarrhea in palliative care. Certain medication classes may be obvious candidates when considering diarrhea as an adverse drug event (laxatives, specific chemotherapeutic drugs, and antibiotics), while other classes may be less prominent and potentially overlooked during a review of a patient's medication profile (GI drugs, cardiovascular drugs, oral hypoglycemic drugs). The risk of diarrhea is compounded whenever multiple medications with different mechanisms for causing diarrhea are used concurrently.

Laxatives

Diarrhea associated with misuse of laxatives in the elderly

Elderly patients who use laxatives chronically may experience diarrhea, and incontinence. Habitual laxative use in this population is well documented [Roerig *et al.*, 2010], and may be a potential cause of unexplained diarrhea despite a comprehensive diagnostic workup. An alternating pattern of constipation and diarrhea, and persistent electrolyte disturbance should increase the level of suspicion in laxative misuse. Diarrhea caused by stimulant laxatives may be accompanied by colic and urgency, while osmotic laxatives and stool softeners often cause stool fecal leakage. Persistent hypokalemia and melanosis coli may result from chronic use of senna (an anthraquinone laxative).

Diarrhea associated with laxatives or methylnaltrexone for OIC

The risk of diarrhea is significantly increased during pharmacologic treatment for OIC. In a meta-analysis of 11 placebo-controlled trials of *mu*-opioid receptor antagonist therapy for OIC, diarrhea was reported by an average of 8.4% of patients in the active treatment groups, compared with an average of 4.7% in the placebo groups (RR=1.61, 95% CI, 1.21-2.13; NNH 33) [Ford *et al.*, 2013]. Likewise, diarrhea is one of the most common side effects reported in comparative trials of laxative therapy for OIC [Candy *et al.*, 2011]. Bowel function should be closely monitored during OIC therapy to minimize the risk of diarrhea.

Chemotherapy

Over 20% of cancer patients receive chemotherapy or other forms of aggressive cancer care near the end of life [Earle *et al.*, 2004; Ho *et al.*, 2011]. 5-fluorouracil, irinotecan, capecitabine, and docetaxel are notable examples. These drugs are associated with high rates of diarrhea ranging in severity from mild to moderate, in 20% to 50% of patients, to severe, in 5% to 10% of patients [Chen *et al.*, 2013; Ilhan-Mutlu *et al.*, 2013; Koucky *et al.*, 2011; Mitry *et al.*, 2009; Muro *et al.*, 2010].

5-Fluorouracil is approved by the U.S. Food and Drug Administration (FDA) for palliative treatment of breast, pancreatic, colorectal and gastric cancer. Diarrhea from 5-Fluorouracil is caused by the drug's antimitotic effects on intestinal crypt cells and villous enterocytes that leads to a reduced surface area for absorption in the GI tract. It is more common at higher (bolus) doses, and during co-treatment with leucovorin.

Irinotecan is FDA approved as first-line treatment of metastatic colorectal cancer in combination with 5-fluorouracil and leucovorin, or as single-agent treatment of metastatic colorectal cancer that has recurred or progressed after 5-fluorouracil-based therapy. Diarrhea from irinotecan can be either early-(during or shortly after infusion) or late-onset (usually 24 hours or longer after infusion). Most early onset adverse events from irinotecan are caused by the drug's activation of cholinergic receptors that result in diarrhea, abdominal cramping, flushing, lacrimation, salivation and other cholinergic symptoms. Late onset diarrhea from irinotecan is unpredictable, and can occur at any dose of the drug. However, lower rates of diarrhea are seen when irinotecan is administered every three weeks, instead of a weekly basis.

Capecitabine is FDA approved for metastatic breast or colorectal cancer. It is an orally administered prodrug of 5-Fluorouracil that is transformed to the active drug by enzymatic conversion at the site of the tumor. Like 5-Fluorouracil, capecitabine reduces the villous enterocyte population, which predisposes individuals to an imbalance between absorption and secretion in the small bowel, and increases the risk of diarrhea. Lower rates of diarrhea are reported with oral capecitabine compared to infusion regimens of 5-Fluorouracil, especially when capecitabine is administered as single-agent chemotherapy. Capecitabineinduced diarrhea is more common in the United States, which may indicate the potential influence of genetic polymorphisms, or variation in dietary intake of folic acid, which is required for 5-Fluorouracil activation.

Docetaxel is FDA approved for locally advanced/ metastatic breast, head and neck, squamous cell disease, non-small cell lung cancer, advanced gastric cancer, and hormone refractory prostate cancer. Diarrhea from docetaxel is typically mild and is caused by the drug's cytotoxic activity in the mucosal lining of the GI tract. As a result of reduced GI mucosal defenses, patients are predisposed to enteritis and colitis. Severe cases of neutropenic enterocolitis, a life-threatening complication of chemotherapy, have been reported in patients receiving high doses of docetaxel when administered along with myeloablative therapies that deplete bone marrow cells [Bremer and Monahan, 2006; Nesher and Rolston, 2013].

High rates of diarrhea are also associated with targeted cancer therapies, such as the epidermal growth factor receptor tyrosine kinase inhibitors; erlotinib, gefitinib, and vascular endothelial growth factors; sorafenib. Close inspection of a patient's medication profile in an effort to identify drugs with the potential to cause diarrhea will facilitate the development of a specific treatment plan for drug-induced diarrhea in patients with cancer.

Other drugs

While chemotherapy, and other cancer treatments should be considered a probable cause of diarrhea in cancer patients, several other drugs should also be recognized for their potential contribution to the prevalence of diarrhea in palliative care (*Table 1*) [Abraham and Sellin, 2007].

Antibiotics

Antibiotics can cause diarrhea through a variety of mechanisms. Most cases of diarrhea are mild and transient.

However, pseudomembranous colitis is a well-known complication of diarrhea from antibiotic therapy and is most closely associated with clindamycin, amoxicillin, ampicillin, and cephalosporins, but may also occur with erythromycin, fluoroquinolones, cotrimoxazole, suflamethoxazole, and penicillin. Fatty diarrhea may occur with aminoglycoside, or tetracycline antibiotics.

Gastrointestinal drugs

In addition to laxatives, several other types of GI drugs are known to increase the risk of diarrhea. Promotility drugs (cisapride, domperidone, metoclopramide, prucalopride) can cause diarrhea due to a direct effect on GI transit. The only drug in this category with FDA approval is metoclopramide. Diarrhea may also be seen in patients receiving a proton pump inhibitor (omeprazole, lansoprazole, pantoprazole, rabeprazole, esomeprazole, dexlansoprazole), although this adverse effect occurs in only 2-5% of patients receiving one of these drugs. Magnesium-containing antacids are poorly absorbed substances that draw fluid into lumen of the bowel can cause an osmotic diarrhea. Misoprostol, a gastroprotectant for prevention of nonsteroidal antiinflammatory drug-induced gastropathy, is also associated with a high rate of diarrhea.

Cardiovascular drugs and oral hypoglycemic drugs

Diarrhea may be a concerning side effect of drugs used to treat cardiovascular disease or diabetes. Digoxin, quinidine, procainamide each have rates of diarrhea less than 5%. Although the rates are low, this side effect could be dose-limiting or lead to treatment nonadherence. In patients with diabetes, oral hypoglycemic drugs, especially biguanides (metformin), alpha-galactocidase inhibitors (acarbose, and miglitol), are associated with high rates of diarrhea. Reported rates of diarrhea for these agents during clinical trials are 53%, 31%, and 28%, for metformin, acarbose, and miglitol, respectively.

Frequency and characterization of diarrhea

The overall rate of diarrhea in palliative care may be as high as 10-20% [Ridley and Gallagher, 2008], and will depend on the prevalence of risk factors in a given population. The onset and worsening of drug-induced diarrhea may correlate with periods of intensification of therapy. This is particularly true with laxative therapy for OIC, and chemotherapy during cancer care. Complications of poorly controlled diarrhea include fecal incontinence, dehydration,

Table 4 Antidiarrheal drugs		
Agent	Dose range	Uses
Psyllium, methylcellulose	3.4 gram psyllium orally two to three times daily or1 teaspoonful methylcellulose orally up to three times daily	Bulking agent for control of mild diarrhea
Kaolin/pectin combinations	30 to 60 mL every 4 hours	Adsorbent/absorbent combination for control of mild diarrhea
Loperamide	4 mg orally, then 2 to 4 mg orally every 4 to 6 hours	Opioid agonist for control of mild to moderate diarrhea
Diphenoxylate/atropine (2.5 mg/0.025 mg per tablet or per teaspoonful)	2.5 mg /0.025 mg to 5.0 mg /0.05 mg diphenoxylate/atropine orally every 4 to 6 hours	Combination of opioid agonist with anticholinergic drug for control of mild diarrhea
Codeine sulfate	15 to 60 mg orally every 4 to 6 hours	Opioid agonist for control of refractory diarrhea
Deodorized tincture of opium (10%)	0.6 to 1.2 mL orally every 4 to 6 hours	Opioid agonist for control of refractory diarrhea

fluid and electrolyte disturbances, and nutritional deficiencies [Ratnaike and Jones, 1998], each of which could lead to serious outcomes such as hospitalization and death [Cherny, 2008]. Early recognition and appropriate therapy can minimize the impact of diarrhea on a patient's quality of life, and activities of daily living.

Therapeutic options for management of diarrhea

The goal of therapy for diarrheal conditions is to address the underlying cause with specific interventions, and manage symptoms with appropriate nonpharmacologic and pharmacologic antidiarrheal treatments (Table 4). Therefore, the first step in treatment is to identify the underlying cause. Bulking agents may provide relief for mild diarrhea, especially in patients with low dietary fiber intake. Laxative- or methylnaltrexone-induced diarrhea can be managed by reducing the dose or discontinuing the culprit drug. Management of chemotherapy-induced diarrhea will depend on the mechanism of diarrhea. Aggressive oral rehydration and electrolyte replacement may be necessary as supportive care for some patients with severe diarrhea. Mild to moderate diarrhea from 5-Fluorouracil, capecitabine, docetaxel, and early- and late-onset diarrhea from irinotecan can be managed with loperamide or diphenoxylate-atropine. Early-onset cholinergic symptoms from irinotecan may be prevented or treated with intravenous or subcutaneous atropine. Adsorbent/absorbent combinations may also be used as adjunctive agents for additional relief from chemotherapy-induced diarrhea.

Summary

The chapter highlights the important contribution of drug-related risk factors for constipation and diarrhea in the setting of palliative medicine. Recognition of important drug- and non-drug risk factors for constipation and diarrhea will help clinicians select an appropriate management strategy to meet the needs of the patient. Effective treatment of constipation and diarrhea should target the underlying cause, provide supportive care, aim to alleviate troublesome symptoms, and prevent recurrence. Patients should be monitored for improvement in bowel function, quality of life, and activities of daily living.

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Part III

Anorexia and cachexia: definitions, clinical presentations, mechanisms and treatments

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Introduction

It is reported that 20% of individuals die from cachexia rather than their cancer [Bruera, 1997; MacDonald et al., 1995]. One can speculate why this occurs. We know that a 30% reduction in weight represents a 75% reduction in muscle mass and is inevitably fatal [Muscaritoli et al., 2006]. Further, cachexia is associated with thrombocytosis and leukocytosis, leading to thromboembolic events, strokes and pulmonary emboli [Kalantar-Zadeh et al., 2013]. The myocardium is subject to atrophy by the same cachectic process leading to death by cardiac failure. There is also an impairment of respiratory muscles, including the diaphragm, which can lead to respiratory failure. Endocrine abnormalities, particularly hypogonadism, leads to accelerated muscle loss, falls, bone fractures and disability [Kalantar-Zadeh et al., 2013]. The immunological impairments caused by advance cancer and chronic inflammation, as well as treatment, lead to infectious complications [Kalantar-Zadeh et al., 2013]. Regardless of the mechanism of death, we know that cachexia can cause it and it should be addressed and minimized as possible. This chapter reviews the diagnosis and definitions, the mechanisms of action and the treatment.

Prevalence

The overall prevalence of anorexia and cachexia reported in the literature is between 12% and 85%. Whether the range is secondary to diagnostic criteria and/or patient-mix or a combination of both is unknown [Wallengren *et al.*, 2013]. Specifically, the definition of cachexia via ICD-9 code 799.4 alone or with anorexia, describes weight loss or feeding difficulty. Thus, the diagnosis of cachexia and anorexia may be completely missed without documentation of weight loss, loss of appetite and associated symptoms. Further, anorexia and cachexia may be so common among cancer patients that physicians may simply fail to document it, or assume that it is the natural outcome to the underlying cancer.

Using unintentional weight loss as criteria, cachexia occurs in 80% of patients with upper gastrointestinal cancers and 60% of those with lung cancer [O'Gorman *et al.*, 1999]. Patients with hindgut malignancies are much less likely to develop cachexia for reasons unknown. It may be speculated that the origin of the cancer may determine the inflammatory response associated with it. There may be genetic predispositions [Tan *et al.*, 2011]. Additionally, many foregut cancers, as well as lung cancer, are associated with comorbid illnesses (chronic obstructive lung disease, coronary disease, and diabetes) which may contribute to its development.

Definition and diagnosis

Anorexia

Anorexia is defined as less than 1,500 kcal per day of energy intake [Loprinzi, 1995]. We however assert that such a definition would discover only advanced and mostly irreversible anorexia. Cancer patients experience early satiety, chemosensory changes in food taste (dysgeusia), diural variations in food intake and loss of enjoyment of eating complicating this diagnosis [MacDonald, 2012]. Thus, the anorexia syndrome is inadequately defined by the amount of food intake. The prominent feature, weight loss, is frequently not noticed by physicians, particularly in societies where obesity is prevalent [Evans et al., 2008; Lainscak et al., 2008]. Sarcopenia may be profound and not evident in those individuals with a normal or high BMI, and patients may not volunteer the symptom of anorexia unless directly asked [Fox et al., 2009; Homsi et al., 2006]. Sarcopenia significantly impairs function and tolerance to chemotherapy, even in individuals with normal or high body mass index (BMI) [Argiles et al., 2006; Giordano and Jatoi, 2005; Tisdale, 2002; Martin et al., 2013, Prado et al., 2007; Prado et al., 2009a; Antoun et al., 2010; Mir et al., 2012]. Pre-cachexia has been defined by consensus as, (I) the presence of an underlying chronic illness; (II) unintentional loss of weight 5% or less over six months; (III) evidence of inflammation as measured by C-reactive protein (CRP) or hypoalbuminemia and (IV) the presence of anorexia.

Cachexia

The hallmark clinical indicator of cachexia is involuntary weight loss [Bozzetti and SCRINION Working Group, 2009; Evans et al., 2008; Lainscak et al., 2008]. A consensus definition by expert opinion and Delphi methodology includes greater than 5% weight loss, a BMI less than 20 kg per meter squared, greater than 2% weight loss, and/or documented skeletal muscle mass loss below population standards. Specifically, skeletal muscle mass less than 55 cm²/m² for men and less than 39 cm²/m² for women at the level of the L3 vertebral body by CT scan seems to be a consistent marker of sarcopenia in the population [Prado et al., 2009b]. Skeletal muscle mass can be measured on CT scans normally used for cancer screening at the level of the third lumbar vertebral body. Subjects with reduced muscle mass, measured by CT scans, and/or reduced muscle density, measured by Hounsfield units on CT scans, show poor prognosis regardless of BMI [Martin et al., 2013]. Sarcopenia is a better indicator of symptom burden than changes in BMI, measured by the Edmonton Symptom Assessment Scale (ESAS) and reduced hand grip strength. Sarcopenia occurs in 50% of lung cancer patients and 15% of colon cancer patients who have a normal to high BMI and less than 5% weight loss. Overall, there is significant heterogeneity in the degree of sarcopenia for those with similar BMIs [Baracos et al., 2010]. It is for this reason that the degree of weight loss and the changes in BMI are relatively inaccurate indicators of cachexia, and should not be used alone in interventional trials as an outcome measure.

We propose that definitions and diagnosis of cancer

cachexia should be validated by clinical outcomes. Weight loss of greater than 10%, food intake of less than 1,500 kcal per day, an albumin less than 3.2 g/dL and a CRP >10 mg/L are strongly associated with reduced quality of life (QOL), impaired activities of daily living, increased symptom burden and shortened survival [Fearon *et al.*, 2006; Stephens *et al.*, 2008; Wallengren *et al.*, 2013]. Symptoms associated with anorexia including dysphagia and early satiety also have prognostic importance [Maltoni *et al.*, 2005; Davis *et al.*, 2006].

Over the years, the definition of cachexia has changed from a single focus of involuntary weight loss to a modular definition which takes into account nutritional intake, catabolic or hypermetabolic changes, and physical function [Blum and Strasser, 2011; Blum *et al.*, 2011]. As a result, interventional trials have changed the focus from single outcomes of weight gain to multiple outcomes including appetite, weight gain, lean body mass, inflammatory markers, function and quality of life [Blum and Strasser, 2011; Blum *et al.*, 2011].

Biomarkers

Biomarkers have been utilized both in defining cachexia and as prognostic indicators. The two most common bio markers are albumin and CRP. Neither is specific for cancer anorexia. Hypoalbuminemia is not due to reduced synthesis of albumin, but rather due to transcapillary migration of albumin into interstitial spaces due to inflammation [Fearon *et al.*, 1998]. Hence, hypoalbuminemia is a negative acute phase reactant (APR). Other markers include inflammatory cytokines such as tumor necrosis factor-alpha (TNF), interleukin-1 (IL-1) and interleukin-6 (IL-6) [Tan *et al.*, 2008]. Elevated CRP and inflammatory markers, as well as hypoalbuminemia, may weigh evidence in favor of cachexia relative to starvation, particularly if anorexia and associated symptoms are present [Blum and Strasser, 2011; Blum *et al.*, 2011].

Additional lab abnormalities include parathyroid hormone-related protein (PTHrP). However, PTHrP may be associated with tumor-related hypercalcemia, and may also reflect systemic inflammation [Deans *et al.*, 2005], insulin resistance and hypercortisolism, as well as low testosterone and gonadotropin levels. In cancer, there are also changes in the angiotensin II levels, reduced leptin and elevated ghrelin serum levels [Tan *et al.*, 2008].

Assessment scales

There are a number of nutritional assessment scales which

Table 1 Domains of cachexia
Symptoms
Caloric intake
Catabolic drive and resting energy expenditures
Sarcopenia
Qualitative muscle dysfunction
Metabolic and endocrine alterations
Physical function
Quality of life
[MacDonald, 2012].

can be helpful clinically and in research trials. However, none of the scales adequately differentiate primary nutritional failure from cachexia [Bauer *et al.*, 2002]. Most are inadequate to assess malnutrition, although there is a negative relationship between weight loss and quality of life [Wheelwright *et al.*, 2013]. Unfortunately, none of the instruments fully assess all the domains of cachexia (symptoms, function, cytopenias, laboratory parameters and quality of life) [Evans *et al.*, 2008] (*Table 1*).

The Patient-Generated Subjective Global Assessment Scale provides information about the impact of symptoms which adversely influence nutrition and functional state [Bauer *et al.*, 2002]. The Functional Assessment of Anorexia Cachexia Treatment scale is validated, includes quality of life and is the only scale which assesses early satiety [Chang *et al.*, 2005; Ribaudo *et al.*, 2000]. The ESAS measures anorexia and secondary symptoms related to nutritional failure (nausea) and outcome (fatigue) [Bruera *et al.*, 1991].

The Mini-Nutritional Assessment Scale incorporates both subjective and objective measures which place individuals at risk in categories of nutritional failure [Huhmann and Cunningham, 2005]. This scale detects malnutrition more accurately than weight loss alone. In non-small cell lung cancer patients, the score correlates with metastatic site, brain metastases and predicts response to first line chemotherapy. It better predicts time to progression and survival and scores correlate with laboratory parameters of cachexia such as anemia, hypoalbuminemia and adiponectin and leptin levels [Gioulbasanis *et al.*, 2011].

Cachectic patients have high CRP and low hemoglobin and albumin levels regardless of whether the underlying chronic illness is cancer or non-malignant in origin. There is no cutoff level which defines cachexia using these laboratory studies. They have a low sensitivity and low predictability [Letilovic *et al.*, 2013]. On the other hand, CRP and albumin have been combined in the Glasgow Prognostic Scale as a three stage system. The Glasgow Prognostic Scale is validated in multiple malignancies, is simple to use, and consists of objective measures. It is not dependent on subjective assessments [McMillan, 2009; McMillan, 2013]. Item banks of questions using a Likert Scale have been formatted and then tested in individuals in hopes of developing adaptive and validated scales of malnutrition [Hane *et al.*, 2013].

Differential diagnosis

As mentioned earlier, starvation is a common differential diagnosis for cachexia and anorexia. In general, starvation is not associated with anorexia or elevated acute phase reactants (APR). In starvation there is a protein sparing metabolism not found with cachexia [Lowell and Goodman, 1987; Gelfand and Sherminw, 1986; Blackburn *et al.*, 1973]. Another diagnosis in the differential is major depression, associated with hopelessness, anhedonia and apathy, which leads to anorexia and weight loss.

Metabolic causes may also mimic cachexia. Malabsorption leads to weight loss and may be a problem after gastrointestinal surgery, particularly for pancreatic cancer. Pancreatic enzyme replacement may lead to weight gain. Apathetic hyperthyroidism mimics cancer related anorexia and cachexia very closely [Palacios *et al.*, 1991; Higgins, 1959; Kalant and Wilansky, 1959; Lillington and Brownell, 1959]. Hypogonadism in males can be associated with lower BMI, muscle wasting, reduced strength, and increased cytokines as well as depression and fatigue [Rajagopal *et al.*, 2004; Svartberg *et al.*, 2008; Burney and Garcia, 2012; Burney *et al.*, 2012]. Finally, drug and treatment toxicity can produce anorexia, nausea, early satiety and weight loss [Mitchell and Schein, 1982; Thiel *et al.*, 1988].

Mechanisms of cachexia

Evolving picture of cachexia

Cancer cachexia was originally thought to be limited to catabolism of myosin heavy chain (MHC) proteins, but is now recognized to not only lead to MHC catabolism, but also to alter mitochondrial function, calcium metabolism and extracellular protein matrix [Lenk *et al.*, 2010; Ushmorov *et al.*, 1999; Fermoselle *et al.*, 2013]. Fat catabolism results in reduced leptin levels and paradoxically anorexia occurs despite elevated ghrelin blood levels



Figure 1 Peripheral mechanisms to cachexia and fatigue. The left panel illustrates mechanisms causing muscle catabolism. Inflammatory cytokines such as TNF, IL-1 and IL-6 are up-regulated as well as certain transcription factors (STAT3, FOXO and NF kappa B) which in turn up-regulate E3 ligases (MuRF and MAFbx or atrogin-1) proteasomes and ubiquitin. At the same time, myostatin through ACT RIIB receptors prevents muscles synthesis. The influences of cachexia on mitochondrion are illustrated in the right panel. Inflammatory cytokines adversely influence mitochondrion function by reducing fusion proteins and increasing vision proteins. Mitochondrial biogenesis is impaired, and tricarboxylic acid cycle proteins are down regulated, such as cytochrome C. oxidase, leading to impaired oxidative phosphorylation and ATP production. In addition, uncoupling proteins (UCP 2 and 3) are up-regulated causing increased resting energy expenditures.

[Engineer and Garcia, 2012; Diakowska *et al.*, 2010; Wolf *et al.*, 2006; Murdoch *et al.*, 1999]. The inflammatory cytokines IL1, IL-6 and TNF produce peripheral and central alterations through up-regulation of nuclear factor-kappa B (NF-kappa B) transcription factor, prostaglandins and cyclooxygenase, resulting in the anorexia and cachexia syndrome [Laflamme *et al.*, 1999; Laflamme and Rivest, 1999; Grossberg *et al.*, 2010a; 2010b] (*Figure 1*).

Qualitative changes occur both peripherally and centrally. Peripherally, there is resistance to insulin and acyl-ghrelin signaling, while centrally, there is potentiation of leptin signaling. In muscle, qualitative changes in mitochondria lead to impaired oxidative phosphorylation, abnormal calcium metabolism, and uncoupling of excitation and contraction [Khamoui and Kim, 2012]. As a result, the close relationship between muscle mass cross-sectional area, and maximum voluntary contraction which occurs in healthy individuals is lost [Roberts *et al.*, 2013a; 2013b]. Individuals are much weaker than the appearance of wasting would suggest.

Certain muscle groups and muscle fibers may be disproportionately influenced by cachexia. Muscle disuse and spinal cord injury cause atrophy of type I muscle and there is a shift towards a higher proportion of fast fiber types (type II). Cancer cachexia produces the opposite effect with a preferential loss of glycolytic fast fiber types and a relative proportional shift towards slow (type I) muscle fiber types [Ciciliot *et al.*, 2013].

Myocardium is not spared. Like skeletal muscle, myocardium atrophy is observed and leads to fatigue, dyspnea and exercise limitations. This can be potentiated by comorbid coronary artery disease, cor pulmonale or delayed myocardium damage from certain chemotherapy agents or radiation [Der-Torossian *et al.*, 2012; Cosper and Leinwand, 2011]. Part III

Table 2 Peripheral mechanisms of cachexia Catabolic

Ubiquitinated myosin heavy chain

Up-regulation of Forkhead -0 (FOXO) transcription factor

Up-regulation of E3 ligases (MuRF, MAFbx)

Up-regulation of transcript factors NF-kappa-B and STAT-3

Up-regulation of cathepsin

Up-regulation of caspases

Up-regulation of proteasomes

Up-regulation of uncoupling proteins (UCP 2, 3)

Up-regulation of angiotensin II

Increased mitochondrial fission proteins

Production of reactive oxygen species (ROS)

Reduced cytochrome c. and tricarboxylic enzymes

impairing oxidative phosphorylation

Reduction in superoxide dismutase and glutathione peroxidase

Anabolic

Allabolic
Increase myostatin
Impaired satellite cell division
Reduced insulin growth factor I (IGF-1)
Reduced testosterone
Ubiquitinated Myo-D reducing muscle synthesis
Reduced activity of synthetic pathways mammalian target
of rapamycin (mTOR/ALK)
Reduced proliferator-activated receptor gamma
co-activator-1 alpha (PGC-1alpha) needed for
mitochondrial biogenesis
Reduced mitochondrial fusion proteins
[Lenk et al., 2010].

Neuroendocrine changes lead to low testosterone, which potentiates muscle loss in males and impairs appetite, mood and increases fatigue [Burney and Garcia, 2012; Burney *et al.*, 2012]. Low testosterone levels are due to reduced gonadotropins. Opioids will potentiate the hypogonadism of cancer by also inducing hypogonadotropic hypogonadism [Paice *et al.*, 1994] (*Table 2*).

Metabolic profile

The metabolic profile of cancer cachexia resembles the metabolic syndrome, which is also associated with insulin resistance and inflammatory cytokines. There is an increase in very low-density lipoproteins (VLDL), low-density lipoprotein (LDL) and, in a subset of individuals, elevated glucose secondary to insulin resistance. The hyperlipidemia, hyperglycemia and reduced levels of branched chain amino acids (BCAA) are distinguishing features in animal models of cachexia [Der-Torossian *et al.*, 2012].

Anorexia

Anorexia is largely a cytokine induced inflammatory hypothalamic process which up-regulates serotonin levels and certain serotonin receptors (5-HT-2C, 5-HT-1B). Proopiomelanocortin (POMC) signals are up-regulated in the mediobasal (arcuate) hypothalamus, resulting in activation of melanocortin (MC4-R, MC3-R) receptors. The downstream effect is anorexia and increased resting energy expenditures. Simultaneously, there is impairment of neuropeptide Y (NPY) and acyl-ghrelin signaling which contributes to anorexia and impairs gastrointestinal motility [Heisler et al., 2003; Tecott, 2007; Heisler et al., 2007a; 2007b; Lam et al., 2009; Lam et al., 2008; Fujitsuka et al., 2009; Plata-Salaman, 1996; Plata-Salaman, 1998a; 1998b; 1998c]. Reduction in NPY signaling through the nucleus tractus solitarius and dorsal motor nucleus of the vagus, combined with increased release of hypothalamic orexigenic hormones (corticotropin releasing factor or CRF, urocortin and cholecystokinin), cause disruption of fasting gastrointestinal motor activity. This may cause early satiety, presumably, through impaired gastric fundus relaxation and gastric emptying [Ron et al., 2011; Fujitsuka et al., 2012a].

While elevated hypothalamic serotonin levels appear to be highly associated with anorexia, reduced dopamine signals (from reduced conversion of tyrosine to dopamine) have been shown in animals to reduce the effort to obtain food [Salamone *et al.*, 2005; Zhou *et al.*, 2005] (*Figure 2*). Reduced dopamine signaling from basal ganglion and the imbalance between serotonin and dopamine levels may be the cause of central fatigue in cancer [Meeusen *et al.*, 2006; Meeusen *et al.*, 2007; Yavuzsen *et al.*, 2009; Capuron *et al.*, 2007]. The association of fatigue with cancer cachexia may be from two separate pathophysiologies: peripheral mitochondrial dysfunction, and central reduced basal ganglion dopamine [Ushmorov *et al.*, 1999; Roberts *et al.*, 2013b; Capuron *et al.*, 2007; Dantzer *et al.*, 2008; Miller, 2009].

Neuroendocrine dysfunction: the second hypothalamic cachectic event

Certain hypothalamic hormones are increased in cachexia



Figure 2 Central mechanisms to cachexia and anorexia. Anorexia is generated through increased hypothalamic serotonin levels caused by inflammatory cytokines. Serotonin binds to 5-HT2C receptors which up-regulates proopiomelanocortin (POMC) signaling imparing neuropeptide Y. (NPY) signaling qualitatively and quantitatively. Corticotropin releasing hormone or factor (CRH or CRF) increases while ghrelin signaling is impaired. Inflammatory cytokines also impair dopamine synthesis from tyrosine reduction in the cofactor BH4 synthesis and diversion of BH4 to nitric oxide production, leading to increased reactive oxygen species. Vesicular monoamine transporter-2, which transporters intracellular dopamine into vesicles, is down-regulated. Surface dopamine transporters which move dopamine from the synaptic site into intracellular sites are increased. The result is impaired dopamine neurotransmission and fatigue, which is central in origin.

and, as such, CRF and others are reduced, particularly testosterone. The mechanism behind hypogonadotropic hypogonadism is not well known. Hypogonadism of cachexia is potentiated by opioids used to treat pain [Skipworth *et al.*, 2011; Del Fabbro, 2010]. Low testosterone levels are more prevalent among those with advanced cancer, elevated CRP, depression, dyspnea and/or insomnia [Del Fabbro, 2010]. Paradoxically, 20% of postmenopausal women will develop pre-menopausal estrogen levels, which may be due to elevated peripheral aromatase levels. Hyperestrogenic postmenopausal women with cancer have a shortened survival [Skipworth *et al.*, 2011].

Treatment of cachexia

Designing studies

Designing treatment trials for cachexia is fraught with

hazards. Because there is no universally accepted definition of cachexia, entrance criteria on studies will significantly differ, impairing generalizability of results. There are no universally accepted guidelines for demonstrating efficacy, and there are a multitude of potential outcomes including anorexia, catabolic markers, cytokines, insulin resistance (insulin levels), inflammatory markers, fat mass, muscle mass and composition. Other possible outcome measures include: qualitative function, hormone levels (leptin, estrogen, testosterone, and ghrelin), function, weight and weight gain, and quality of life. The number of outcome measures needed to improve, in order to declare a response clinically relevant, has not been established. Changes in weight, inflammatory markers or skeletal muscle mass without improvement in function or quality of life may be inadequate surrogate outcomes [Grossberg, 2010a; Irwin, 2008; Koller et al., 2013].

Most nutritional interventions are adjunctive to antitumor therapy. The primary trial outcome (whether disease-free or progression free survival or overall survival) may be influenced by cancer therapy rather than the anti-cachectic therapy initiated during the trial [Koller et al., 2013]. Disease modifying therapy may diminish or enhance nutritional outcomes. Stratification based on nutritional status is not commonly done in trials. The usual stratification includes age, gender, disease stage, or cancer stage and/or severity of illness (as an example, the APACHE score in intensive care units). A placebo group is not well defined. Placebo nutritional therapy is often not feasible. On the other hand, there are no FDA approved pharmaceuticals for cancer cachexia, hence "best supportive care" has been the control group, which is also not well defined [Koller et al., 2013]. Nutritional interventions are complex interventions with patient related and objective outcomes in individuals who frequently have terminal illnesses.

Type I statistical errors will occur if investigators do not correct for multiple outcomes or repeat measures. Compliance may be an issue and needs to be measured. Attrition will favorably affect patient related outcomes, since only those relatively well will complete questionnaires. Missing data confounds patient related outcomes in trials, particularly if multiple long questionnaires are used as an outcome measure. Single outcomes, like weight, may improve with antitumor therapy or with water gain from hydration. Patient related outcomes in questionnaires may be influenced by antitumor toxicity such as cis-platinum induced anorexia [Hattori et al., 2013; Ohno et al., 2006]. Interventional trials targeting far advanced cancer patients with irreversible cachexia may be an unfair test of nutritional or anti-cachectic therapies. In addition, such therapies may be incongruent with the goals of care which include care and comfort. Severe adverse reactions are more likely to occur in patients with lower quality of life and preclude adequate nutritional or drug trials [Davis et al., 2011]. The use of surrogate markers for clinical outcomes may not be clinically relevant. Many have not been validated, nor has the minimally important clinical change been established to gauge response and numbers to treat. Quality of life is a broad concept influenced by patient expectations, relationships, and psychological make-up and, to a certain extent, non-cachectic symptoms [von Gruenigen et al., 2010; Rustoen et al., 2000; Costantini et al., 2000]. Quality of life instruments with modular units geared towards cachexia should be used [Koller et al., 2013]. Finally, the cost of the intervention is rarely calculated. Increased direct cost of the intervention may be offset by improved indirect cost, such as reduced hospitalization, reduced caregiver absenteeism and reduced office visits. There are also intangible costs including the inconvenience and opportunities lost because of the side effects to therapy, which are rarely taken into account. Trade-off in quality adjusted life year benefits have not been assessed for supportive nutritional interventions.

Indirect treatment of cachexia

Treating the cancer, particularly if responsive to chemotherapy or targeted therapies, favorably influences cachexia. Successfully treating symptoms which adversely influence nutritional intake, such as stomatitis, dysphagia, nausea and vomiting, may enhance nutrition. Nausea, vomiting, early satiety and anorexia may be caused by constipation from opioids which, if appropriately treated with laxatives or enemas, will resolve the symptoms and improve nutritional intake [Davis, 2005]. Treating comorbid illnesses including psychiatric depression, heart failure and chronic obstructive lung disease, will improve nutrition. Dietary counseling is also beneficial [van den Berg *et al.*, 2010].

Single drugs with little to no benefit

There are a multitude of pharmaceuticals which, as single agents, did not significantly improve anorexia and/or cachexia. Due to the multiple mechanisms involved, it is unlikely that a single agent will significantly improve anorexia and cachexia. It is also possible that a single agent may be ineffective alone, but act in synergy when added to a second agent with complementary actions by inhibiting multiple pathways associated with cachexia.

Neither enteral nor parenteral nutrition reverse cachexia nor does either reverse hypoalbuminemia. Adverse effects include an increased risk of infection, electrolyte abnormalities and fluid overload [Dev *et al.*, 2012; Bozzetti and Forbes, 2009; Bozzetti *et al.*, 2009]. Branched chain amino acids (BCAA) are thought to be anti-cachectic through regulation of protein translation initiation and blocking tryptophan uptake into the CNS, thus reducing serotonin [Kimball and Jefferson, 2006; Cangiano *et al.*, 1996]. An eight week trial showed no improvement in lean body mass. However a second trial demonstrated some increase in muscle protein synthesis in ovarian cancer patients [Berk *et al.*, 2008; Dillon *et al.*, 2007]. Branched chain amino acids are unlikely to significantly influence

cachexia overall. Cyproheptadine, a nonspecific serotonin receptor blocker, has little to no benefit as a single agent [Kardinal et al., 1990]. Metoclopramide is often used to treat early satiety, but in the single recorded study only a small minority (4/18, 22%) responded [Nelson and Walsh, 1993]. Metoclopramide is effective in relieving nausea associated with advanced cancer [Bruera et al., 2000; Bruera et al., 1994; Bruera et al., 1988; Bruera et al., 1987]. Growth hormone improves nitrogen balance in critically ill patients, but is associated with increased mortality [Trobec et al., 2011]. Corticosteroids have short-term benefits in improving appetite, but accelerate cachexia. Appetite benefits are lost in 4-6 weeks. Side effects include: neuropsychiatric toxicity, an increase risk for thromboembolism, worsening insulin resistance, hyperglycemia and fluid overload [Bruera et al., 1985; Moertel et al, 1974; Popiela et al., 1989]. Cannabinoids do not improve appetite in cancer, but can improve chemosensory distorted perceptions of taste (dysgeusia) [Cannabis-In-Cachexia-Study-Group et al., 2006; Brisbois et al., 2011]. Melatonin has been reported to improve weight and reduce chemotherapy related toxicity [Messina et al., 2010; Lissoni, 2002]. A recent randomized control trial comparing melatonin to placebo demonstrated no evidence of weight gain or improved QOL [Del Fabbro et al., 2013]. Trials of anti-TNF antibodies in advanced cancer patients failed to demonstrate any particular benefits [Jatoi et al., 2007; Jatoi et al., 2010]. The beta adrenergic agonist formoterol and clenbuterol block proteasome upregulation, but have significant cardiac side effects [Ryall et al., 2008; Busquets et al., 2004; Chance et al., 1991]. Lycopenes found in tomatoes, red carrots, watermelon and papavas block NF-kappa B, but there is no evidence that lycopenes alone influence the course of cancer or cachexia [Gupta et al., 2011]. Insulin growth factor (IGF-1) stimulates muscle synthesis through activation of downstream mTOR/ALK pathways and certain anabolic kinases (MAP kinases) [Macciò et al., 2012a]. However, IGF-1 has the propensity to stimulate tumor growth [Yang and Yee, 2012; Tognon and Sorensen, 2012; Yap et al., 2011; Chakravarti et al., 2011; Olmos et al., 2010]. Resveratrol, found in wine, blocks NF kappa B. It appears to protect against skeletal muscle loss and cardiac atrophy in animal models, but there is very little clinical evidence for its use in humans [Shadfar et al., 2011; Busquets et al., 2007a; 2007b].

Single agents with evidence of benefit

Progesterone improves appetite in those with advanced

cancer. At least one mechanism involves increasing neuropeptide Y (NPY) levels [McCarthy et al., 1994]. Megestrol acetate has been reported to reduce IL-1 expression [Mantovani et al., 1998]. In animal models, megestrol acetate down regulates proteasomes and E2 and E3 ligases [Melstrom et al., 2007; Vadell et al., 1998]. Therapeutic megestrol acetate doses range from 160-320 mg with benefit seen up to 800 mg a day. Weight gain is largely fat or water, and quality of life is usually not improved as measured by standard scales [Ruiz Garcia et al., 2013; Berenstein and Ortiz, 2005]. If used while individuals are on chemotherapy, there is a risk of fluid overload and thromboembolism. Prophylactic heparin may be considered while on megestrol acetate [Koller et al., 1999; Bodenner et al., 2007]. Thromboembolism is most common within the first three months of treatment. Hyperglycemia can be seen during treatment and hypocortisolism with withdrawal or discontinuation of megestrol acetate [Bulchandani et al., 2008; González Villarroel et al., 2008]. Other side effects are acne, hirsutism, diarrhea, flatulence, insomnia, headache, confusion and dyspnea. Megestrol acetate selectively improves appetite and should be used for those with a life expectancy of three months or more. Anorexia should be significant. Additionally, patients with a negative body image may benefit from the use of megestrol acetate. This drug does not improve fatigue, performance, activities of daily living, or survival [Pascual López et al., 2004; Leśniak et al., 2008]. It is important, therefore, to review reasonable goals of treatment with patients and families when using megestrol acetate for cancer anorexia.

Androgens have been used to treat cancer cachexia. Nandrolone decanoate used weekly during chemotherapy has been reported to reduce weight loss and improve survival in a small group of patients [Chlebowski et al., 1986]. The benefits to testosterone may be more than its effects on muscle synthesis [Burney et al., 2012]. There are anti-inflammatory properties associated with the androgen as demonstrated by down-regulation of TNF, IL-6 and IL-1b [Malkin et al., 2004; Corrales et al., 2009; Zhang et al., 2007]. There are time-dependent effects of testosterone on muscle. Initially, testosterone increases muscles synthesis through increased expression of IGF-1; over time testosterone reduces muscle breakdown [Ibebunjo et al., 2011; Wolfe et al., 2000; Sheffield-Moore et al., 2011]. Testosterone replacement in deficient men improves mood and the ability to concentrate with a trend toward improved fatigue [Jockenhövel et al., 2009]. In a phase III study, comparing oxandrolone 10 mg twice daily to megestrol

acetate 800 mg daily, oxandrolone increased to lean body mass, reduced fat mass and improved anorexia relative to megestrol acetate [Gullett *et al.*, 2010]. Side effects with testosterone are increased transaminases, decreased highdensity lipoprotein, and interactions with oral anticoagulants, hypoglycemics and adrenal steroids. Oxandrolone has a better side effect profile than other androgens, and is well tolerated by women [Gullett *et al.*, 2010].

Nonsteroidal selective androgen receptor modulators (SARMs), such as ostarine, increase lean body mass and performance score, as demonstrated in phase I and phase II trials. Total fat tissue within muscle is reduced. This class of drug has anabolic benefits associated with minimal side effects, and therefore can be used in women as well as men [Zilbermint and Dobs, 2009]. The SARM GTx-024 (endosarm) is presently being tested in individuals with non-small cell lung cancer. Lean body mass and stair climbing power are the two primary outcomes [Anker *et al.*, 2013].

Nonsteroidal anti-inflammatory drugs (NSAIDS) not only treat pain associated with cancer, but also blunt cachexia and muscle loss. Cyclooxygenase inhibitors down-modulate NF-kappa B and reduce mitochondrial dysfunction caused by inflammation [Setia and Sanyal, 2012; Tegeder et al., 2001; Niederberger et al., 2001; Kopp and Ghosh, 1994; D'Acquisto et al., 2002]. In an animal model, indomethacin dose-dependently impaired tumor growth and reduced muscle levels of TNF and E3 ligases [Hitt et al., 2005]. In a retrospective study, indomethacin plus nutritional replacement reduced resting energy expenditures, and improved performance status and pain. There was no improvement in lean body mass relative to those with nutritional replacement alone in advanced cancer patients [Lundholm et al., 1994]. Celecoxib 200 mg twice daily compared with placebo produced a nonsignificant weight gain and a significant improvement in QOL in cancer patients [Lai et al., 2008]. A second celecoxib phase II study used 300 mg daily. Celecoxib reduced inflammatory cytokines, increased lean body mass, reduced the Glasgow Prognostic Scale score and increased hand grip strength [Mantovani et al., 2010a].

The omega-3 polyunsaturated fatty acids (n-3 PUFAs), eicosapentaenoic acid (EPA) and its metabolite docosahexaenoic acid (DHA) are found in fish oils and have been extensively used to treat cancer cachexia. EPA in animal models down-regulates TNF and IL-1 production. Blood levels of acute phase reactants decrease. In phase II studies, EPA and DHA curtailed weight loss in pancreatic cancer patients. In older phase III studies, there have been mixed

results [Barber et al., 1999; Dewey et al., 2007; Jatoi, 2005]. Recent studies have been largely positive. EPA preoperatively reduces surgically induced immune dysfunction and the intensive care admissions [Takagi et al., 2001]. EPA preserved lean body mass and reduced TNF and IL 1 levels in individuals undergoing esophageal cancer surgery [Ryan et al., 2009]. The combination of EPA, plus nutritional support for those undergoing head and neck cancer surgery, increased weight and lean body mass relative to nutritional support alone [Weed et al., 2011]. In a randomized trial, which utilized 2.5 g of n-3 PUFAs daily during chemotherapy for patients with lung cancer, an improved tumor response rate was seen compared to non-supplemented individuals (60% versus 25%); there was an increased one-year survival (60% versus 39%) [Murphy et al., 2011a; 2011b]. In another trial involving patients undergoing multimodality anticancer therapy for lung cancer, 2.9 g of n-3 PUFAs better maintained weight, improved fat-free mass at three and five weeks, reduced resting energy expenditures, lowered IL-6 levels and improved energy and protein intake more than supplements without n-3 PUFAs [van der Meij et al., 2010]. Side effects with n-3 PUFAs are bloating, fish taste or breath and diarrhea. Doses are usually 2-6 g daily. Individuals can be offered capsules or liquid. Blood levels can be measured to gauge absorption and compliance. Therapeutic levels are not established. The greatest benefit appears to occur when used with treatment for early stage cancer or during palliative chemotherapy in newly diagnosed advanced cancer patients [Murphy et al., 2011c].

The spice curcumin, which is closely related to the polyphenol tumeric, inhibits proteasomes and reduces muscle wasting in the MAC-16 cancer animal model. The gain in muscle mass is also due to reduced E3 ligases and inhibition of NF kappa B [Jobin *et al.*, 1999; Singh and Aggarwal, 1995; Bharti *et al.*, 2004]. In a study involving colon cancer patients, 360 mg daily over 10-30 days improved body weight and reduced TNF [Gullett *et al.*, 2011].

L-carnitine in the AH-130 Yoshida ascites hepatoma model increases food intake and muscle mass. The mechanism appears to be due to inhibition of proteasomes, ubiquitin and E3 ligases expression. L-carnitine reduces caspases necessary to initiate muscle catabolism [Busquets *et al.*, 2012]. L-carnitine increases muscles synthesis, reduces reactive oxygen species and improves mitochondrial function [Ringseis *et al.*, 2013]. In addition, l-carnitine preserves hepatic lipid metabolism, as demonstrated in tumor animal models [Silvério *et al.*, 2012]. One of the important functions of l-carnitine centers on oxidative phosphorylation. L-carnitine is necessary for beta-oxidation of amino acid by pyruvate dehydrogenase which is important to the tricarboxylic acid cycle [Gramignano *et al.*, 2006]. In a trial involving individuals with pancreatic cancer randomization between 4 g of l-carnitine versus placebo, L-carnitine improved BMI, lean body mass and quality of life with a trend towards improve survival [Kraft *et al.*, 2012].

Rikkunshito, a traditional Japanese herbal preparation, is commonly used to treat anorexia and gastrointestinal disorders and has been used to treat anorexia associated with cancer. It down-regulates and blocks 5-HT 2C receptors, which decrease activation of POMC containing neurons. Active ingredients are hesperidin and atractylodin, which increase ghrelin release and reduce ghrelin resistance [Arai *et al.*, 2013; Hattori, 2010; Kusunoki *et al.*, 2010; Takeda *et al.*, 2012a; 2012b; Takeda *et al.*, 2010]. Ghrelin signaling is enhanced through up-regulation of hormone secretogogue receptor [Fujitsuka *et al.*, 2012b; Yakabi *et al.*, 2010; Yada *et al.*, 2012]. Rikkunshito blocks cis-platinum induced anorexia and improves appetite after gastrectomy [Hattori, 2010; Takeda *et al.*, 2012b; Yakabi *et al.*, 2010].

Grehlin signaling is impaired in cancer, but can be overcome by increasing ghrelin levels. Intravenous ghrelin temporarily reduces cancer anorexia [Strasser *et al.*, 2008]. An oral ghrelin mimetic, anamorelin, is presently in clinical trials [Northrup *et al.*, 2013; Garcia and Polvino, 2009]. In sixteen patients with different cancers and cachexia, a crossover trial of anamorelin 50 mg/day or placebo for three days, followed by a 3- to 7-day washout period and then a switch to the alternative agent, demonstrated increased body weight compared to the placebo (0.77 *vs.* –0.33 kg) and a trend toward increased food intake [Garcia *et al.*, 2013]. Phase III trials in patients undergoing chemotherapy for lung cancer have just been completed.

Thalidomide reduces TNF and NF kappa B expression [Majumdar *et al.*, 2002; Rowland *et al.*, 2001; Keifer *et al.*, 2001]. Several trials have demonstrated improvement in appetite in cancer patients [Davis *et al.*, 2012; Yennurajalingam *et al.*, 2012; Bruera *et al.*, 1999; Gordon *et al.*, 2005]. Anti-IL-6 monoclonal antibodies (AID 518) have improved anemia of cancer and some of the cachexia domains in phase I and phase II trials [Trikha *et al.*, 2003; Bayliss *et al.*, 2011]. An IL-6 receptor blocker, tocilizumab, is presently undergoing clinical trials [Ando *et al.*, 2013].

Selumetinib inhibits the kinase (MEK) which inactivates mitogen activated protein kinase (MAPK). The MAPK kinase family has been implicated in growth and differentiation of skeletal muscle and proper responses to reactive oxygen species [Roux and Blenis, 2004; Kramer and Goodyear, 2007]. In a study involving individuals with cholangiocarcinoma, 84% of individuals receiving the drug gained muscle mass [Prado *et al.*, 2012].

Angiotensin-converting enzymes (ACE) are upregulated in cachexia and lead to increased muscle catabolism, reduced synthesis and reduced appetite [Yoshida *et al.*, 2013]. The ACE inhibitor, imidapril, in the MA16 colon cancer model blocks tumor growth and loss of lean body mass [Sanders *et al.*, 2005]. In a phase III study, imidapril reduced fatigue, maintained hand grip strength and had a trend toward sparing lean body mass in advance cancer [Onder *et al.*, 2002].

MT-102 is a multiple receptor drug which blocks beta-1 and 2 adrenergic receptors, reducing catabolism and blocking 5-HT 1a and b receptors. MT-102 has a multifunctional effect upon three potential pharmacological targets, each of which is relevant for cancer cachexia, as follows: (I) reduced catabolism through non-selective β -blockade; (II) reduced fatigue and thermogenesis through central 5-HT_{1a} antagonism; (III) increased anabolism. The ACT-ONE trial, a multicenter, randomized, double-blind, placebo-controlled, dose-finding study of MT-102 is near completion [Stewart Coats *et al.*, 2011].

The melanocortin receptor, MC4-R, mediates anorexia and increases resting energy expenditures resulting from activation of POMC neurons within the hypothalamus. Orally active MC4-R blocker, BL-6020/979, has been developed. BL-6020/979 increased food intake and reduced energy expenditures in an animal model, and is presently undergoing clinical trials [Dallmann *et al.*, 2011].

In tumor bearing rats, simvastatin reduced loss of lean body mass and improved cardiac function as well as reduced mortality [Palus *et al.*, 2013]. There are no clinical trials which have specifically tested simvastatin in cancer cachexia.

Exercise and cachexia

Exercise reverses disuse muscle atrophy by stimulating synthesis through up-regulation of the mTor/Akt sympathetic pathway. Exercise blunts the adverse effect of inflammatory cytokines on muscle catabolism and improves mitochondrial oxidative phosphorylation [Bodine, 2006; Gleeson *et al.*, 2011; Daneryd *et al.*, 1990; Adams *et al.*, 2011]. Exercise benefits will depend on the type (aerobic or resistant), time frame and underlying pathology as well as compliance. Compliance may be hindered by bone and CNS metastases and cancer related fatigue. However benefits have been observed in cancer [Lenk *et al.*, 2010; Gould et al. 2013; Ardies, 2002; Argiles et al., 2012]

Combination therapy

Treatment of cachexia, if it is to be successful, needs to be multidrug or multimodal [Macciò *et al.*, 2012a]. Older studies compared single agent megestrol acetate to EPA or cannabinoids, and found the combination of megestrol acetate plus EPA or cannabinoids are no better than single agent therapy in improving anorexia or weight [Jatoi *et al.*, 2002; Jatoi *et al.*, 2004]. A recent study, however, which combined megestrol acetate with olanzapine, a 5-HT 2 receptor blocker, demonstrated improved appetite, weight gain, nausea and quality of life compared with megestrol acetate alone [Navari and Brenner, 2010].

Combinations of different anti-cachectic drugs have been shown to improve certain cachexia domains in animal models. The combination of megestrol acetate plus an NSAID, such as indomethacin, reduced inflammatory markers, blunted tumor induced hypercalcemia, and weight and lean body mass loss in an animal model [Diament *et al.*, 2006]. In another animal model, branched chain amino acids plus EPA and a high protein diet improved weight and normalize daily activities [van Norren *et al.*, 2009].

Nonsteroidal anti-inflammatory drugs combined with EPA, nutrition, l-carnitine and megestrol acetate have demonstrated benefits in cancer patients. The combination of ibuprofen plus megestrol acetate increased body but not water weight, and reduced CRP levels [McMillan et al., 1997]. A combination of megestrol acetate plus ibuprofen improved cachexia better than either agent alone. The combination of megestrol acetate/ibuprofen reversed weight loss and appeared to improve quality of life in patients with advanced gastrointestinal cancer [McMillan et al., 1999]. A combination of EPA plus celecoxib (200 mg twice daily) improved muscle strength and reduced CRP to a greater extent than EPA alone [Cerchietti et al., 2007]. A combination of insulin, erythropoietin, indomethacin and nutritional supplement improved nutritional parameters and physical function, as well as nutritional deficiency, in individuals with gastrointestinal cancers [Lindholm et al., 2004]. A combination of medroxyprogesterone (500 mg twice daily), celecoxib (200 mg twice daily) and food supplements for six weeks in a small group of lung cancer patients prevented weight loss, reduced nausea, early satiety, fatigue and improved appetite and performance status [Cerchietti et al., 2004]. A combination of megestrol acetate plus celecoxib, antioxidants and l-carnitine was

superior to megestrol acetate alone with the outcomes of lean body mass, resting energy expenditures, fatigue and quality of life. The inflammatory cytokines, IL-6 and the acute phase reactants, CRP, were reduced with the combination, but not with t progesterone alone [Macciò et al., 2012b]. The combination of l-carnitine plus celecoxib was as effective as a three drug combination of l-carnitine plus celecoxib plus megestrol acetate. Lean body mass, by dual-energy X-ray absorptiometry and by L3 computed tomography, increased significantly in both arms as well as physical performance assessed by the six-minute walk time. Toxicity was quite negligible and comparable between arms [Madeddu et al., 2012]. The combinations of megestrol acetate plus meloxicam, megestrol acetate plus meloxicam plus EPA and meloxicam plus EPA improved weight, lean body mass and reduced TNF and IL-6 blood levels in 60 patients with advanced cancer [Kanat et al., 2013]. The combination of the beta-adrenergic receptor blocker propranolol plus the NSAID etodolac reversed weight loss in five of seven patients in a phase I study. In the phase II study, 44% had a meaningful (greater than 5%) increase in lean body mass [Benish et al., 2008]. In a large five arm study, antioxidants, megestrol acetate, EPA, l-carnitine plus thalidomide improved appetite and performance status and reduced cytokines, as well as improved a Glasgow Prognostic Scale score compared with single drug therapy [Mantovani et al., 2010b].

In a review of multiple drugs studies for cancer cachexia, it appears that the addition of EPA or a NSAID are important to improve lean body mass [Solheim and Laird, 2012]. Most of the studies are small and probably underpowered. However, it does appear that combination therapy is better than single agent therapy. The use of a NSAID with megestrol acetate, EPA and l-carnitine would be reasonable. The toxicity of EPA and l-carnitine are minimal. If anorexia is a significant problem, then the combination of olanzapine and megestrol acetate should be considered. The number of drugs and dosages are not wellestablished. Hopefully, future trials will provide answers to these questions.

Summary

Cancer cachexia and anorexia adversely affects patients' activities, quality of life, tolerance to anticancer therapy and survival. Physicians need to assess multiple domains to adequately gauge the severity of cachexia on patients. There are multiple simultaneous mechanisms that lead to the clinical manifestation of anorexia and cachexia. These mechanisms occur both centrally and peripherally. There are quantitative reductions in muscle, fat and appetite and qualitative impairments of muscle activation, taste and smell. Single drug therapies are unlikely to have a significant benefit. Combination therapies have recently been tested and show promise. Improved outcomes with treatment include reduction of acute phase reactants and inflammatory cytokines, improved appetite and lean body mass, as well as performance abilities and quality of life. Combinations of drugs plus exercise need to be explored further.

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Part III

Anorexia and cachexia: definitions, clinical presentations, mechanisms and treatments

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Fatigue and sleep difficulties

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Introduction

Fatigue and sleep difficulties used to be considered an inevitable constituent of progressing chronic and debilitating medical conditions in terminally ill patients, with negligible medical relevance or treatment. However, there is a growing recognition on the part of the clinician that attention to fatigue and sleep difficulties is an important and fundamental aspect of caring for this patient population.

Fatigue is one of the most common and enigmatic symptoms in medicine. Our understanding of its pathophysiology is limited for most conditions, particularly in chronically ill patients and patients with progressive degenerative conditions. Fatigue can be difficult to distinguish from potentially similar entities, such as somnolence, depression, and apathy. Several studies have shown that fatigue is an independent phenomenon that is commonly associated with other conditions in patients with terminal diseases, including medication side effects, chronic pain, physical deconditioning, anemia, respiratory dysfunction, depression, and sleep disorders. It is critical to identify and screen for these issues in patients complaining of fatigue and to treat when they are present. Although there may be clinical overlap and interactions between these symptoms and fatigue, they are distinct clinical phenomena. Their relationship is complex and homeostatic-central, peripheral, and psychological factors all contribute to fatigue [Kluger et al., 2013].

The terminally ill patient population is particularly at risk for development of these symptoms. Typically, reported fatigue is a consequence of several factors, including the disease process, treatments, and physiological stress. Cancer itself may lead to problems in cognition, sleep quality, nutrition, and muscle endurance. These issues combined lead to an inability to adapt to daily stressors, which manifests as fatigue [Olson *et al.*, 2008]. Fatigue and sleep disturbances correlate with depression and pain, reducing overall quality of life as well as the patient's ability to cope with their illness and overall situation. To compound the matter, a patient's caregivers are also under tremendous pressure and fatigue, and disturbances in their sleep-wake cycle also may be problematic. In this chapter, we review the different factors associated with fatigue and sleep disturbances in the terminally ill population, the effect of fatigue on other symptoms, and potential treatment options.

How common and troublesome are sleep disturbances and fatigue in terminally ill patients?

Sleep difficulties are common in patients who are terminally ill, leading to significant morbidity and impaired quality of life. Sleep disorders in palliative medicine are exceptionally challenging and devastating to patients and their families. It is important to highlight the diverse spectrum of patients under palliative care. Causes of fatigue and insomnia are multifactorial and encompass a wide spectrum of potential culprits depending on the terminal illness and associated comorbidities. It also is important to establish the distinction between tiredness, sleepiness, and fatigue along with intelligible patient-level assessment of drowsiness, sleep intrusions, and irresistible sleep or napping during the daytime and under circumstances of physical activity. The reported incidence of difficulty sleeping in the palliative population ranges from 32% to 95% [Delgado-Guay *et al.*, 2011; Laugsand *et al.*, 2011; Liu *et al.*, 2011; Sandadi *et al.*, 2011; Miyajima *et al.*, 2013].

Insomnia is often caused by multiple factors in terminally ill patients, and both physical and psychological elements are considered to be etiologically important [Hugel *et al.*, 2004]. These disturbances manifest most commonly as not feeling rested in the morning (72%), difficulty staying asleep (63%), and difficulty falling asleep (40%) [Sela *et al.*, 2005]. In self-reported inventories of patients in palliative care units, severe pain and increased urinary frequency were cited as the symptoms most often contributing to impaired sleep efficiency [Grond *et al.*, 1994; Hugel *et al.*, 2004]. Conversely, improvement in pain control significantly reduced prevalence of sleep disturbances [Meuser *et al.*, 2001].

The presence of depression and worsening anxiety has been associated with impairment in sleep initiation [Sela *et al.*, 2005]. Concerns about family and the future most often create this sense of worry, and about 50% of patients report sleep-disturbing thoughts. Patients have identified family, their diagnosis, and the future as the most prevalent concerns affecting their sleep. These findings were confirmed by a survey of prevalence and nature of insomnia in 982 cancer patients attending oncology outpatient clinics, in which 52% of patients with insomnia attributed worrisome thoughts (38.7% concerns about health, 33% concerns about family and friends, and 32% concerns about cancer diagnosis) to their insomnia [Davidson *et al.*, 2002; Hugel *et al.*, 2004].

Studies have also consistently identified gender differences, with women appearing more prone to insomnia (70%, compared to 51% for men) [Davis *et al.*, 2013]. Other common risk factors for sleep disturbances include younger age, poorer Karnofsky performance status, undertreated pain and discomfort, and primary lung cancer [Khan *et al.*, 2011]. Although most studies involve self-reported symptoms, studies using wristwatch uniaxial accelerometers as markers of nocturnal arousals and sleep disruption have revealed sleep disturbances, showing that patients have increased sleep fragmentation despite sleeping for 7-8 hours [Gibbins *et al.*, 2009]. Sleep fragmentation correlated with pain and anxiety [Gibbins *et al.*, 2009].

Insomnia and sleep maintenance difficulties are directly associated with daytime fatigue. Specifically, there is a correlation between early awakening and difficulty falling asleep with fatigue [Sela *et al.*, 2005]. Cancer-related fatigue is defined as "a persistent, subjective sense of tiredness related to cancer or cancer treatment that interferes with normal functioning" and is not relieved by rest. Fatigue is the most common symptom reported by patients with cancer and has been reported in up to 98% of terminally ill patients [Liu *et al.*, 2011]. Importantly, when asked what symptom is the most troublesome and severe, up to 25% of patients in the palliative care population reported fatigue [Hoekstra *et al.*, 2007]. Fatigue can seriously impact cancer patients' daily lives, more so than pain and depression [Auret *et al.*, 2009]. In contrast with the expectations of doctors, alleviation of fatigue, rather than pain, is the priority for many patients.

Fatigue independently predicts survival time to the same extent as lack of appetite, with a hazard ratio for dying of 1.39 and 1.33, respectively [Liu *et al.*, 2011]. Although sleep disturbances generally remain stable over time in this population, the severity of fatigue may accelerate in the last 90 days of life [Giesinger *et al.*, 2011]. The pathophysiology of fatigue in terminally ill patients remains unknown. Several theories emphasize the importance of proinflammatory cytokines, serotonin, vagal afferent activation, chronic anemia, and disturbances in adenosine triphosphate dysfunction [Wang, 2008].

Sleep disturbances have also been reported in 23% to 42% of caregivers [Gibbins et al., 2009; Carlsson, 2012]. Caregivers have been found to have normal sleep duration but increased fragmentation, which correlates with their anxiety [Gibbins et al., 2009]. Another small study examined 13 caregivers by using structured interviews, self-report questionnaires, and activity monitor data to assess their sleep quality [Hearson et al., 2011]. The interviews indicated that caregivers had light, fragmented sleep that was due to a mixture of hypervigilance, nighttime needs of the patient, lack of support or perceived lack of support through the health care system for overnight needs, and caregiver wellness. Five of the 13 caregivers had excessive daytime sleepiness as scored by the Epworth Sleepiness Scale (ESS), whereas all caregivers had Pittsburgh Sleep Quality Index (PSQI) scores indicating moderate to severe sleep disturbance. Caregivers were awake again for an average total of 41.9 minutes after having fallen asleep, and the total number of sleep interruptions ranged from 4 to 39 per night. Caregivers who are younger and female may be more prone to sleep disturbances [Carlsson, 2012].

Part III

Effect of fatigue and sleep disturbances on other symptoms

The deleterious effects of sleep disruption and fatigue reduce a patient's ability to function during the day and to accomplish everyday activities. Social and family interactions, which are of extreme importance at the end of life, can be compromised. The relationship between different symptoms is complex and in consequence sleep disruption and fatigue can exacerbate other symptoms. Particularly, impaired sleep quality leads to reduced quality of life measures: emotional quality, social interaction quality, physical quality, functional quality, and depression [Sandadi et al., 2011]. The causality of these relationships remains unclear. There is increased recognition of the high prevalence of pain and depression in patients with sleep disturbances [Davis et al., 2013]. Approximately one-third of cancer patients reported pain that interfered with sleep onset, while two-thirds complained of difficulty maintaining sleep through the night because of pain [Banning et al., 1991].

Mystakidou *et al.* [2009] assessed the relationship between sleep quality, depression, and hopelessness in 102 cancer patients in palliative care. Of the 73.5% who had significant sleep deficits, 12.8% had severe depression, 19.6% had moderate to severe depression, 9.8% had mild to moderate depression, and 37.3% had mild depression. In this same group of patients, 16.7% had severe hopelessness, whereas 36.3% were not hopeless. Sleep quality appears to mediate the relationship between depression and hopelessness [Mystakidou *et al.*, 2009]. Despite the tremendous benefit in managing this potentially treatable condition, few health care providers aggressively pursue sleep symptoms in terminally ill patients.

Most sleep disturbances remain stable during advanced cancer diagnosis and treatment. In the subset of patients whose sleep disturbances increase in severity over time, this may be a warning sign of impending delirium and cognitive dysfunction. A change in the "rest and sleep" symptom cluster in one study tended to be the first delirium-associated symptoms to be noted by the family caregivers, and were noted as occurring substantially before cognitive symptoms [Kerr *et al.*, 2013]. This could indicate that the emergence of sleep disturbances is a sign of the decline preceding more obvious delirium [Kerr *et al.*, 2013]. Of the 77 patients with an abnormal sleep measure in one study, 71 experienced at least one episode of delirium as assessed by the observer-rated confusion assessment method [Slatore

et al., 2012]. Poor sleep quality leads to an increased risk of delirium, with a hazard ratio of 2.37 [Slatore *et al.*, 2012].

Maintenance of normal sleep pattern is critical to maintain an appropriate homeostatic balance. Terminally ill patients are particularly at risk for circadian rhythm disorders. When patients have disrupted nighttime sleep, there is a natural tendency to nap during the day and delay the onset of sleep on a subsequent night. This is a vicious cycle that ultimately reverses sleeping patterns so that patients sleep during the day and stay up at night. Conversely, in other patients, pain and disrupted sleep lead to early morning awakenings, in turn leading to evening somnolence and early bedtime. Circadian rhythm disorders cause a significant burden to caregivers because they need to attend to the patient's needs at all hours. Disturbances of the sleep-wake cycle are an integral part of the delirium which affects the vast majority of patients at the terminal stage of their disease [Fainsinger et al., 1991]. Patients with delirium display reversal of the sleep-wake cycle and become agitated and confused at night. Efforts should be directed to correct the specific causes of delirium, particularly medications and intercurrent infections.

Similarly, fatigue may be a result of a decline in status. Data from 63 cancer patients obtained at admission and at discharge assessed on the Edmonton Symptom Assessment Scale (ESAS; 0-10 scale) showed the most intense symptom was poor appetite at the time of admission, followed next by fatigue (3.4 ± 2.6) [Guo *et al.*, 2007]. The same pattern emerged on discharge, although the fatigue score was then 2.2±2.1, indicating a significant decrease in severity of fatigue at discharge. There was also a significant improvement in the poor sleep measure in the discharged patients [Guo *et al.*, 2007].

Etiology of sleep disturbances

Although fatigue and sleep disturbances remain a major concern for terminally ill patients and their caregivers, very few receive adequate treatment. While primary sleep disorders may occur in patients with terminal conditions, sleep disturbances more commonly develop as a consequence or complication of the terminal condition afflicting the patient, and therefore may have multiple causes. Only 20-50% of patients who describe sleep difficulties receive a trial of pharmacological sleep aids [Laugsand *et al.*, 2009; Mystakidou *et al.*, 2009; Laugsand *et al.*, 2011]. A recent study looking at patients who were not adequately treated for sleep problems found they tended to be younger, male, and less active/hospitalized, had physicians rate their sleep problems as less severe than they did themselves, and had cancer that was classified as "other" in the study's criteria (sarcoma, skin, brain, etc.) [Laugsand *et al.*, 2011].

When assessing potential causes and treatment for sleep disturbances and fatigue in any group of patients, it is essential to consider the numerous categories of sleep disorders to identify in individual patients [Sateia and Lang, 2008]. Insomnia, sleep-related breathing disorders, hypersomnolence of central nervous system origin, circadian rhythm sleep disorders, movement disorders, parasomnias, and isolated symptoms/normal variants are the most common forms of sleep disturbances [Sateia and Santulli, 2004]. In cancer patients, the goals for management of dysfunctional sleep focus on treatment of insomnia, daytime sleepiness, and breathing disorders. A comprehensive evaluation of all disorders escapes the scope of this chapter, but we refer the reader to an excellent review of the topic by Sateia and Lang [2008], who describe detailed assessment tools (single-answer and comprehensive selfreport questionnaires, sleep diaries, objective measures such as actigraphy and polysomnography), risk factors (younger age, anxiety, depression, pain, breathing problems), and comorbid disorders that could contribute to insomnia (e.g., depression, breathing difficulties, hot flashes).

A systematic approach to assess potential causes of fatigue and insomnia along with accompanying comorbidites is critical. Medications used to palliate other symptoms or to treat other medical conditions can contribute to insomnia and fatigue, namely, corticosteroids, stimulant antidepressants, bronchodilators/theophylline, and diuretics [Hugel et al., 2004]. Depression and anxiety are common in the terminally ill. It might be difficult to separate clinical depression from normal grief, frustration, or fear encountered in palliative care patients. A high level of suspicion for affective and sympathetic signs of depression is important along with frequent screening for the disease. A simple and widely available self-report questionnaire like the Beck Depression Inventory (BDI) may be helpful. Sleep initiation difficulties are common in patients with anxiety. Early delirium, shortness of breath, pain, nightmares, or medication withdrawal can exacerbate or induce anxiety.

Sleep studies may provide additional information and treatment for patients at risk for physiological causes of sleep disturbances such as obstructive sleep apnea, nocturnal hypoxemia, or restless leg symptoms. Sleep impairment on PSQI significantly correlated with dyspnea [DelgadoGuay *et al.*, 2011]. In a study of 100 cancer patients with nighttime hypoxemia (defined as overnight SaO₂ of <90% for $\geq 2\%$ of sleep time), most subjects had lung cancer or another lung disease [Wilcock *et al.*, 2008]. Patients who had less pain after radiation of symptomatic bone metastases were significantly more likely to have improved sleep at 4- and 12-week follow-up assessments [Khan *et al.*, 2011] Patients may also have electrolyte abnormalities and nutritional deficiencies. Carnitine-deficient patients (n=27) were given doses ranging from 250 to 3,000 mg/day and reported improvements in fatigue, mood, and sleep, with the fatigue improvement being dose dependent [Cruciani *et al.*, 2006].

In some groups of patients, such as those with advanced Parkinson disease (PD) or neurodegenerative tauopathies, restless leg syndrome (RLS) can significantly impair sleep. A study of 385 patients with advanced PD demonstrated benefit for global sleep quality by improved Parkinson Disease Sleep Scale (PDSS) scores at 24 weeks when treated with prolonged-release ropinirole compared to placebo; the unadjusted odds ratio for positive response was 2.9 (95% CI: 1.42, 5.95, P=0.004) [Ray Chaudhuri *et al.*, 2012]. Other medications that have been used in advanced neurodegenerative diseases include melatonin, eszopiclone, and quetiapine.

Two randomized control trials have evaluated melatonin's effectiveness for this patient population. Medeiros et al. [2007] reported statically significant improved sleep quality as measured by the PSQI but no change in polysomnographic abnormalities in 18 patients with PD. The second randomized control trial, by Dowling et al. [2005], revealed significant improvement in subjective sleep disturbance, sleep quantity, and daytime sleepiness as measured by the General Sleep Disturbance Scale (GSDS). Eszopiclone, a nonbenzodiazepine hypnotic like zolpidem, was evaluated in a 6-week randomized controlled trial and improved quality and maintenance of sleep in patients with PD [Menza et al., 2010]. Periodic limb movements of sleep (PLMS) are stereotyped, repetitive leg movements occurring at night at 20-40 second intervals. PLMS are commonly associated with RLS and can result in frequent arousals, impaired sleep efficiency, and somnolence. Treatment with dopamine agonist is the first line of therapy.

There are other frequent causes of insomnia that might affect specific subpopulations of patients. These include the presence of severe nausea at night due to chemotherapy, endocrine difficulties with hot flashes, nocturia, and recurrent muscle cramps.

Approach to diagnosis and critical management decisions

The goal in managing any symptomatic condition in the palliative care model shifts from a curative and preventive approach to one of palliation and symptom management. The management of sleep disorders is no exception. Comprehensive management of sleep disturbances involves addressing medical and psychosocial causes contributing to the problem, as well as treating the symptom as an entity in itself. Proper care will differ greatly among patients and is made more arduous by the subjective rather than objective measure of success. Other factors that must be considered include overall management of pain, how sleep deprivation affects pain threshold and perception, and how psychological factors, such as anxiety and depression, modify the sleep-pain relationship. The majority of patients, however, continue to believe that fatigue is a symptom to be endured, and only half will discuss it with their doctor [Vogelzang et al., 1997].

The first step is to identify the specific problem (fatigue, daytime sleepiness, insomnia, non-restorative sleep) and associated medical comorbidities. Evaluation of psychosocial factors playing a role in patients sleep difficulties and fatigue is commonly ignored, but they play a fundamental part in patients' sleep disturbances. It is useful to distinguish between sleep initiation versus sleep maintenance difficulties, non-restorative sleep (despite seemingly normal amount of sleep), and exacerbating factors. When patients report sleep difficulties, a methodological approach to assess insomnia is recommended, starting with a sleep diary. A systematic approach to evaluate potential factors affecting sleep is suggested. Evaluation of davtime activities, including naps, energy and concentration levels, and motivation is often necessary. A complaint of insomnia should lead to impaired functional activity during the day due to insufficient sleep. Close attention should be paid to new or changes in medications or potential treatable infections. A multidisciplinary approach is encouraged.

Treatment of sleep disturbances

Successful management of insomnia in terminally ill patients requires careful tailoring of the specific causes of sleep difficulties, since there is rarely a single cause. Significant sleep improvement can be achieved with cognitive-behavioral intervention and sleep hygiene. Appropriate sleep depends on psychophysiologic (internal) and environmental (external) circumstances, both of which can be modified with skillful intervention. In terminal patients, daytime activity is often substantially curtailed, and a blurring of the wake-sleep cycle develops, particularly when the daytime routine involves prolonged periods of recumbency. Nighttime mind-racing, anxiety, agitation, and restlessness result in extended non-restful periods of time in bed, which in itself becomes a source of frustration. Improving sleep can greatly improve quality of life. Adequate sleep hygiene is at times, the only intervention required. More commonly, sleep hygiene recommendations are the initial step in a patient's treatment plan (*Table 1*).

Awareness by patients and their providers is the first step. The severity of fatigue and sleep disturbances decreased significantly in 1,373 advanced cancer patients as assessed on the ESAS initially and at the first follow-up appointment (range of 1-4 weeks) after management by an outpatient interdisciplinary team consultation led by palliative care specialists [Yennurajalingam *et al.*, 2013]. After medication and physiological issues are addressed, pharmacological adjuncts may be used. Progressing in this stepwise pattern is essential, as one study showed that only 62% of patients' insomnia improved with pharmacological sleep aids [Hugel *et al.*, 2004]. When these patients were asked what would help them to sleep better, 38% said better control of other symptoms and 21% said addressing their worries [Hugel *et al.*, 2004].

There is no consensus regarding the most effective antidepressant in terminally ill patients. The selection of antidepressants depends on other symptoms or comorbidities. Tricyclic antidepressants have the potential advantage of mild sedation and chronic analgesic proprieties, which can help patients with insomnia or pain. Mirtazipine can be useful in patients with insomnia and weight loss due to weight gain properties and selective serotonin reuptake inhibitor (SSRI) and serotoninnorepinephrine reuptake inhibitor (SNRI) depending on the dose. In patients complaining of daytime sleepiness or sedation due to narcotics, the use of bupropion or fluoxetine can be entertained. Citalopram or escitalopram are good alternatives in patients with concerns for drug interactions, gastrointestinal complaints or with agitated depression. Sertaline can be useful as well as might cause initial activation and increased alertness. Duloxetine and venlafaxine are good alternatives in patients with depression and chronic pain, or patients that failed SSRIs. Sleep

Establish a regular time for going to bed and getting up in the morning. Stick to this schedule even on weekends and during vacations Avoid unnecessary time in bed during the day. Use the bed for sleep and sexual relations only, not for reading, watching television, or working Avoid naps, especially in the evening Maintain an active schedule during the day Exercise if possible before dinner. A low point in energy occurs a few hours after exercise; sleep will then come more easily. Exercising close to bedtime, however, may increase alertness Consider taking a hot bath about 1.5-2 hours before bedtime. This alters the body's core temperature rhythm and helps people fall asleep more easily and more continuously. (Taking a bath shortly before bed increases alertness) Engage in relaxing activities 30 minutes before bedtime. Reading, meditation, and a leisurely walk are all appropriate activities Keep the bedroom relatively cool and well ventilated Avoid looking at the clock. Obsessing over time will just make it more difficult to sleep Eat light meals, and schedule dinner 4-5 hours before bedtime. A light snack before bedtime can help sleep, but a large meal may have the opposite effect Spend at least half hour in the sun each day. The best time is early in the day. (Take precautions against overexposure to sunlight by wearing protective clothing and sunscreen.) Avoid fluids just before bedtime so that sleep is not disturbed by the need to urinate Avoid caffeine, nicotine or alcohol in the hours before sleep If still awake after 15-20 minutes, go into another room, read or do a quiet activity using dim lighting until feeling very sleepy. (Don't watch television or use bright lights) Maintain appropriate pain control through the night as indicated

Maintain appropriate pair control through the right as indicated

If a specific worry is keeping one awake, thinking of the problem in terms of images rather than in words may allow a person to fall asleep more quickly and to wake up with less anxiety

deprivation negatively impacts pain perception, particularly at night. There is consistent evidence showing that improved pain control translates into better sleep. We refer the reader to the comprehensive review of pain issues in previous chapters.

Table 1 Sleep hygiene recommendations for patients

Behavioral therapy

Cognitive-behavioral intervention has emerged as a mainstay in the management of chronic insomnia. Cognitive behavioral therapy (CBT) can be useful for management of pain and insomnia. Pigeon *et al.* [2012] studied CBT in patients suffering from both. Insomnia, fatigue, and depression did improve in patients with either sleep-focused or sleep/pain-combined CBT. Pain measures did improve in some for interventions targeting pain, but not significantly across the group. CBT for insomnia essentially attempts to control negative thoughts of difficulties falling asleep, not acquiring adequate duration of sleep, or number of nighttime awakenings and replaces them with improved sleep behaviors such as sleep hygiene, stimulus control, and relaxation [Mallick, 2009]. Harvey *et al.* [2007] report the results of an open trial of CBT for chronic insomnia with follow ups at 3, 6, and 12 months. In terms of primary outcomes, the group reported statistically significant reduction of Insomnia Severity Index (ISI) to 11.66 at 12 months as compared to a pretreatment value of 23.92. In terms of secondary outcomes, daytime impairment as assessed by the Work and Social Adjustment Scale (WSAS) was significantly lessened even after 12 months indicating a role for cognitive therapy as an intervention to improve daytime functioning in insomnia.

Biofeedback and progressive muscle relaxation have been investigated in small trials with reported reduction in sleep latency and increase in total sleep time [Morin *et al.*, 1994]. Other non-traditional modalities of treatment may also be of benefit. Bright light exposure in the morning, allday light exposure, dawn-dusk simulation light exposure, evening light exposure, and dim but short-wavelength (blue) evening light exposure have all shown some success in increasing sleep efficiency and/or consolidating sleepwake cycles [Hanford and Figueiro, 2013]. A proposed ideal lighting situation is 600 whole-day or 1,000 lux at the cornea 2-hour light stimulation during the day, no more than 60 lux light available during the evening, and 5-10 lux motion sensor nightlights to provide some light to prevent falls, and/or dim LED strip lighting to orient patients to doorframes and pathways [Hanford and Figueiro, 2013].

Aromasticks are sniffable cartridges for personal use that contain aromatherapy scents. For insomnia, 71% of 31 patients in one study found the sticks helpful, with 89% of those using it every 2-3 hours reporting a beneficial effect, whereas 77% of occasional users found it beneficial [Stringer and Donald, 2011].

Pharmacological therapy

When considering the use of pharmacological therapy, several factors need to be considered, including drug pharmacokinetic properties, tolerance, drug escalation, potential interactions, long-term efficacy, and possible risks. Pharmacological treatment generally starts with the use of a benzodiazepine. The clinical safety of these drugs has been well established. Short-acting benzodiazepines administered before bedtime result in less daytime sedation and are the accepted standard of care. Clinicians should be aware of potential rebound insomnia following abrupt withdrawal of medication. In a study comparing temazepam and zolpidem, 26 of 50 patients prescribed temazepam (52%) had their insomnia completely improved, whereas only 11 (22%) of the patients initially prescribed zolpidem showed improvement [Weschules et al., 2006]. No improvement was seen in 26% of temazepam patients and 34% of zolpidem patients. Matsuo and Morita [2007] compared 104 patients that received midazolam for an average of six days to 59 patients that received flunitrazepam for an average of nine days. There was a trend for better sleep in the midazolam group. The flunitrazepam group experienced more respiratory depression, but otherwise there were no significant differences in common side effects (e.g., delirium, treatment-related death).

Other medications have also been discussed. Thirty cancer patients with insomnia who did not respond well to standard hypnotics (benzodiazepines and/or zolpidem) were prescribed trazodone [Tanimukai *et al.*, 2013]. After dose titration, 50% of the patients showed improvement

in their insomnia. Fifty percent of patients with distressful nightmares (2 of 4) also had improvement. Trazodone has a shorter half-life than most tricyclic antidepressants and milder anticholinergic side effects, increasing tolerance and limiting adverse effects. Starting dose is typically 50 mg daily and may be titrated up to 300 mg daily if needed. Despite the lack of large clinical trials, melatonin has received increased attention in supportive care with sleep difficulties, and it can be extremely beneficial in circadian rhythm disorders when administered at the right time of the day [Mahmoud *et al.*, 2005; Zee *et al.*, 2013].

Treatment of fatigue is difficult. Appropriate management of identified risk factors and measured physical activity and exercise can be helpful. Methylphenidate and other stimulants have been evaluated with partial success. In one study of 50 patients, 96% had improvement in depression and/or fatigue [Lasheen *et al.*, 2010]. A retrospective study showed fatigue improved in 61% of patients with methylphenidate [Yennurajalingam *et al.*, 2011]. Response on day 1 was a predictor of benefit on day 8.

Although atypical antipsychotics are widely used in the treatment of delirium, well-designed studies do not exist. Among the existing studies, stronger data support the use of risperidone and olanzapine, and also quetiapine may be considered in the treatment of delirium. Recommendations are made on the basis of existing data and literature. The need for well-designed studies to validate the use of atypical antipsychotics in the treatment of delirium continues [Boettger and Breitbart, 2005]. Risk and benefits of using dopamine-blocking agents need to be carefully balanced due to potential side effects and concerns of increased cardiovascular morbidity and mortality.

Summary

Sleep and fatigue are common concerns in terminally ill patients that greatly impair their quality of life. The cause of these symptoms is multifactorial, and several organic and psychosocial conditions play important roles. Adequate identification and treatment of associated comorbidities and individual factors causing or exacerbating fatigue and impaired sleep are necessary to appropriately treat patients. Appropriate sleep hygiene measures and nonpharmacological interventions are a critical component of management. If pharmacological treatment is deemed necessary, a variety of treatment options are available. Further studies for treatment of fatigue and sleeping difficulties are needed in the palliative care population.

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Etiology, pathogenesis and management of pruritis

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Introduction

Pruritis or itch is a sensation that causes the desire or reflex to scratch [Bergasa, 2004]. While it is not the most common symptom experienced by palliative care patients, it can be a very intrusive and distressing symptom that has a very negative impact on quality of life [Sheehan-Dare *et al.*, 1990; Seccareccia and Gebara, 2011]. According to one study, patients with moderate to severe pruritis were more likely to have poor sleep quality and receive a diagnosis of depression when compared to patients with mild or no pruritis [Wikstrom, 2007]. The condition can be very frustrating for patient and physician alike, since there usually is little effective treatment.

Most pruritic conditions in the palliative care patient population do not originate in the skin. Rather, they result from systemic illnesses such as renal failure, solid tumor malignancies, hematologic issues or iatrogenically from chemotherapy, radiation therapy, surgery, or opiates given to patients for pain management (*Table 1*). Unfortunately, there is no one cure for all pruritic symptoms. In nearly all of these types of pruritis, the pathogenesis of the pruritis remains unclear; this makes it very difficult to design effective treatments regimens for many of these cases.

To make matters more difficult, the volume of literature on the management of pruritis is sparse because the prevalence of severe pruritis is low and the causes are numerous (thus making sample sizes small). However, the prevalence of pruritis in palliative care patients may be higher than what is reported in the literature for the following reasons: (I) many of these patients have other symptoms, such as nausea, pain, vomiting or constipation, which are more likely to be reported to a physician; (II) physicians are less likely to ask a patient about pruritis than the other aforementioned symptoms; and (III) pain, a very common symptom of this patient population, may suppress pruritis [Zylicz, 2004].

This chapter will focus on the different types of pruritis, the typical presentation of each category of pruritis, the current literature regarding proposed pathogenesis of each type of pruritis, and current successful treatments in the management of pruritis in these particular patient populations. In addition, information on general skin care, which can be applied to any patient experiencing pruritis regardless of etiology, will be described (*Table 2*).

Categories of pruritis

Pruritoceptive pruritis

Pruritoceptive pruritis is one that originates from the skin or mucus membranes (peripheral origin). The itching sensation is the direct result of activation of dedicated mechano-insensitive unmyelinated free nerve endings in the skin known as C fibers (pruriceptors) that are located superficially in the skin. These C fiber nerve endings become activated once they interact with any one of a number of pruritogens. Once activated, these nerve endings send impulses to the dorsal horns of the spinal column, and then continue to send the signal up the spinothalamic tract and finally up to the somatosensory cortex in the brain, where the input is then processed and perceived as an itch [Yosipovitch *et al.*, 2003; Zylica *et al.*, 2004; Seccareccia and Gebara, 2011].

The most well known pruritogen is histamine. Several other less common pruritogens include various cytokines, proteases, amines, neuropeptides (e.g., substance P), growth factors, and eicosanoids which either stimulate the release of histamine from local mast cells in order to activate C fibers and/or do so directly [Lerner, 1994; Twycross *et al.*,

Table 1 Common causes of pruritis in the palliative care patient
population
latrogenic
Opioids
Chemotherapy
Radiation therapy
Surgery
Renal
Chronic renal failure
Hepatic
Cholestatic
Intrahepatic causes
Primary biliary cirrhosis
Sclerosing cholangitis
Cholangiocarcinoma
Chronic Hepatitis C
Extrahepatic causes
Pancreatic cancer
Other intraabdominal masses
Solid tumor
Obstruction of biliary tree
Paraneoplastic syndrome (e.g., breast, prostate, lung,
stomach, nasopharynx, larynx, colon, and uterus)
Other malignancies (cerebral tumors)
Hematologic
Polycythemia vera
Hodgkin's lymphoma
Sézary's syndrome
Multiple myeloma
Myocosis fungoides
Leukemias
Psychogenic
Depression
Generalized anxiety disorder

2003; Seccareccia and Gebara, 2011]. This fact explains why not all itching sensations respond to antihistamine agents. Examples of pruritoceptive pruritis include urticaria and any type of dermatitis.

Neuropathic pruritis

This is a type of itch that can originate at any point along the afferent pathway as a result of damage to the nervous system. Lesions anywhere in the peripheral nervous system or central nervous system that damage itch-transducing, conducting, or processing neurons appear capable of causing neuropathic itch [Oaklander, 2011]. This type of pruritis can be observed in cases of peripheral nerve lesions, which can result from herpetic infections [Oaklander et al., 2002], in cases of peripheral nerve entrapment, as in notalgia paresthetica [Savk et al., 2000], or can be secondary to brain masses or multiple sclerosis [Adreev and Petkov, 1975; Yosipovitch et al., 2003]. Patients with itch often develop skin changes from prolonged scratching (e.g., lichenification), but scratching into deeper tissues is virtually pathognomonic for neuropathic itch. For this to develop requires not only intractable itch but also colocalizing severe sensory loss that renders scratching painless and permits it to continue to the point of self injury [Oaklander, 2011]. The most common location is on the face (trigeminal trophic syndrome). Treating neuropathic itch is difficult; antihistamines, corticosteroids, and most pain medications are largely ineffective. Current treatment recommendations include local or systemic administration of inhibitors of neuronal excitability (especially local anesthetics) and barriers to reduce scratching [Oaklander, 2011].

Neurogenic pruritis

This is an itch that is sensed in response to an accumulation of circulating endogenous or exogenous toxins in the central nervous system, in the absence of any neural damage. These toxins either act directly or indirectly on the pruritogenic pathway. One of these "toxins" includes opioids, which are thought to be produced in greater amounts or abnormally retained in patients with either uremia or cholestasis [Peer *et al.*, 1996; Jones and Bergasa, 1999]. Several experts believe that opiates have direct excitatory effects on C fibers in the spinal cord that transmit the itch sensation, thereby causing neurogenic pruritis [Ballantyne *et al.*, 1988]. Examples of neurogenic pruritis include intraspinal administration of opioids, as well as cholestatic and uremic itches [Greaves, 2010].

Psychogenic pruritis

Psychogenic pruritis, the least common of the four types, has no identifiable cause and is associated with psychiatric disorders, such as the delusional state of parasitophobia, picker's nodules, generalized anxiety disorders, depression, and stress related chronic anogenital pruritis [Yosipovitch *et al.*,

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	Other considerations	oation, (I) First-line treatment for indication sorption (II) Morning dosing is preferred	(l) Second-line treatment for indictation(ll) Requires close follow-up with physician	 al-like reaction (I) Third-line treatment for pruritis of sure, cholestasis lis, nightmares, (II) Requires close follow-up with hepatotoxicity physician 	 val-like reaction (I) Third line treatment for pruritis of cholestasis (II) Can also be administered as patient-controlled analgesia (PCA) 	t gain (I) Wide therapeutic index so it can be used safely with many other drugs (II) Sparse evidence in the literature of efficacy	 (I) Typically relieves pruritis within 3 days of starting regimen (II) Degree of initial nausea and vomiting appears correlated to efficacy as anti-pruritic 	 zziness, (I) First-line treatment for patients with pruritis secondary to solid tumor (II) Well tolerated (III) Does not change the levels of anesthesia 	laise, flu-like (I) Also effective at treating PV itself Igia, bone pain (Iowers platelet and leukocyte counts, decreases need for phlebotomy)	ache (II) Beware of numerous drug interactions (III) Can potentiate the effects of several opioids	ise, nausea (I) Generally well-tolerated
Table 2 Evidenced-based pharmacologic interventions for the various types of pruritis	Side effects	Bloating, consti intestinal malab	Hepatotoxicity	Opioid withdraw (high blood pres tachycardia, chi abdominal pain)	Opioid withdraw	Sedation, weigh	Nausea, fatigue	Constipation, di headache	Generalized ma symptoms, mya	Dizziness, head	Headache, mala
	Mechanism of action	Bile acid sequestrant (prevents reabsorption by gut)	Induces hepatic metabolism	Opioid receptor antagonist	Opioid receptor inverse agonist	5-HT ₂ , 5-HT ₃ , H, receptor antagonist (major receptors associated with pruritis	Selective serotonin (5-HT ₃) reuptake inhibitor	5-HT _a receptor antagonist	Not fully understood but known to have antiproliferative effects	Histamine H ₂ -receptor antagonist	Antagonizes substance D/nonvokinia_1
	Dosage	4 g PO every 2-4 hours (max dose 16 g/day)	150 mg PO daily if serum bilirubin <3 mg/L; 150 mg PO twice daily if serum bilirubin ≥3 mg/dL	12.5 mg PO daily increased by 12.5 mg every 3-7 days as tolerated (up to 50 mg) until pruritis abets	0.2 µ/kg/min intravenous continuous infusions preceded by 0.4 mg intravenous bolus	15-30 mg PO at night	10-20 mg PO daily	8 mg intravenous	3 MU TIW or 1.5 MU six times/week, given subcutaneously	200 mg PO tablet at meals and 400 mg PO tablet at bedtime (1 g/day)	day 1 and 80 mg PO
	Indications & studies showing efficacy	Cholestasis [Datta and Sherlock, 1966; Van Itallie <i>et al.</i> , 1961] Renal [Robertson and Mueller, 1996; Silverberg <i>et al.</i> , 1977; Peer <i>et al.</i> , 1996]	Cholestasis [Ghent and Carruthers, 1988; Podesta <i>et al.</i> , 1991]	Cholestasis Wolfhagen <i>et al.</i> , 1997; Terg <i>et al.</i>] Renal [Peer <i>et al.</i> , 1996]	Cholestasis [Bergasa <i>et al.</i> , 1995] Opioid Induced [Murphy <i>et al.</i> , 2011]	Cholestasis [Davis <i>et al.</i> , 2003] Renal [Davis <i>et al.</i> , 2003] Hematologic [Davis <i>et al.</i> , 2003]	Cholestatic Unotoro <i>et al.</i> , 2010; Zylicz <i>et al.</i> , 2003] Solid Tumors [Zylicz <i>et al.</i> , 2003] Hematologic [Zylicz <i>et al.</i> , 2003; Demierre and Taverna, 2006]	Opioid Induced [Borgeat and Stiremann, 1999; Tan <i>et al.</i> , 2010; Charuluxananan, 2003]	Polycythemia vera (PV) induced pruritis [Muller <i>et al.</i> , 1995]	Hodgkin's Disease [Aymard <i>et al.</i> , 1980]	Cutaneous T-cell lymphomas [Booken <i>et al.</i> , 2011]
	Treatment	Cholestyramine	Rifampin	Naltrexone	Naloxone	Mirtazapine	Paroxetine	Ondansetron	Interferon-a2b	Cimetidine	Aprepitant

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2003; Zylicz et al., 2004; Weisshaar et al., 2008; Greaves, 2010].

Opioid induced pruitis

Overview

Itch is a common and well known side effect of opiate administration, but it is more commonly seen in patients receiving opiates via spinal and epidural administration than systemic administration. Pruritis occurs in approximately 1% of patients who receive systemic opioids, whereas 8.5% and 46% of patients receiving epidural and spinal opiates experience pruritis, respectively [Ballantyne *et al.*, 1988], although the incidence depends on whether or not the patient is opioid-naïve and which opioid was used [Twycross *et al.*, 2003; Ballantyne *et al.*, 1989].

The distribution of pruritis depends upon the route of administration as well. Patients who receive systemic opiates typically experience generalized pruritis. On the other hand, patients who receive epidural and spinal opiates usually experience a segmental distribution of pruritis that usually centers at the level of the injection or is localized to a particular area of the body— often times the face [Ballantyne *et al.*, 1988]. In terms of timing, pruritis usually begins within 6-12 hours of an intrathecal administration, and can resolve within the first or second day of administration as a result of tolerance [Cousins and Mather, 1984].

Pathogenesis

Although the exact mechanism of pruritis development in patients receiving systemic, epidural and spinally administered opiates remains unknown, some experts postulate that pruritis may be due to the fact that opiates have excitatory effects within the spinal cord and thereby can activate pruritic pathways in the central nervous system. However, systemic opioids may also act at other areas in the peripheral and central nervous system, possibly the midbrain, to exert anti-pruritogenic effects, which would explain the lower incidence of pruritis observed in these patients. In the case of intradermally administered opioids, pruritis may also be due in part to histamine release from dermal mast cells [Schmelz and Handwerker, 2004; Levy *et al.*, 1989].

Treatment

The most effective treatment is an opioid antagonist like naloxone, an opioid inverse agonist. One metaanalysis of 800 post-surgical patients experiencing pruritis secondary to opioid administration found that compared to patients who received IV saline, those who were given IV naloxone were 60% less likely to suffer from pruritis. Additionally, when compared to the control group, there was no significant difference between the amount of opioid consumption, the risk of sedation, or emesis [Murphy et al., 2011]. Nalbuphine, a mixed opioid agonist-antagonist, has also proven effective in the treatment of pruritis secondary to intrathecal and epidurally administered opioids, without reversing analgesia after administration [Penning et al., 1988; Somrat et al., 1999]. Finally, granisetron and ondansetron, serotonin 5-HT₃ receptor antagonists, are also effective in relieving pruritis caused by intrathecal morphine [Charuluxananan et al., 2003; Tamdee et al., 2009; Tan et al., 2010]. In one study, 80% of patients experienced symptomatic relief within 15 minutes of receiving ondansetron [Tamdee et al., 2009].

Renal pruritis

Overview

Renal pruritis is the most common internal systemic cause of pruritis. It can be generalized or localized, present intermittently or constantly, and often times, can be intractable. It is a severe form of pruritis experienced by up to 80% of patients with chronic renal failure (dialysis and non-dialysis patients alike) [James *et al.*, 2011]. It appears to occur independent of age, gender, specific underlying renal disease, or dialysate used. Despite the fact that recent studies have found a reduction in the prevalence of pruritis among hemodialysis patients (perhaps due to newer dialysis equipment and technology), this distressing symptom still occurs at unacceptably high rates among end stage renal disease (ESRD) patients and its etiology and management require discussion and further exploration [Pisoni *et al.*, 2006; Narita *et al.*, 2006].

Pathogenesis

Although several hypotheses have been proposed, the pathogenesis of pruritis in chronic renal failure patients remains largely unknown, although there are believed to be several causal factors. Many of these patients suffer from xerosis ("dry skin"), which is a known cause of pruritis. Chronic dialysis patients are also known to have increased skin divalent ion content (namely calcium, magnesium, and phosphorus), resulting in microprecipitation if calcium or magnesium phosphate, which can cause itch [Blachley *et al.*, 1985]. In addition, uremic patients are more likely to have

secondary hyperparathyroidism, increased serum histamine and serotonin levels, hypervitaminosis A, dysfunction of the immune & opioidergic systems, and iron deficiency anemia than the general population, and all of these factors have been postulated to cause pruritis [Balaskas *et al.*, 1998; Schwartz and Iaina 1999; Biro *et al.*, 2005; Lugon, 2005; Pisoni *et al.*, 2006; James *et al.*, 2011].

Treatment

Given that a great majority of these patients have xerosis, emollients, otherwise known as moisturizers, can be administered to these patients and should be combined with all other treatments. See the section on general skin care for further information. Ultraviolet B (UVB) therapy, while its mechanism of action remains unclear, has also been shown to be quite effective in alleviating pruritic symptoms in this patient population. One study that found 100% of chronic dialysis patients treated with UVB experiencing resolution of symptoms [Blachley *et al.*, 1985]. A new UVB option—narrow band UVB therapy, has been proven effective and is well tolerated in patients with generalized pruritis, although more controlled trials are needed to determine its true effectiveness in patients with renal pruritis [Seckin *et al.*, 2007].

Cholestyramine may also be an effective anti-pruritic agent for this patient population, given that some experts believe bile acids may play a role in the pathogenesis of renal pruritis. However, only one double-blinded placebo study that included ten patients with renal pruritis found it to be efficacious, with four out of five patients receiving cholestyramine experiencing resolution of symptoms [Silverberg et al., 1977]. Naltrexone, an opioid receptor antagonist, was shown to offer short-term alleviation of renal pruritis in a small randomized, double-blinded, placebocontrolled crossover trial, consisting of 15 dialysis patients [Peer et al., 1996]. Given the known antipruritic activity of serotonin reuptake inhibitors in patients with generalized pruritis and the postulation that serotonin is implicated in renal pruritis [Zylicz et al., 1998], these patients can also be given a trial of mirtazapine and paroxetine. Other therapies that have shown positive effects on renal pruritis in small studies include acupuncture, activated charcoal, heparin, cholestyramine, and thalidomide [Narita et al., 2008]

Of note, while H₁-antihistamines are valuable treatment modalities in patients with other forms of pruritis, studies have shown that these agents do not provide significant relief to those with renal pruritis. Therefore, it is postulated that histamine alone is not a major contributing factor to pruritis in these patients [Ponticelli and Bencini, 1992; Krajnik and Zylicz, 2001a].

Pruritis of cholestasis

Overview

Pruritis is very commonly seen in patients with cholestasis; in fact, 25-80% of patients with jaundice or chronic cholestatic liver diseases, such as primary sclerosing cholangitis and primary biliary cirrhosis complain of pruritis [Jones and Bergasa, 2004; Bergasa, 2005; Lindor *et al.*, 2009]. Fluctuation in severity is common and can lessen as end-stage liver disease develops. In this setting, pruritis tends to be migratory but generalized, and is typically worse on the hands, feet and body regions constricted by clothing. The itching is not relieved by scratching, and is typically worse at night [Weisshaar *et al.*, 2008].

Pathogenesis

It remains unclear as to how cholestasis causes pruritis. Similar to patients with renal pruritis, these patients also have increased serum and tissue concentrations of histamine and serotonin, as well as steroid hormones, endogenous opioids and steroid hormones. However, currently, none of these substances have been found to directly cause pruritis [Decock *et al.*, 2012].

In the past, experts postulated that bile acids that deposit in the skin were responsible for the pruritis but there was no clear correlation between the level of bile acids in the patient's serum and the severity of pruritis experienced by the patient. Furthermore, bile acids were never found to be able to induce neurophysiological changes to mediate pruritis [Jones and Bergasa, 2004]. Therefore, the theory has lost favor. Determining what causes pruritis in patients with cholestasis is further confounded by the fact that a decrease in itching in a patient with known cholestasis is not associated with a decrease in severity of cholestasis or improvement in hepatocellular function.

One current thought is that pruritogenic substances, which remain unknown, are produced in the liver and normally excreted from the body in bile, accumulate in body tissues are a direct result of the patient's cholestatic process. A second thought is that pruritis of cholestasis is mediated by increased opioidergic tone in the central nervous system given the fact that opiate antagonists decrease the perception of pruritis [Jones and Bergasa, 1990]. Needless to say, without a clear and
comprehensive understanding of the underlying pathogenesis of pruritis in this patient population, management pruritis secondary to cholestasis remains challenging.

Treatment

The first step in management of pruritis in a patient with cholestasis is to determine if the patient has cholestasis due to biliary obstruction, as this can be relieved by endoscopic, surgical, or radiologic corrective treatment. Once an obstructive cause of pruritis is either treated or ruled out, therapy is mainly systemic.

The American Association for the Study of Liver Diseases (AASLD) and European Association for the Study of the Liver (EASL) recommend using the oral bile acid resin cholestyramine as first line treatment. Although it is usually well tolerated, some patients experience gastrointestinal symptoms such as diarrhea, constipation or bloating [Beuers et al., 2009; Lindor et al., 2009]. Rifampin, an antimycotic agent that upregulates the expression of liver enzymes involved in detoxification and clearance of toxic substances from the body, is effective in treating pruritis in patients with pruritis of cholestasis secondary to primary biliary cirrhosis, according to the literature [Ghent and Carruthers, 1988; Podesta et al., 1991], and is currently a second line treatment. Patients put on this medication require close and regular follow-up with their physician given that there are known cases of patients developing hepatitis, renal and/or hepatic failure and hemolysis.

Since there is evidence suggesting that cholestasis may lead to increased opioidergic neurotransmission, opioid antagonists are third line treatment in management. A meta-analysis that included five trials of opioid antagonists found that opioid antagonists, such as naloxone and naltrexone, were significantly more likely to control pruritis than control interventions [Tandon *et al.*, 2007]. Ultraviolet B phototherapy also appears to be a promising modality of therapy, as reported by one small observational case study that included patients with pruritis due to a variety of cholestatic liver disorders [Decock *et al.*, 2012]. Other agents used that have been tried in this patient population, but with limited success, include ondansetron and sertraline [Lindor *et al.*, 2009].

Pruritis of solid tumors

Overview

Pruritis, while certainly not the most discussed symptoms

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a cancer patient may complain of in the clinical setting, has been shown to affect roughly one quarter of patients with solid tumors, according to one study which looked at the prevalence of different symptoms that patients with colon, prostate, breast and ovarian cancer experience [Portenoy *et al.*, 1994]. Nevertheless, as previously discussed, the presence of pruritis can have a profound impact on a patient's quality of life. Although infrequent, generalized pruritis can be the one of the earliest presenting symptoms of an underlying solid tumor, and can sometimes present several years before the solid tumor is discovered [Cormia, 1965; Beeaff, 1980; Lober, 1993].

Pruritis can be a direct result of an underlying solid tumor, as in the case of cutaneous metastases [Tjalma and Watty, 2003; Twycross et al., 2003], or it may be indirectly related to the ongoing cancer. This indirect relationship between the cancer and its symptom is known as a paraneoplastic symptom-a consequence of the presence of the cancer or tumor growth within the body, but not due to the local presence of the cancer process [Darnell and Jerome, 2011]. This can occur in patients with an ongoing cholestatic picture as a result of a tumor of the biliary tree (e.g., cholangiocarcinoma), or compression of the biliary tree, as seen with pancreatic and hepatic cancers, or metastasis. Unfortunately, in the case of pancreatic cancer, symptoms are usually absent until the overall prognosis of the patient is poor [Holly et al., 2004]. Other types of malignancies in which pruritis has been reported as a paraneoplastic symptom include tumors of the breast, prostate, lung, stomach, nasopharynx, larynx, colon, and uterus, and others [Cormia, 1965].

As a general rule, itching associated with solid tumor cancers can be generalized or localized, can wax and wane in intensity, and the skin is typically free of visible lesions. If it is localized, it is usually experienced on the upper thorax, shoulders, extensor surfaces of the upper extremities, pretibial areas, and inner aspects of the thighs [Krajnik and Zylicz, 2001b]. Certain types of cancer are associated with very specific localized areas of pruritis. These include scrotal itch in prostate cancer, vulvar itch in cervical cancer, perianal itch in colon and rectal cancers, and nasal itch in brain tumors in the vicinity of the fourth ventricle [Twycross *et al.*, 2003].

Pathogenesis

The pathogenesis of neoplastic pruritis remains poorly understood but appears to involve an immunological response to tumor specific antigens. Other have proposed that pruritis due to toxins presents on necrotic products of tumor that break off, gain access to the systemic circulation, and provoke a cellular response. Another thought is that the disease state of cancer may make skin more sensitive to external irritants [Krajnik and Zylicz, 2004a].

Treatment

Treatment of pruritis in the cancer population should focus primarily on treating the underlying malignancy unless the patient's underlying process is incurable and he or she presents solely for symptomatic management. In cases of extrahepatic biliary obstruction, decompression through the use of biliary stents can be effective, and are currently the treatment of choice as the procedure is well tolerated and the risks are minimal [Krajnik and Zylicz, 2001b; Twycross *et al.*, 2003].

For patients with paraneoplastic pruritis, the first line treatment is paroxetine. One study found that twenty four of twenty six patients (seventeen of whom had solid tumors) experienced at least a 50% reduction in their pruritic symptoms after an average of three days on the medication. However, half of the patients suffered the side effects of nausea and vomiting [Zylicz *et al.*, 2003] For cases in which paroxetine is not effective or cannot be tolerated by the patient, mirtazapine, an H₁, 5HT₂, and 5HT₃ receptor blocker, can be tried [Davis *et al.*, 2003]. However, there is not much evidence in the literature to suggest it has much efficacy.

Pruritis of hematologic disorders

Overview

Pruritis is a fairly common symptom associated with several hematological disorders such as polycythemia vera (PV), Hodgkin's lymphoma, and Sézary's syndrome, and less common with other blood disorders such as multiple myeloma and mycosis fungoides. In patients with PV, Hodgkin's lymphoma, and Sézary's syndrome the prevalence of generalized pruritis is roughly 50%, 25%, and 100% respectively [Winkelmann and Muller, 1964; Arroyo and Aubert, 1971; Steinman and Greaves, 1985; Diehn and Tefferi, 2001].

A majority of patients with PV suffer from temperatureinduced itching, which is characterized by intense itching, sometimes co-occurring with burning sensation, after contact with water. This is known as "aquagenic pruritis." There are no observable skin lesions in these patients. Patients with PV need not have contact with water to experience pruritis; pruritis can also develop when the patient experiences sudden environmental temperature change or it can occur spontaneously [Saini *et al.*, 2010].

Pruritis in patients with Hodgkin's disease is often worse at night. It typically starts in the legs and later generalizes. Of note, generalized pruritis tends to be more common in patients with nodular sclerosing type Hodgkin's disease that is associated with a mediastinal mass [Krajnik and Zylicz, 2001b].

Cutaneous T-cell lymphomas (CTCL), which include primary CTCL, mycosis fungoides, and Sézary's syndrome, predominantly occur in males, typically over the age of 50, and are known to causes severe pruritis. In these lymphomas, the pruritis typically worsens as the disease progresses, and generalized pruritis usually does not occur in the absence of cutaneous manifestations. Mycosis fungoides should be suspected in any patient with severe pruritis in the presence of visible dermatological manifestations [Krajnik and Zylicz, 2004b].

Pathogenesis

Similar to most other disorders with associated pruritis, pruritis of many of the hematological disorders is poorly understood. Pruritis in PV appears to be associated with elevated serum and urine histamine concentrations. One study found increased serum histamine levels in 60% of patients with uncontrolled PV as compared to 7% in patients with well-controlled PV. These patients with poorly controlled PV were seven times more likely to experience pruritis when compared to patients in the group with normal histamine levels [Gilbert et al., 1966]. Additionally, the JAK2 mutation seen in patients with PV and other myeloproliferative disorders is known to induce cytokine hypersensitivity in cell lines and has been shown to induce constitutive activation and hypersensitivity in basophils [Tefferi et al., 2006; Pieri et al., 2009]. Similar to PV, pruritis as a result of Hodgkin's disease is thought to be caused by elevated levels of basophils and histamine in the blood [Karnath, 2005]. However, given that one study found that more than 50% of patients who died with Hodgkin's lymphoma had hepatic involvement upon autopsy, there may well be a cholestatic component to their pruritis as well [Hubscher et al., 1993; Krajnik and Zylicz, 2004b].

Patients with CTCL have higher levels of (I) eosinophils, which are known to drive skin inflammation, and (II) mononuclear cells in the peripheral blood, that produce significantly higher levels of certain interleukins, which can act as pruritogens [Ahern *et al.*, 2012]. In addition, in advanced staged of disease, other organs may be involved, such as the liver or kidney, which can lead to cholestatic or renal pruritis.

Treatment

If treatable, the first step in the management of pruritis secondary to hematological disorders is to treat the underlying disorder. Beyond that, there are some specific treatments for the three hematological disorders discussed in this section.

Interferon alfa (IFN- α) is a drug effective at managing PV as well as PV-associated pruritis and should be considered first [Finelli *et al.*, 1993; Muller *et al.*, 1995]. Aspirin is also extremely effective at reducing pruritis: a 300 mg tablet can exert its effects within 30 minutes and last up to one day [Twycross and Zylicz, 2004]. Selective serotonin reuptake inhibitors have shown promising results in certain patients in PV-associated intractable pruritis in a small sample study [Tefferi and Fonseca, 2002]. Finally, phototherapy has also been found useful in controlling PV-associated pruritis; in one study, 80% of patients went into complete remission [Baldo *et al.*, 2002].

For patients with Hodgkin's lymphoma, there currently is no standardized treatment for pruritis. In addition to treating the underlying malignancy, patients can be given a trial of corticosteroids or cimetidine, both of which have been shown to be effective in management of pruritis in this patient population [Aymard *et al.*, 1980; Twycross *et al.*, 2003].

Besides using radiation, chemotherapy, and/or phototherapy to induce remission of CTCL, there treatments aimed at the symptomatic management of the pruritis many of these patients experience. Topical corticosteroids are widely used in all stages of CTCL to control pruritis and contain the dermatological manifestations. Aprepitant (an antagonist of the neurokinin-1 receptor of substance P) has proven efficacious in patients with Sézary's syndrome and other myeloproliferative disorders [Duval and Dubertret, 2009; Booken *et al.*, 2011]. Other clinicians have noted that mirtazapine and gabapentin have provided their patients some relief as well [Demierre and Taverna, 2006].

latrogenic causes of pruritis

Sometimes, treatment, rather than an actual disease process itself, is the root cause of a patient's pruritis. A wide range of chemotherapeutic agents are known have numerous adverse effects on the skin, which include, but are not limited to skin dryness, scaling, rashes and infections—all of which can precipitate pruritis. Chemotoxic agents can also cause peripheral neuropathy, which can lead to pain, discomfort, paresthesias, and pruritis.

Radiation can also have harmful effects on normal, healthy tissues. Acute radiation damage, similar to that of chemotherapy, is most prominent in tissues composed of rapidly proliferating cells, such as the skin and digestive tract. Shortly after therapy, patients may experience erythema, dry or moist desquamation, pain, hypersensitivity, and pruritis, all of which may not resolve until weeks after completion of treatment [Stone *et al.*, 2003].

Pathogenesis

Pruritis secondary to chemo- and radiation therapy can be attributed to several causes. Both interfere with the cell division and hence, proliferation process, thereby destroying not only proliferating cancer cell lines, but also normal cells, such as neurons. Radiation therapy also causes scar tissue formation, which can compress neurons [Vasić, 2007]. Nerve damage as well as nerve compression can both lead to peripheral neuropathy, which can lead to symptoms such as numbness, tingling, burning, pain, and itching [Stone *et al.*, 2003]. Additionally, the dryness, itchiness and scaling seen in patients on chemotherapy may be due to the effects of the agents on the sweat and sebaceous glands [Krajnik and Zylicz, 2004a].

Treatment

Research on management of this type of pruritis is limited. Nevertheless, it appears that the key to tailoring treatment to patients in this population requires a full assessment of how his or her quality of life is affected by the pruritis and other side effects. Depending on the severity of such symptoms, therapy may be discontinued until they improve. Patients who experience dry skin, a common side effect of chemoand radiation therapy, should be advised to regularly lubricate with emollients and other skin care products (see "General Recommendations Regarding Skin Care" section).

One case report of a patient who suffered from chemotherapy induced anal pruritis stated briefly discontinuing chemotherapy until symptoms resolved and then administering dexamethasone prior to chemotherapy infusions effectively prevented recurrence of pruritis [Hejna *et al.*, 1999]. SSRIs, tricyclic antidepressants (TCAs), and gabapentin, while known to be effective in treating various types of neuropathic pain and pruritis, have not been shown to alleviate symptoms in patients with chemotherapy related peripheral neuropathies [O'Connor and Dworkin, 2009].

Alternative and supplemental treatments for pruritis

Acupuncture

Several small studies have shown that acupuncture is more effective than placebo-acupuncture in reducing the duration of experimentally induced histamine-related itch and flare [Belgrade *et al.*, 1984; Lundeberg *et al.*, 1987]. Additionally, a study utilizing electrical needle stimulation, a modified acupuncture technique, on patients with intractable uremic pruritis had encouraging results, as several patients experienced drastic improvements in pruritic symptoms during or after treatment [Duo, 1987].

Besides directly alleviating pruritis in uremic patients, acupuncture may indirectly alleviate opioid-induced pruritis by reducing postoperative opioid consumption and thereby reducing opioid-related side effects like pruritis. One systematic review reported that after various surgeries, analgesic consumption was significantly lower in patients who received acupuncture as compared to patients in the placebo group who received a sham procedure [Sun *et al.*, 2008]. Despite these documented successes of acupuncture alleviating pruritis, the sample sizes remain small and the studies are few.

Nutritional therapy

Nutritional therapy has been helpful in the treatment of pruritis when used in conjunction with other treatment methods. Although further research is needed and efficacy has been variable, linolenic acid and vitamins D and E can be used in the treatment of various pruritis causing skin conditions, including psoriasis and atopic eczema. Additionally, in terms of diet, anything that increases blood flow to the skin, such as hot and/or spicy food and drinks and alcoholic beverages, are more likely to cause itching [Szepietowski and Twycross, 2004]. Any patient with complaints of pruritis should be given this information and advised to discontinue consumption of such products if the patient observes exacerbations in pruritic symptoms after ingestion.

Bath additives

Oats have a high mucilaginous content that helps to heal

tissue, moisten and soften skin, and decrease pruritic sensory inputs. Similarly, tar bath oil soaks are also effective for patients with pruritis; particularly that associated with psoriasis and atopic eczema. Both oatmeal and tar bath oils are safe and potentially effective treatment modalities for patients with pruritis looking for alternative treatment plans [Millikan, 2003].

General recommendations regarding topical skin care treatment of pruritis

Regardless of the etiology of pruritis, patients should receive advice on proper skin care techniques to either alleviate or avoid exacerbating pruritis. It is important to keep in mind that dry skin can accompany all causes of pruritis in the palliative care patient population. Emollients can prevent and treat dry skin, maintain skin hydration, and rehydrate dry skin. Therefore, patients should be encouraged to apply emollients to pruritic skin areas at least twice per day, (although more frequent use can be more effective), and always after bathing in order to keep skin moist.

Topical agents other than emollients can also be helpful. Camphor (1.0-3%), phenol (0.5-2.0%), and menthol (0.5-2.0%), are three compounds that are common ingredients in many over-the-counter anti-pruritic lotions [Sharma et al., 2009]. For patients in whom pruritis persists, stronger topical anesthetics, such as lidocaine (2.5%) and benzocaine (20%) can be utilized. Although topical corticosteroids are known for their anti-inflammatory activity, they are also effective in reducing pruritis in patients who experience pruritis but do not have any visible lesions [Szepietowski and Twycross, 2004]. Finally, topical capsaicin (0.025-0.075%) is a compound that depletes substance P which is a known mediator of pruritis and can be effective in managing localized pruritis. It has proven efficacy in treating renal pruritis according to several studies, including two double-blinded placebo trials when applied to pruritic areas 3-5 times per day [Breneman et al., 1992; Tarng et al., 1996; Cho et al., 1997].

Summary

Pruritis is a widespread, yet underreported symptom experienced by the cancer and palliative care patient population. It can become an incredibly disruptive symptom that can worsen quality of life. Though many diseasespecific therapies exist, treatment of pruritis is often inadequate. This is likely due to the dearth of large clinical

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studies on the efficacy of available treatment modalities and the fact that experts still lack a full understanding of the pathogenesis of pruritis.

Despite lacking a full understanding of the mechanisms of pruritis in a majority of cases, there are numerous treatment options that can be tried for each patient once the healthcare provider can determine a likely etiology of the pruritic symptoms. As such, it is critically important to obtain a thorough history and careful physical exam to ensure appropriate therapies are attempted. Healthcare providers should adopt the "test and revise" mentality, so that patients who fail one therapy may be tried on other agents that have proven effective on patients with pruritis of the same etiology in the past.

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Part III

Supportive and palliative care in dentistry and oral medicine

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Introduction

Local and systemic diseases may manifest in the oral cavity, and side-effects of therapeutics are also commonly seen in the mouth. These complications or adverse events present with various symptoms and may give rise to secondary complications, including infection. This occurs more frequently in oncology patients. Patients usually seek medical attention because of pain, xerostomia, halitosis (bad breath), and dental or periodontal symptoms. Impaired masticatory function in edentulous patients may be a primary reason for rehabilitation. The variety and severity of oral complaints highlights the importance of oral tissues for daily function and their impact on quality of life.

This chapter contains an overview of concepts of supportive and palliative care for various oral and dental disorders, with an emphasis on conditions prevalent in cancer patients. Recognition of oral pathological conditions and an understanding of the fundamentals of their management will enable healthcare providers to deliver primary care or to consult with a specialist for evaluation and treatment.

The terms "supportive care" and "palliative care" may represent symptom control and enhancement of quality-of-life for patients with life-limiting illnesses at different time points (i.e., from in-therapy care to survivorship care to end-of-life care) [Hui *et al.*, 2013]. However, in this chapter these terms are used interchangeably. Oral diseases that are not related to supportive care, even those that are relevant to the same patient populations, are beyond the scope of this chapter.

Concepts of palliative management

Pharmacological and non-pharmacological modalities can be used for palliation and treatment of oral conditions. In addition, oral hygiene has an important role in achieving and maintaining oral health and in the palliation of oral diseases.

Pharmacological palliation

One of the basic principles of pharmacological treatment of lesions in the oral cavity is related to the selection of topical therapy versus systemic therapy. Efficacy and side-effects of each agent influence the clinical decision.

Oral diseases may be treated with systemic medications. Oral, intravenous or transdermal analgesics and narcotics provide effective pain relief for various oral conditions. However, one advantage of the oral mucosa is ease of access for direct topical delivery. Medications delivered topically ensure the desired concentration of the therapeutic agent and reduce systemic side effects [Ogle and Ofodile, 2001].

Nevertheless, topical applications may cause local adverse events. For example, ironically, some agents that aim to relieve local oral pain may cause painful burning of the mucosa (*Figure 1*). Furthermore, there is systemic absorption of drugs through the oral mucosa, therefore topical interventions also need to be prescribed and used carefully,



Figure 1 Painful ulceration over the buccal mucosa (arrowhead) caused by misuse of a topical preparation for the palliation of pain related to necrotizing ulcerative gingivitis (arrow).

and patients monitored for both local and systemic effects.

Because topical oral preparations are commonly used, they may be erroneously perceived as risk-free by care providers, and patients may consider them as bland mouthwashes or equivalent to over-the-counter oral hygiene products. It is important to note that the diagnosis must be confirmed before starting any topical treatment as in some instances the treatment may mask the signs of the disease, causing a diagnostic delay.

There are several principles in the formulation of topical remedies specific to the oral cavity: consistency and adherence to the oral mucosa, taste and temperature and properties of the vehicle.

Consistency and adherence to the oral mucosa

The common formats for topical medications are creams, ointments, pastes, rinses, gels, and lotions. A cream is a semi-solid emulsion of oil and water intended for external application. An ointment is a semi-solid emulsion of water droplets suspended in oil that melts at body temperature and penetrates the skin. A paste is a thick ointment that does not flow at body temperature. A rinse is a liquid preparation that can be swished in the oral cavity. The active material may be dissolved in water or in alcohol. A gel is a semi-solid emulsion that liquefies at body temperature. A lotion is a suspension of insoluble powder in a liquid or a pourable emulsion of oil in water; its duration of effect is shorter than creams or ointments [Ogle and Ofodile, 2001].



Figure 2 Removable dental appliance with a "pocket" (light-blue area) to deliver therapeutic agents to the mucosa. The appliance was custom made on a gypsum model.

Rinses, gels, ointments and pastes can be used for oral topical application. Agents may be applied to the gingival mucosa using custom-made dental appliances to enhance localization and longevity of application (*Figure 2*).

Consistency is selected based on the planned use. Rinses are the preferred vehicle in the watery intra-oral environment. Most patients would be willing to apply a thin gel over the oral mucosa; however, compliance may be limited if the gel is thick [Bellm *et al.*, 2001]. Solutions are commonly used when large areas of the oral mucosa are affected. Ointments adhere poorly to the oral mucosa; however, pastes adhere well and may serve as a protective coating.

Taste and temperature

Taste is an important factor in patient compliance. Some topical preparations include sugar to mask a bitter taste, putting the patient at risk for dental caries. Other topical preparations are mint flavored, which can cause a burning sensation in some patients. Room temperature is preferred by patients for intra-oral formulations [Bellm *et al.*, 2001].

Properties of the vehicle

A common vehicle for oral paste formulations is orabase. Orabase contains gelatin, pectin, and carboxymethylcellulosesodium in plastibase, which is a plasticized hydrocarbon gel. This vehicle is exceptional in that it may serve as the active agent when a coating effect is needed. Diluted alcohol is the vehicle in many commercial oral rinses. However, if

Part III



Figure 3 (A) A flexible mouth-guard covering the teeth of 13-year-old girl suffering from chronic graft-versus-host disease (GVHD), with extensive buccal ulcerations (B). Note that the ulcers are located along the occlusal line, where frictional trauma is the greatest.

ulceration or erythema of the oral mucosa is present an elixir may not be bearable. In these instances, an aqueous vehicle may be better tolerated.

Non-pharmacological palliation

Various non-pharmacological methods have been employed to relieve oral symptoms. This treatment modality may be the sole treatment or may be used concurrently with pharmaceuticals, or may be combined with pharmacological treatment.

A simple and readily available technique for relieving intra-oral pain is sucking ice cubes or taking sips of cold water. The mechanism of action depends on the disease: vasoconstriction in chemotherapy-induced oral mucositis (OM), and reduced edema in local inflammation. In addition, heat-activated ion-channels and receptors, which probably play pivotal role in inflammation-related pain, are affected by cooling [Kichko and Ree, 2004].

Non-pharmacological means to relieve xerostomia (symptomatic dry mouth) include gustatory stimulation by chewing a sugar-free sour gum or candy, and continuous sipping of water with a few drops of fresh lemon. Caution is needed when a dentate patient is advised to continuously sip an acidic solution because the hard dental tissues can erode in such environments. Another non-pharmacological therapy for xerostomia is an individually fabricated intraoral salivary electro-stimulator [Zadik *et al.*, 2013a].

Chronic dental and periodontal diseases should be

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addressed as part of a comprehensive dental treatment plan for all patients in their primary dental clinic. In addition, urgent-care for hospitalized patients is invaluable. The management of dental-related symptoms includes restoration in cases of decayed or broken teeth, and dentalpulp extirpation (pulpotomy or pulpectomy) in cases of pulpitis, pulp necrosis, and other pulp disorders [Zadik *et al.*, 2010]. Traumatic mucosal ulcers may require polishing the sharp edges of teeth, restorations or dental appliances, or covering the sharp edges of the teeth with a mouthguard (*Figure 3*). Splinting may be helpful for symptomatic mobile teeth when extraction is contra-indicated (*Figure 4*). Function and aesthetics may be improved by relining illfitting/unstable dentures. A detailed description of these dental procedures is beyond the scope of this chapter.

Oral bygiene

The beneficial effects of daily oral hygiene maintenance cannot be over-emphasized. The reduction of the bacterial load by oral hygiene procedures may reduce inflammation in the adjacent oral tissues. In addition, adequate oral hygiene is essential for patient comfort, esthetics and selfesteem. Oral hygiene is even more important after tumor excision from the head-neck region, because the procedure often results in extensive three-dimensional defects that complicate reconstruction and predispose to the leakage of saliva and other secretions and predispose for accumulation of microorganisms and debri.



Figure 4 Palliative splinting of symptomatic mobile teeth in a patient with terminal metastatic breast carcinoma. The mobility of the teeth was caused by a metastatic lesion in the maxilla. The teeth were not extracted because of current bisphosphonate treatment and the high risk of post-extraction osteonecrosis.



Figure 5 Oral hygiene with a sponge. The sponge can be soaked in an antiseptic solution or normal saline.



Figure 6 Poor hygiene of the lower (right) and upper (left) dentures of hospice patient.

Hygiene measures to mechanically remove food debris as well as the dental bacterial bio-film include twice-daily tooth brushing, inter-dental cleaning (with dental floss or toothpick), and tongue brushing. These procedures should be continued regardless of blood counts [Qutob *et al.*, 2013]. The preferred instrument is an extra- or supersoft nylon toothbrush, which should be replaced when worn or at least every 2-3 months, and some authors recommend toothbrush replacement after each neutropenic cycle [Qutob *et al.*, 2013]. Oral sponges can be used temporarily when the patient cannot tolerate using a toothbrush (*Figure 5*). Electric toothbrushes may improve hygiene, especially in individuals with impaired manual skills. A gentle fluoridated (>1,000 ppm) toothpaste should be used. The clinician should consider the application of a highly-concentrated fluoride preparation in xerostomic and other patients at high-risk for caries. Some xerostomic patients, and patients with ulcers cannot tolerate sodium lauryl sulfate (SLS)containing toothpastes [Wiseman, 2006]. In this instance an SLS-free toothpaste is preferable and, if unavailable, a children's toothpaste is a good alternative (although fluoride concentration is lower in children's formulations).

Mouth washing with a chlorhexidine gluconate (alcoholfree) solution may improve oral hygiene and reduce halitosis. Alcohol containing solutions should be avoided because of the drying effect, and the unpleasant sensation in patients with ulcers, although these solutions probably do not have a local carcinogenic effect [La Vecchia, 2009].

For optimal mucosal hygiene, dentures should be removed at night (and before daytime sleeping), washed with a gentle brush and soap, and soaked in an antiseptic solution such as water, sodium bicarbonate solution or chlorhexidine mouthwash (*Figure 6*). Periodic decontamination of dentures may be achieved by soaking them within benzalkonium chloride (a quaternary ammonium antiseptic) for 30 minutes; non-metal-based dentures may be periodically soaked in diluted sodium hypochlorite for 30 minutes. In inpatient settings it is important that dentures be stored in well labeled containers to eliminate confusion between residents.

palliative care settings					
	Source (Authors, years)				
	Aldred et al.,	Jobbins et al.,			
	1991 (%)	1992 (%)			
Xerostomia	58	77			
Sore mouth	42	33			
Dysphagia	37	35			
Denture problems	71	45			
(among dentures wearers)					
Taste alterations	26	37			
Overall patient reports of oral symptoms	74	89			

Table 1 Prevalence of oral symptoms in cancer patients in

The dental practitioner in the palliative care team

The concept of a holistic multidisciplinary team is fundamental for providing comprehensive care for the complex patient. Unfortunately, in many palliative care teams a dental care provider is not available [Lapeer, 1990]. Additionally, the literature highlights the limited knowledge of oral health issues among non-dental health care providers in hospices [Wyche and Kerschbaum, 1994]. Therefore, it seems that the role of a dental care provider and oral medicine practitioner in the palliative care setting needs to be rectified.

From the point of view of the dental care provider, there are two main challenges in the management of terminal, cancer, and other highly medically complex patients.

(I) Most dental treatments are technique-sensitive and require specialized equipment and facilities including the dental turbine (air-compressor), effective suction and lighting systems, and sterile instruments, which are not available in the patient's home or hospital ward. This challenge can be partly resolved by mobile dental units and hospital- or hospice-based dental clinics. Nevertheless, a bedside oral examination can, and should, be performed regularly, and when symptoms arise a basic armamentarium may be sufficient for the initial consultation.

(II) Most dental practitioners have limited training or experience in treating very high risk patients with complex systemic medical conditions and in diagnosing cancerrelated lesions in the oral cavity [Zadik et al., 2012a; Zadik et al., 2013b]. Moreover, dentists encounter dying patients infrequently. In contrast to medical schools, most dental schools do not train undergraduate students to deal with end-of-life issues. This challenge may be solved by postgraduate education, and by consultation with the treating physician and an oral medicine specialist.

Treatment goals and clinical approach

The oral cavity in general, and the teeth and gingivalperiodontal tissues in particular, are major sources of illness in the general population [U.S. Department of Health and Human Services, 2000]. Terminally-ill patients are no exception; cohort studies reveal a prevalence of oral symptoms in this population of 74% to 100% [Aldred et al., 1991; Jobbins et al., 1992; Wiseman, 2006]. The most prevalent symptoms and complaints in the palliative care setting are xerostomia, a sore mouth and poorly fitting dentures (Table 1). Some oropharyngeal symptoms may be worse in certain patient populations. For example, patients with a malignant lesion in the head and neck are may also suffer from compromised airways, dysphagia, wounds and fistulas, excessive oral/airway secretions, speech difficulty, and reduced body image [Bridges and Mulder, 2006].

The treatment of these patients has four primary objectives: pain relief, restoration of oral function and nutrition, elimination of oral infection, and the rehabilitation of esthetics and social interactions. Clearly the medical background of the patient and ethical issues must be considered during the treatment planning.

Relief of dental and oral pain

Sore mouth is reported in 31-42% of palliative care patients (Table 1). Oral pain is different than pain in other regions of the body, because its potential impact extends well beyond the actual affected site. Oral pain may impair essential oral functions such as eating, drinking, and speaking, as well as facial expression, quality of life and social behavior. Oral pain also interferes with oral hygiene maintenance, which can lead to a further deterioration in dental health [Zadik et al., 2013c]. Thus, oral pain may impart significant medical, nutritional, functional, and social-psychological impact on the patient. In oncology patients, the debilitating effects of oral pain may limit the administration of anti-cancer radioor chemo-therapy or require other treatment modifications [e.g., percutaneous endoscopic gastrostomy (PEG) for feeding] [Raber-Durlacher et al., 2010].

For most oral pain, the treatment is systemic (will be discussed later). Traditionally, systemic treatment follows a 3-step ladder recommended by the World Health Organization; in which (I) non-opioids analgesics ± adjuvant (e.g., anticonvulsants, antidepressants and anxiolytics, and muscle relaxants) are recommended for mild pain; (II) opioid analgesics \pm non opioid analgesics \pm adjuvant are recommended for mild to moderate and (III) stronger opioids analgesics possibly in combination with adjuvants are used for moderate to severe pain [Meuser *et al.*, 2001]. Other approaches have been proposed for mild to severe pain, suggesting the titration of the lowest effective dose of a "strong" opioid to provide adequate pain control [Elad *et al.*, 2008a].

The preferred non-opioid analgesics for oral pain are non-steroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen. If NSAIDs are contra-indicated, an analgesic preparation that combines an orally active opioid at an effective dose with acetaminophen may be prescribed. The patient should be instructed to take the primary analgesic on a fixed schedule, not "as needed" [Huynh and Yagiela, 2003]. A pain specialist may be consulted about the best pain management.

When pain originates from the dental or periodontal tissues, dental interventions, such as scaling and root planning, dental restoration, dental pulp extirpation, or tooth extraction, may be helpful depending on the dental diagnosis. The dental care provider should be able to customize the treatment to fit the systemic condition of the patient.

Restoration of oral function and nutrition

The oral cavity has many functions that are essential for life and has a strong impact on quality of life. Restoring oral function starts with restoring the dentition, replacing missing teeth and rehabilitating the occlusion. An adequate dentition and occlusion facilitates better eating, talking, swallowing, and in some cases esthetics will also improve. This may be achieved with a range of treatments from simple dental restorations to maxillofacial prostheses.

Replacement of missing teeth in the context of palliation care setting may be achieved with transitional partial or full removable dentures. Removable dentures may rapidly improve function and esthetics. However, replacing lost teeth and restoring oral masticatory function is challenging in the elderly or terminally ill patient because of the combination of conditions that affect oral function, such as alveolar resorption, surgery-related loss of supporting anatomical structures (jaw bone), resected or paralyzed tongue, and dry mouth. These conditions can reduce denture stability and may lead to reactive mucosal lesions. Rehabilitation of mutilating oral and maxillofacial defects is of extreme importance following head and neck surgeries and should be performed by a team of specialists.

Restoration of oral function also includes the management of salivary dysfunction. Qualitative and/ or quantitative changes in saliva may impair the essential physiological roles of saliva: washing and self-cleaning; moisture and lubrication; buffering and re-mineralization of the teeth; antimicrobial defense; primary digestion and bolus preparation; and taste perception. Xerostomia is a major complaint among terminally ill patients [Rohr *et al.*, 2010] (*Table 1*), affecting up to 100% in one cohort [Wiseman, 2006]. Restoring salivary gland function may be achieved with topical and systemic interventions [von Bültzingslöwen *et al.*, 2007; Jensen *et al.*, 2010]; however, the response is frequently partial.

Rehabilitation of the dentition, salivary gland function and integrity of the mucosal tissue is essential for adequate nutrition. Malnutrition is reported in 40-80% of oncology patients [Petzel, 2011]. Patients with head-neck malignancies are at higher risk for malnutrition and feeding tube dependence because of both the functional limitations imposed by the tumor site and treatment side effects; these patients often suffer from significant reductions in their body mass index (BMI) during therapy. Due to the chronic nature of many of oral and maxillofacial diseases and drug-induced oral adverse effects, compromised nutritional may persist chronically, and reduce performance status and quality of life.

Counseling with a dietician is required to ensure proper caloric and protein intake [Czerninski *et al.*, 2013]. Generally for oral diseases, small, frequent meals are preferred. The patient should be instructed to choose soft foods that are atraumatic to the oral mucosa, to chew and swallow small amounts carefully (using a small spoon), and to ease chewing and swallowing by wetting the food using small sips [Petzel, 2011]. Other intake deficiencies may be corrected by vitamin and mineral supplementation. Additional measures to support nutrition are needed when a patient suffers from severe dysphagia, such as delivery of nutrition by a nasogastric or gastrostomy tube PEG [Bridges and Mulder, 2006; Lalla *et al.*, 2011].

Elimination of oral infection

Cancer patients may experience some level of immune compromise and suboptimal leukocyte function. Thus, the suspected etiology of oral lesions should include infection, which may not present with the appearance of classical inflammatory signs due to myelosuppression [Lerman *et al.*, 2008]. From the palliative perspective, elimination of oral

Supportive and palliative care in dentistry and oral medicine

infections also refers to the prevention of systemic sequalae and reducing pain. These infections can be classified as bacterial, fungal or viral.

Viridans streptococcal are a major concern in immunosuppressed neutropenic cancer patients, causing up to 60% of documented bacteremias with a 6-30% mortality rate [Graber *et al.*, 2001; Lockhart *et al.*, 2007]. The oral infections may arise from the commensal oral flora that becomes virulent in immuno-compromised individuals. A decision tree analysis showed that lack of preceding dental treatment (i.e., elimination of actual as well as potential infectious sites in the oral cavity) in immunosuppressed cancer patient may lead to mortality [Elad *et al.*, 2008b].

The most common oral fungal infections involve Candida albicans, which is found in the oral cavities of 40% to 70% of patients in palliative care settings [Aldred *et al.*, 1991; Lavy, 2007]. This infection is often associated with underlying systemic conditions such as immunosuppression, hyposalivation, steroid therapy, uncontrolled diabetes mellitus, antibiotic-induced changes in the oral flora, anemia and nutritional deficiencies. In addition, Candida is more common among denture wearers [Moskona and Kaplan, 1992], as this organism can colonize the acrylic base [Segal *et al.*, 1992].

The most common viral infection in adults is from the herpes family and may affect the peri-oral and intraoral tissues. Reactivations are prevalent when the immune system is suppressed [Elad *et al.*, 2010a].

Esthetic and social aspects

The oral cavity and the lips play important social roles, including speaking and facial impressions. Harmonic esthetic appearance is important for self-image and sociality. A poor oral condition may negatively affect sociability. The terminallyill patient, especially the head and neck cancer patient, may suffer from severe disfigurement, restricted mouth opening, speech difficulties, loss of teeth, decayed teeth, an unpleasant smile, halitosis, and swallowing difficulties (dysphagia), all of which may significantly reduce self-esteem and cause upset among peers and visitors. Since a pivotal aspect of palliative care is to encourage social interaction and family support, facial and oral esthetics is essential.

In the last four decades, surgeons began to consider function and esthetics in addition to patient survival, such that reconstructive procedures have significantly improved [Goldstein *et al.*, 2008]. Collaboration between the head-neck surgeon (i.e., oral and maxillofacial/otolaryngology), plastic surgeon, dental surgeon, and maxillofacial prosthodontist enables the optimal functional and esthetic results.

Voice rehabilitation is extremely important to maintain social interaction and communication. This may be achieved by speech therapy and/or acoustic assistive devices.

Halitosis also affects sociability and a bad smell from the mouth may deter people from interaction with the patient. Generally, halitosis is managed by treating the cause, if it is known (e.g., periodontal disease and accumulation of oral bacteria), and by avoiding smoking and minimizing periodontal disease. Meticulous oral hygiene, including dental flossing and tongue cleaning with a scraper, is recommended. Antiseptic mouthwashes may help, especially products containing chlorhexidine, triclosan, essential oils, and zinc chloride. Another anti-halitosis product is a twophase mouthwash (oil water) [Kozlovsky et al., 1996]; the first phase includes natural essential oils with triclosan and the second watery phase contains cetylpyridinium chloride and sodium fluoride. Some authors suggest that a short antibiotic course (such as metronidazole) might eliminate unidentified anaerobic bacteria that can cause halitosis [Scully, 2008a].

Medical considerations in the delivery of dental care

When an invasive dental procedure is required, the clinician must modify the dental treatment plan based on the patient's medical and dental history as well as current status, including up-to-date laboratory tests. Two of the major medical considerations are infection control and bleeding control.

Most oral surgeries are categorized as clean-contaminated procedures; therefore a pre-operative (and post-operative) antiseptic mouth rinse (such as chlorhexidine gluconate alcohol-free solution) should be used. In cases of moderate neutropenia (500 to 1,000 cells/mm³) clinical judgment is required; and in cases of severe neutropenia (<500 cells/mm³) the treatment should be postponed. If the dental procedure cannot be delayed, then prophylactic antimicrobials should be given 30-60 minutes before the procedure, with amoxicillin (2 g) as the drug of choice [Little *et al.*, 2013]. In addition, administration of colony-stimulating factors should be considered when repeated invasive procedures are needed in neutropenic patients. It is important to note that an indwelling central venous catheter is not an indication for pre-operative prophylactic antibiotics [Hong *et al.*, 2010].

The risk for intra- and post-operative excessive bleeding increases with platelet counts <50,000/mm³. Platelet transfusion (one platelet concentrate per 10 kg body weight) is the current primary method for managing

thrombocytopenia, and is employed when a surgical procedure cannot be postponed in a patient with <50,000 platelets/mm³. However, for minor procedures (such as a single tooth extraction), the practitioner should consider only using local hemostatic methods [Ogle and Saker, 2006].

Ethical considerations in the delivery of dental care

The clinician should collaborate with patients who have advanced serious illness to align treatment plans with patient needs, goals and preferences, being mindful of the following ethical and practical considerations.

Is the dental intervention essential?

Medical necessities and patient preferences should be prioritized. For example, not every chipped tooth or early dental decay requires immediate restoration, particularly when the patient perceives the requisite time and effort and discomfort as outweighing the treatment's intended health benefits.

Is the patient interested in extensive treatment?

When life expectancy is short, the patient may prefer to waive non-essential and time consuming dental treatments, which could impair the opportunity and ability to enjoy preferred activities. A dental plan which only includes essential treatments should be considered.

Is the patient interested in expensive treatments?

For some patients, rehabilitation of the dentition is an emotional need which trumps concerns about treatment cost. However, others, particularly at the end of life, may prefer to waive expensive treatments, to focus treatment not on repair but on symptom management, and in the process to save money for their other needs and for their survivors.

Palliative agents for oral conditions

The main topical agents used for palliation of oral conditions will be reviewed and classified by mode of action. The description of therapeutic agents for the treatment of oral conditions (such as corticosteroids and other immunomodulators) is beyond the scope of this chapter.

Analgesics and anesthetics

Topical anesthetics have been widely used in the dental setting and self-applied by patients (Table 2). Lidocaine, an amide anesthetic, can be used topically as a solution, gel, ointment or spray. Benzocaine is available for topical intraoral use as well in various preparations with a concentration of up to 20%. These agents are useful at times of severe intra-oral mucosal pain, or when mucosal pain is anticipated, such as when eating. Theses agents are contraindicated in patients with known hypersensitivity. Common adverse effects include local erythema, edema, and burning sensation. Even though systemic absorption has not been shown to reach toxic arrhythmic levels, it is better to limit the dose [Elad et al., 1999]. Benzocaine has been reported to cause methemoglobinemia [Ship et al., 2008], but this complication is rare. Importantly, as opposed to pain originating from the oral mucosa, dental pain is not relieved by topical anesthetic administration.

Rinsing the mouth with the antihistaminic diphenhydramine (e.g., 25 mg/10 mL) elixir may relieve oral mucosal pain. The patient should be instructed to rinse 10 mL of elixir every 4-6 hours, and expectorate (to avoid sedative effects of the medication) [Ship et al., 2008].

Numerous topical NSAIDs have been suggested for the treatment of oral diseases [Elad et al., 2010b; Elad et al., 2011]. Benzydamine is a locally acting non-steroidal analgesic with anti-inflammatory properties. Mouthwash containing 0.15% benzydamine hydrochloride prevent erythema, ulceration, and pain associated with OM in patients received moderate doses of radiotherapy to the head and neck [Epstein et al., 2001]. Numbness or stinging sensations of the oral tissue may be experienced transiently.

Opioid mouthwashes such as morphine solution (10 mg/5 mL), swish and expectorate 15 mL solution, up to six times a day, may decrease the severity and duration of OM pain [Cerchietti et al., 2002]. Ketamine oral rinse (20 mg/5 mL) may decrease pain associated with OM in patients following hematopoietic stem cell transplantation (HSCT) [Ryan et al., 2009].

Capsaicin is effective in relieving pain, especially that of neuropathic origin (e.g., burning mouth syndrome), and may be beneficial when there is no response to other medications. It acts by depleting substance P in local sensory nerve endings, causing the release of substance P and intensifying pain temporarily. Capsaicin is available in 0.025-0.075% gel and cream preparations for application three or four times a day. Pain relief is seen within 14-28 days of regular administration [Ogle and Ofodile, 2001]. A home-made capsaicin solution (dissolving 4-6 drops of Tabasco sauce in one teaspoon of water) may be used instead of the commercial preparations. Patients should be

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Table 2 Summary	of selected palliative analg	gesics and anestnetics formulations for va	arious oral conditions
Agent	Formulations	Dosing	Precautions and comments
Lidocaine	20-50 mg/mL solution, 10 mg/dose metered spray, 2-5% gel	As needed (up to x4-6/d, and before painful functions such eating). Solution should be expectorated	Limit use to no more than 120 mL/24 hrs. Should be avoided in patients with risk for aspiration. Un-metered spray should be avoided. Rarely
		after 1-4 min mouth rinsing	patient reports of local burning sensation
Benzocaine	0.2-20% solution, 5-20% gel, 2-10 mg troche	As needed (up to ×4-6/d, and before painful functions such eating). Solution should be expectorated after 1-4 min mouth rinsing	Serious adverse effect of methemoglobinemia (rare, occasionally occurred in low-weight children). Un-metered spray should be avoided. Should be avoided in patients with risk for aspiration. Rarely patient reports of local burning sensation
Diphenhydramine	25 mg/10 mL elixir	Rinse for 2 min and expectorate,	Sedative (especially if swallowed). Should be
		as needed (up to ×4-6/d)	avoided in patients with risk for aspiration
Dyclonine	0.5-1.0% solution	Rinse for 2 min and expectorate, before eating	
Benzydamine hydrochloride	0.15% solution, elixir	Rinse for 2 min and expectorate, as needed (×4-8/d)	Commercial preparations may contain alcohol. Protocol may change for various oral conditions
Morphine	5-10 mg/5 mL solution	Rinse for 2 min and expectorate, $15 \text{ mL}, \times 1-6/d$	Advised to follow same precautions as with systemic administration
Ketamine	20 mg/5 mL solution	Rinse for 1 min and expectorate, $15 \text{ mL}, \times 1-6/d$	Advised to follow same precautions as with systemic administration
Capsaicin	0.025-0.075% gel, cream, Home-made solution (1 part of Tabasco sauce in 2-4 parts of water)	Apply a thin film of gel or cream ×2-4/d. Rinse with a solution for 1 min ×4/d and expectorate	Pain may be intensified initially. Caution with spreading the material to the eyes

cautioned regarding unintentional contact with the eyes.

Coating agents

Coating is presumed to create a protective barrier and thus provide relief for ulcerative lesions.

Sucralfate binds to proteins (e.g., fibrinogen and albumin) on the ulcer surface, forming a stable insoluble complex that acts a protective barrier, preventing further damage and reducing pain. It was originally approved for the treatment of duodenal ulcers. Sucralfate may stimulate the production of epidermal growth factor. The use of this agent in the mouth is controversial; some authors doubt that topical sucralfate can decrease the intensity of OM and discomfort [Cengiz et al., 1999; Clarkson et al., 2010], while other authors have recommend topical intra-oral use of a sucralfate suspension, mouth rinse by 10 mL, four times a day [Wiseman, 2006].

A hyaluronate based- viscous bio-adherent gel is available over-the-counter. It has been assessed for various oral ulcerative conditions, and probably has a protective bandage effect. Some patients experience relief with this gel, but response is variable.

Similarly, aluminum hydroxide solution (e.g., 300 mg/5 mL) used as a mouthwash (e.g., mouth rinsing and swallowing of 10 mL solution four times a day) may also have a protective coating effect due to ionic adhesion to proteins on the damaged oral mucosa.

Topical hydration and lubricating agents

Saliva substitutes are commonly used to relieve dry mouth. The early products were based on viscous methylcellulose; e.g., 0.5% sodium carboxymethyl cellulose aqueous solution, to be used as a mouth rinse as frequently as needed [Siegel et al., 2006]. Nowadays, the preparations are watery and include electrolytes and enzymes that mimic the natural composition and consistency of saliva. The enzymes added (lactoperoxidase, lysozyme, and lactoferrin) in commercial preparations, have antimicrobial properties [Amerongen and Veerman, 2002; Eveson, 2008]. The patient is instructed to apply a thin film all around the mouth. This product should not be used in patients allergic to milk or eggs.

Mouth rinses containing alcohol should be avoided, as they desiccate the mouth and increase burning sensations (especially when ulcers are present). Alcohol-free rinses are currently available, including the powerful anti-septic chlorhexidine gluconate. Milk of Magnesia should not be used as a base for mouth rinses in these patients because of its drying effect. Petroleum-based products are not favorable since they are anhydrous and hydroscopic, absorbing water from the tissues, occluding harmful bacteria and preventing their removal by saliva [Wiseman, 2006].

Anti-bacterials

The primary indication for topical anti-bacterial agents is to prevent or minimize local mucosal and gingival infection. The use of systemic antibiotics for the treatment of dentoalveolar infections is beyond the scope of this chapter. Topical chlorhexidine, hexetidine and delmopinol reduce the oral bacterial inoculum. Fluoride (either amineand stannous-fluoride), triclosan, and phenolic compounds may inhibit the development and maturation of the dental bacterial biofilm and affect bacterial metabolism [Baehni and Takeuchi, 2003]. In addition to these antiseptic agents, antibiotic-based tetracycline fibers and doxycycline gel for subgingival applications are available.

Chlorhexidine gluconate (0.12% or 0.2%) is commonly used as the first line topical antiseptic mouthrinse for gingival and mucosal infections. Significant reduction in the oral bacterial biofilm, especially gram-negative rods, and gingivitis indices, has been shown. Chlorhexidine also inhibits the development of supra-gingival dental bacterial biofilm [Moran et al., 1994]; this is significant in the palliative care setting when mechanical oral hygiene measures may be limited. This agent also has weak anticaries and anti-fungal effects. Chlorhexidine binds to soft and hard oral tissues and is released slowly, prolonging the duration of its effect [Scully, 2008b]. Adverse effects include dental staining, enhanced calculus accumulation, transient taste alteration, overgrowth of enterobacteria, mucosal desquamation, and rarely hypersensitivity. These adverse events are manageable, and usually the benefits

of using chlorhexidine outweigh these side-effects. This agent is also available as 0.5-1% oral gel and toothpaste. Inoffice subgingival chlorhexidine irrigation or placement of a 2.5 mg chlorhexidine biodegradable hydrolyzed gelatin chip may be indicated for subgingival infections.

The non-ionic triclosan, in combination with a polymer delivery system (the so-called copolymer), reduces the dental bacterial biofilm, gingivitis, supragingival calculus and dental caries, and, unlike the older agents, may be used in combination with fluoride without staining teeth, increasing calculus, or altering the oral microbial ecology [Gaffar *et al.*, 1997].

Anti-fungals

Most topical anti-fungal agents act against the most common fungal species found in humans, Candida albicans. Topical agents usually belong to the polyene family (nystatin and amphotericin B) or azole family (e.g., clotrimazole, miconazole, and ketaconazole). These agents are available as gels, suspensions, powders, creams and troches (Table 3). All delivery forms need at least two weeks of therapy to prevent relapse. Common adverse effects include altered sensation in the mouth, nausea, vomiting, diarrhea, and abdominal pain, although most patients tolerate these medications well. Xerostomic patients often have candidal infections, and lozenges are not practical in these patients, as saliva is needed to dissolve them in the mouth. Some topical products have a high sugar content, which may cause glycemic intolerance and increase the risk of dental caries. In edentulous patients with clinical signs of oral candidiasis, the denture should be cleaned and placed in an anti-fungal solution (e.g., nystatin). For the prevention of angular cheilitis (an often painful fungal infection of the corners of the lips in which diminished vertical dimension is a contributing factor) a thin layer of anti-fungal cream can be applied over the peri-oral region after denture removal at bedtime.

Anti-virals

Systemic treatment is effective for herpetic infections. Topical anti-virals are available (e.g., 5-10% acyclovir cream or ointment, 1% penciclovir cream, and the overthe-counter 10% docosanol cream), but their efficacy is limited. Treatment with topical agents should start during the prodrome or as soon as the lesions are noticed, and they are to be applied every two hours for four days [Ogle and

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Table 5 Topical and -ungais for india- and peri-oral use (selected formulations)					
Agent	Intra-oral		Peri-oral		-Potential adverse effects, precautions, and comment
Agent	Formulations	Dosing ^a	Formulations	Dosing	
Chlorhexidine	0.12% (0.2%°) rinse,	×2/d	N/A		Tooth staining (reversible), Taste alterations, Increased
	1% gel, toothpaste				dental calculus formation; Alcohol-based solution may
Clotrimazole	10 mg troches	x5/d	10 mg/ml	x2/d	Nausea vomiting abnormal liver function (elevated
Clotinnazolo	to hig trochoo		cream, lotion	×2, G	AST level). thin coat of cream may be applied over
					the inner surface of the dentures after meal; Intra-oral
					formulation may contain sugar
Miconazole	50 mg buccal	BT ×1/d	2% cream	×2/d	Thin coat of cream may be applied over the inner sur-
	tablet (BT), 2% gel ^c	×3/d			face of the dentures after meal; Buccal tablet is con-
					tra-indicated in hypersensitivity to milk protein
Kataoanazala	N1/A		20/ 01000		This cost of cream may be applied over the inner
Keloconazole	N/A		2% cream	x4/u	surface of the dentures after meal
Amphotericin B	10 ma troches	x5/d	3% cream.	x2/d	Burning sensation, itching, erythema, diarrhea, nausea,
	g	, u	lotion, ointment		vomiting
Nystatin	100,000 units/mL	×4-5/d	100,000 units/g	×2-4/d	Nausea, vomiting, diarrhea, abdominal pain,
	suspension, 200,000		cream, ointment		urticaria, thin layer of nystatin powder may be applied
	units, 400,000 units				under the dentures after meal. Intra-oral formulation
	troches, 200,000 units	i			may contain sugar
	vaginal suppositories				
Nystatin with	N/A		Nystatin-100,000	×2-4/d	Dryness, maceration, atrophy, irritation
corticosteroid			units with 0.1%		
			triamcinolone		
			acetonide cream,		
			ointment		

Table 3	Topical	anti-fungals	for intra- and	neri-oral	use (selected	formulations)
Table 3	TOpical	and-iungais	101 mua-anu	peri-orai	use (selected	1 IOI III uiauoiis)

AST, aspartate transaminase; INR, international normalized ratio; N/A, non available; ^a, All agents should be used for at least 14 days (to prevent relapse); ^b, Systemic absorption of these topical preparations may enhance additional adverse events and implicate on drug-interactions; ^c, N/A in the USA.

Ofodile, 2001]. Adverse effects include mild local erythema, urticaria, edema, altered sensation (e.g., burning, stinging, or tingling), pain and headache. Topical sunscreens may reduce the incidence of recurrent herpes infections in patients whose recurrences are known to be triggered by sunlight [Ship *et al.*, 2008].

Fluorides

Highly-concentrated fluoride products for topical application are indicated for the prevention of dental caries and for re-mineralization of initial carious lesions. In the palliative care setting, these fluoride agents are important in dentate patients with hyposalivation. These patients are at a high risk for caries and need a daily application of >1.0% sodium fluoride gel. The gel is applied to the teeth after meticulous brushing, using a cotton applicator, extra-soft toothbrush, or soft individual trays. In addition, a professional application of a veryhigh-content fluoride gel or varnish is recommended at intervals of 4- to 6-months or at each recall appointment. The smallest amount possible should be applied and excess expectorated, as accidental ingestion of a large amount of fluoride can cause gastrointestinal upsets. Topical fluoride application may be useful for relief of cervical dental hypersensitivity.

"Magic mouthwashes"

"Magic mouthwash" is a solution with several active ingredients that aims to relieve pain and sometimes also moistens a dry mouth. The formula varies between institutions, but it often contains viscous lidocaine (2%), diphenhydramine hydrochloride (5%) or another antihistamine, aluminum hydroxide, sometimes with the addition of coating agents. Dyclonine hydrochloride (0.5-1.0%), corticosteroids, anti-fungals, antibiotics and/ or guafenesin (an expectorant) may also be incorporated as needed [Siegel et al., 2006]. The patient is instructed to use the mouthwash three times a day, to shake the solution well before using, and to swish for 3 min, gargle and expectorate or swallow, depending on the desired effect in the oropharyngeal region and absorption in gastrointestinal tract. Despite the combination of ingredients, several authors have reported that "magic mouthwash" does not have a significant beneficial effect [Dodd et al., 2000; Worthington et al., 2004].

Special conditions and considerations in cancer patients

Cancer or the adverse effects of its treatment often manifest in the oral cavity [Zadik and Nitzan, 2012], and these manifestations can persist for years after the completion of therapy. The following section describes common oral conditions affecting cancer patients.

Oral mucositis (OM)

OM is defined as inflammation and mucosal breakdown caused by radio- and/or chemo-therapy. Mucositis can cause extreme pain, resulting in oral dysfunction, including the inability to eat, drink and speak. This debilitating condition can interrupt or alter the anti-cancer treatment plan. Exacerbations of OM by secondary infection and the possibility of the spread of infection from the oral cavity to the circulation highlight the significance of this condition.

The 5-step model of pathogenesis of mucositis [Sonis, 2011] demonstrates its complexity, and its simultaneous effects on epithelium, macrophages, endothelium and connective tissue.

The term *Stomatitis* was suggested for oral mucosal manifestations induced by targeted medications such as mammalian target of rapamycin (mTOR) inhibitors and tyrosine-kinase inhibitors [Boers-Doets *et al.*, 2012], to

differentiate these adverse reactions from radio- and chemotherapy-mucositis [Watters *et al.*, 2011]. The clinical presentation of mTOR inhibitor-related oral ulcers is distinct. Most are discrete aphthous-like ulcerations. In contrast to chemo- or radio-therapy induced mucositis, the pathogenesis is more specific and the management is different.

OM needs to be differentiated from other oral ulcerations and other causatives factors such as local trauma or secondary infection, and it should be identified and eliminated.

The 2012/13 systematic review of the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO) provides clinical practice guidelines developed using sound methodology and objectively assessed evidence [Bowen et al., 2013; Elad et al., 2013; Jensen et al., 2013; Lalla, 2013; McGuire et al., 2013; Migliorati et al., 2013; Nicolato-Galitis et al., 2013; Peterson et al., 2013; Raber-Durlacher et al., 2013; Saunders et al., 2013; Yarom et al., 2013]. Table 4 summarizes the evidence-based guidelines for the management of OM. Additional guidelines (including agents that are not recommended, or not found to be beneficial) as well as detailed reviews of numerous interventions are available in the MASCC/ISOO series. Based on expert opinion, the panel acknowledged that normal saline and sodium bicarbonate is a harmless bland rinse that can be helpful for oral hygiene maintenance and patient comfort [Mcguire et al., 2013]. Daily mouth rinsing with 0.12% chlorhexidine gluconate in an alcohol-free solution is reasonable for the prevention of super-infection, although there is no proof that it affects mucositis per se. Various interventions for relief of mucositis-related pain can be found in the literature. The MASCC/ISOO guidelines concluded that systemic opioids are effective and local measures may also be beneficial (Table 4) [Peterson et al., 2013; Saunders et al., 2013].

Patients suffering from mucositis must be monitored to prevent malnutrition and/or dehydration; they may need hospitalization for intravenous fluids, total parentral nutrition or Nasogastric- or gastrostomy- delivered feedings for nutrition. Routine dental care is not recommended during periods of intense chemo- or radio-therapy.

Oral ulcers (non-mucositis)

In the palliative cancer patient, oral infection (viral, bacterial or deep fungal), graft-versus-host disease (GVHD), and neutropenia may present as painful oral ulcers (*Figure 3B*)

Category	Intervention	Guideline
Anti-inflammatories	Benzydamine	Benzydamine mouthwash is recommended for the prevention of OM in patients with head and
		neck cancer receiving moderate dose radiation therapy (up to 50 Gy), without
		concomitant chemotherapy (recommendation)
Opioids	Morphine: PCA	PCA with morphine is recommended as the treatment of choice for OM pain in patients
		undergoing HSCT (recommendation)
Opioids	Fentanyl:	Transdermal fentanyl may be effective for the management of pain due to OM secondary to
	trans-dermal	standard dose chemotherapy or high dose chemotherapy prior to HSCT (suggestion)
Opioids	Morphine:	Morphine 2% mouth rinse may be effective for the management of pain due to OM in
	mouth rinse	patients receiving chemo-radiation for head and neck cancer (suggestion)
Tricyclic	Doxepin	0.5% Doxepin mouth rinse may be effective for the management of pain due to OM
antidepressant		(suggestion)
Basic oral care	Oral care	Using oral care protocols is suggested in the prevention of OM in all age groups and across
	protocols*	all cancer treatment modalities (suggestion)
Cryotherapy	Local ice-cubes	Cryotherapy (30 minutes) is recommended for patients receiving bolus 5-FU chemotherapy
	application	to prevent OM (recommendation)
Cryotherapy	Local ice-cubes	Cryotherapy is suggested for patients receiving high-dose melphalan, with or without TBI,
	application	as conditioning for HSCT to prevent OM (suggestion)
Growth factors	Palifermin	KGF-1 (palifermin) in a dose of 60 µg/kg per day for 3 days prior to conditioning treatment
		with chemotherapy and TBI and for 3 days post-autologous transplantation is recommended
		for the prevention of OM (recommendation)
Laser and	Low level light	Low level laser therapy in the wavelength around 650 nm, the intensity of 40 mW, and each
light therapy	therapy	square centimeter treated with the required time to a tissue energy dose of 2 J/cm ² is
		recommended for the prevention of OM in HSCT (recommendation)
Laser and	Low level light	Low level laser therapy in the wavelength around 632 nm is suggested for the prevention of
light therapy	therapy	OM in patients undergoing radiotherapy, without concomitant chemotherapy, for head and
		neck cancer (suggestion)
Naturals	Zinc	Systemic zinc supplements administered orally may be of benefit in the prevention of OM in
		oral cancer patients receiving radiation or chemo-radiation therapy (suggestion)
HSCT, hematopoieti	c stem cell trans	plantation; ISOO, International Society of Oral Oncology; MASCC, Multinational Association
of Supportivo Coro i	n Canaar: OM ar	al muccosition PCA potient controlled applaceia, TPL total body irradiations * "Oral care proto

Table 4 MASCC/ISOO evidence-based clinical practice guidelines for the management of OM

HSCT, hematopoietic stem cell transplantation; ISOO, International Society of Oral Oncology; MASCC, Multinational Association of Supportive Care in Cancer; OM, oral mucositis; PCA, patient-controlled analgesia; TBI, total body irradiation; *, "Oral care protocols" refers to those actions that maintain oral hygiene and promote oral health. [Bowen *et al.*, 2013; Elad *et al.*, 2013; Jensen *et al.*, 2013; Lalla, 2013; McGuire *et al.*, 2013; Migliorati *et al.*, 2013; Nicolato-Galitis *et al.*, 2013; Peterson *et al.*, 2013; Raber-Durlacher *et al.*, 2013; Saunders *et al.*, 2013; Yarom *et al.*, 2013].

[Elad *et al.*, 2010a; Meier *et al.*, 2011]. Other common causes for oral ulcerations, such trauma and recurrent aphthous stomatitis {which may be stress related [Zadik *et al.*, 2012b]}, need to be ruled out (*Figure 7*). Importantly, ulcers may also be caused by malignancy (primary, recurrent lesions or metastasis).

Evaluation of oral ulcers includes a thorough history (systemic health, including past therapies, blood count, oral habits, oral symptoms, etc.), a clinical evaluation of the oral lesions (number, location, size, boundaries, identification of intra-oral traumatic sources), and occasionally laboratory tests (e.g., swab for viral and microbial evaluation, biopsy for histologic evaluation).

The management depends on the diagnosis. Oral infections may require anti-microbial therapy in medically-compromised patients. Culture and sensitivity results assist in selecting the appropriate antimicrobial agent. Palliation for oral chronic GVHD may include pharmacologic modalities or light therapy [Meier *et al.*, 2011]. Neutropenia-related ulcers usually resolve when the neutrophil levels rise. Traumatic ulcers heal quickly once



Figure 7 An ulcer on the corner of the mouth. It is likely that the tape used to secure the endotracheal tube in this hospice patient caused this traumatic ulcer.



Figure 9 Post-radiation hyposalivation and extensive rampant dental caries.

the traumatic source is eliminated; however, this process tends to be slower in diabetic, or immune-compromised patients. Generally, an ulcer of unknown etiology that does not respond to local measures in two weeks should be biopsied and evaluated histopathologically.

Pain relief for oral ulcers using topical anesthetics may be necessary (e.g., 2% lidocaine, 20% benzocaine). Gel application or mouthwashes can be used.

Xerostomia

In cancer patients the main cause of dry mouth is late



Figure 8 A sialometry sample from a post-radiation xerostomic patient. Hyposalivation is defined as the secretion ≤ 0.1 mL/min of saliva (unstimulated).

effects of radiotherapy to the head and neck area (*Figure 8*). Chemotherapy may also cause salivary gland damage, which tends to be at least partially reversible. In patients who undergo HSCT, GVHD may affect the salivary glands, mimicking Sjögren syndrome. Thyroid radio-ablation or chemotherapy with agents marked with radioactive iodine may also cause salivary gland dysfunction. The abovementioned anti-cancer therapies induce hyposalivation, reduce salivary pH, and limit salivary buffering and tooth re-mineralizing capacity.

Numerous medications cause dry mouth, including anti-depressants and anxiolytics, diuretics and other antihypertensives, anti-cholinergics, and bronchodilators. Other factors associated with dry mouth in the palliative care setting are depression and dehydration.

Severe dry mouth may impair oral function (i.e., eating and speaking), and cause deterioration in oral health and quality of life, including sleep quality. When the washing effect of saliva is reduced, plaque accumulation increases, as does the risk of oral infections. The quantitative and qualitative changes in saliva significantly increase patient susceptibility to dental caries (*Figure 9*) and dental hypersensitivity. Dry mouth *per se* does not cause pain, however the associated rampant dental caries, oral infections (e.g., candidiasis), and sialadenitis (salivary gland inflammation) are painful.

Topical agents that enhance patient comfort and relieve xerostomia (see above) are also used in cancer patients. A systematic review addressing the available interventions for dry mouth in cancer patients concluded that muscarinic agonist stimulation (e.g., pilocarpine, cevimeline), oral mucosal lubricants, and acupuncture may be beneficial [Jensen *et al.*, 2010; Witsell *et al.*, 2012; Brimhall *et al.*, 2013]. Irrigation of affected parotid gland may also temporary relieve xerostomia [Izumi *et al.*, 1998; Habu *et al.*, 2010]. Humidifiers in the sleeping area may alleviate oral dryness while sleeping [Siegel *et al.*, 2006]. However, the treatment of chronic salivary dysfunction is challenging.

Whereas radiotherapy-related salivary dysfunction is profound and often irreversible, substituting medications can minimize drug-induced salivary gland dysfunction. For example, the physician treating depression should consider that amitriptyline and mirtazapine cause more symptoms of dry mouth than nortriptyline and most selective serotonin reuptake inhibitors [Keene *et al.*, 2003]. Smoking may exacerbate oral dryness and should be avoided.

Topical fluoride should be applied in dentate xerostomic patients to prevent dental caries, and oral hygiene instructions are also very important. Enzyme-containing lubricating agents may relieve symptoms and provide a washing effect. Oral candidiasis is prevalent in patients with hyposalivation, and should be treated (see above).

Nutritional modifications that may be helpful in xerostomic patients include consuming tart foods which stimulate saliva secretion and soft diet which is easier to swallow (e.g., applesauce, banana, fruit nectar, pureed or mashed vegetables, avocado, and yogurt). Moistening food with gravy, broth, or sauces, and avoiding alcohol is also recommended [Petzel, 2011]. Consultation with a dietitian and specialized therapy (e.g., swallowing exercises) may be needed in patients with severe swallowing impairment.

Taste disorders

Taste alterations (dysgeusia, ageusia, hypogeusia, hypergeusia) affect 56-76% of cancer patients treated by chemo- or radio-therapy [Hovan *et al.*, 2010]. This condition may be caused by injury to the neuroepithelial taste receptors, specifically their microvilli, or to the innervating fibers. Taste alterations appear within the first week of radiotherapy to the head and neck. Most often, patients report a bitter taste. The phenomenon of taste loss begins with a cumulative radiation dose of 20 Gy, while at 30 Gy all taste qualities are affected, and at 60 Gy there is usually a complete loss of taste [Fischer *et al.*, 2008]. This taste impairment may be exacerbated by concomitant therapy-

induced nausea, vomiting, and hyposalivation [Epstein *et al.*, 2002]. Chemotherapeutic agents can diffuse into the mouth, aggravating adverse sensations, causing a bitter taste, halitosis and aversion to various food types [Little *et al.*, 2013; Lalla *et al.*, 2011]. Radioactive iodine (I^{131}), used to treat differentiated papillary and follicular thyroid gland cancer, becomes concentrated in the salivary glands and is subsequently secreted in the saliva and can alter taste sensation [Mandel and Mandel, 2003]. Because taste receptors have a relatively rapid turnover, taste dysfunction usually begins to recover within weeks or months of treatment completion, and within one year most patients have normal or near-normal taste function [Fischer *et al.*, 2008]. In some patients this process takes as long as five years, and others suffer from permanent hypogeusia.

The sense of smell is also important for flavor and the clinician should check that this sense is intact. Eating pleasure may be augmented using aromatic enhancers and by warming the food [Lalla *et al.*, 2011]. Adding spices, especially monosodium glutamate, intensifies the taste of food [Wiseman, 2006]. Chewing sugar-free flavored gum may help some (dentate) patients with taste alterations [Lalla *et al.*, 2011]. The efficacy of zinc sulfate supplementation for recovering taste is controversial. Currently, no evidence-based treatment exists for persistent taste alterations [Hovan *et al.*, 2010].

Dental hypersensitivity

Hypersensitivity of teeth is usually triggered by local thermal changes (e.g., cold or hot oral intake), and by definition it is less intense than dental "pain". Common causes of dental hypersensitivity include caries, faulty restorations, gingival recession, and abrasion or erosion of the cervical region of the tooth. In cancer patients, dental hypersensitivity may be caused by anti-cancer therapy (e.g., vincristine, cyclophosphamide), and the post-HSCT administration of cyclosporine [Zadik *et al.*, 2010; Zadik *et al.*, 2013c]. Quantitative and qualitative changes in saliva may exacerbate tooth sensitivity.

Dental hypersensitivity may be transient and subside gradually after cessation of chemotherapy. The patient may be advised to use a highly concentrated neutral fluoride gel, a desensitizing toothpaste, and to avoid food and drink that trigger discomfort [Zadik *et al.*, 2013c].

Osteonecrosis

Osteonecrosis of the jaw can be caused by radiation-therapy

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Figure 10 Drug-related osteonecrosis of the mandible (lingual view) in a patient with metastatic breast cancer treated with zoledronic acid.



Figure 11 Panoramic radiograph of a patient diagnosed with nasopharyngeal carcinoma and treated with radiotherapy. The patient suffered from a pathological fracture of the mandible (right) due to osteoradionecrosis (ORN).

[i.e., osteoradionecrosis (ORN)] or medication (including bisphosphonates, denosumab, sunitinib, and bevacizumab) (*Figure 10*), and can manifest with pain and neuropathy, swelling, suppuration, halitosis, intra- or extra-oral sinus tracts, and pathological fractures of the jaw (*Figure 11*).

ORN is defined as a condition in which radiated bone becomes exposed for three to six months. In patients treated with radiotherapy to the mandible, the prevalence of ORN may be up to 15% [O'Dell and Sinha, 2011].

Bisphosphonate-related osteonecrosis of the jaw (BRONJ) is defined as the presence of necrotic bone for more than eight weeks anywhere in the oral cavity of an individual on bisphosphonate therapy or with history of bisphosphonate therapy, with no history of radiation to the head and neck region [Ruggiero *et al.*, 2009]. An oral fistula may be the presenting sign of BRONJ, too [Fedele *et al.*, 2010; Yarom *et al.*, 2010]. In patients that were treated with intravenous bisphosphonates for multiple myeloma, bone metastasis, and cancer-related hypercalcemia or bone pain, the prevalence of BRONJ may be up to 13% [Migliorati *et al.*, 2010].

BRONJ-associated pain is mostly due to secondary infection of the lesion [Ruggiero and Woo, 2008], but may also be due to altered alveolar bone metabolism (involving ischemia) [Assael, 2009], and neuropathy [Elad *et al.*, 2010c; Zadik *et al.*, 2012c]. Pain is reported in about 50% of patients with drug-induced osteonecrosis [Migliorati *et al.*, 2010], and therefore, pain control is a key treatment goal [Ruggiero *et al.*, 2009]. The mainstay management of symptomatic osteonecrosis includes long-term systemic antibiotics (e.g., amoxicillin, clindamycin, doxycycline),

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topical antiseptics (e.g., 0.12% chlorhexidine gluconate mouthwash), and analgesics. Jaw necrosis-associated painful neuropathy may be managed with amitriptyline [Zadik *et al.*, 2012c]. Surgical intervention is generally not recommended because of the risk of worsening the condition; however, surgery may be needed in advanced BRONJ (stage 3).

ORN management ranges from conservative measures (e.g., avoidance of ill-fitting dentures, tobacco, alcohol, and weekly local debridement with antiseptics and gentle removal of loos separated sequestra) in early stage lesions, to systemic antibiotics in episodes of acute infection, to hyperbaric oxygen (HBO) and surgical intervention (i.e., resection and reconstruction) for advanced lesions. The accepted HBO protocol for ORN patients is 20-30 dives (each of 90-120 minutes) at 2.0-2.5 atmospheres, daily (5 days a week). If a surgical procedure is performed, an additional 10 dives are taken after the procedure [O'Dell and Sinha, 2011]. However, the use of HBO for ORN has recently been challenged [Lubek *et al.*, 2013].

Loss of peri-oral elasticity

Post-therapy fibrosis and loss of peri- and intra-oral elasticity may present after head-neck radiation therapy (affected up to 38% of these patients) and in patients with chronic GVHD. Limited jaw movement may be also caused by post-surgery scar tissue, discontinuity of the mandible due to tumor excision, and impaired function of the temporomandibular joint due to radiation therapy. Severe limitation of mouth opening may significantly disrupt oral functions (e.g., eating and speaking) and may further Supportive and palliative care in dentistry and oral medicine



Figure 12 Dynamic bite opener.

impair oral hygiene maintenance leading to halitosis and a deterioration of dental health. The limited mouth opening may also impede appropriate evaluation of the oral soft tissues, which may delay the detection of oral malignancy.

Measures for partial restoration of the range of motion include physiotherapy and daily self-exercise, use of tongue depressors stacked together (where the number of tongue depressors is gradually increased) or dynamic bite openers (Figure 12) [Zadik and Nitzan, 2013]. However, caution should be used following mandibular reconstruction with titanium plates, to avoid injury during forced exercises with dvnamic bite openers [Kamstra et al., 2013]. Pentoxifylline, a methylxanthine with immunomodulatory properties, may down-regulate pivotal cytokines in the radiation-related fibrosis process, and there are data that administration of pentoxifylline to patients with radiation-fibrosis significantly increases the range of motion of the mandible [Fischer and Epstein, 2008]. In sclerodermatous-type chronic GVHD, palliative incisions were reported to provide relief [Treister et al., 2012]. However, these measures were only assessed in small samples of patients.

The delivery of dental care may be impossible when opening is severely limited, and general anesthesia may be required. Since daily self-oral hygiene procedures are also significantly compromised in these patients, the administration of topical fluoride (see above) is of utmost importance to prevent dental deterioration.

Summary

The oral cavity, which plays a pivotal role in multiple functions and general well-being, is a site of significant adverse effects in palliative care patients. This chapter presents common oral conditions, treatment options and challenges in order to enhance care delivery in the palliative care setting.

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Genitourinary issues

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Introduction

Palliative care includes disease directed treatment as well as functional, psychosocial and spiritual support. Palliative care plays an important role in quality cancer care throughout active treatment and survivorship. A patient is considered for palliative care when he or she is not a candidate for any form of curative treatment or does not wish to accept the related morbidity. The goal of palliative care is to provide comprehensive relief from disease-related or treatmentrelated conditions or side effects in order to achieve the highest possible quality of life and survival prolongation. Palliative care has been consistently shown to improve quality of life by addressing the harmful effects of pain, other physical symptoms, and emotional distress, while also reducing the family caregiver burden [Meier and Brawley, 2011]. In response to this increasing number and needs of people living with serious, complex, and chronic illnesses like cancer, the number of palliative care teams in hospitals has more than doubled within the past 5 years.

Demographics of urological malignancies

Regarding cancer prevalence in general, an estimated 13.7 million Americans with a history of cancer were alive on January 1, 2012 and nearly one-half (45%) of cancer survivors are aged 70 years or older, while only 5% are younger than 40 years. As of January 1, 2012, it is estimated that the population of cancer survivors will increase to nearly 18 million [Siegel *et al.*, 2012].

Urological malignancies are traditionally affecting people of older age, are not usually upfront lethal, especially prostate cancer, and therefore urological patients often live many years with their disease. Although there are many effective medical and surgical palliative treatments for urological patients, there is a lack of relevant comprehensive guidelines. This chapter will review the various palliative treatments available for the three most common urological malignancies, namely prostate cancer, bladder cancer and renal cancer. The issue of pain management in relation to the palliative urologic malignancies will not be addressed here since it has been a subject or extensive discussion in previous chapters of this book.

Urologic malignancies

Prostate cancer (PCa)

PCa is the most frequently diagnosed cancer in men worldwide and is the second leading causes of death from malignancies in men only preceded by lung cancer [Ferlay *et al.*, 2006; Jemal *et al.*, 2008]. Men of black race or men with a family history of PCa share a higher risk. The incidence of PCa in European countries has been increasing lately, mainly as a result of increased screening methods, and is relatively higher in men living in Western and Central Europe [Parkin *et al.*, 2005]. It is currently estimated that there are nearly 2.8 million men living with a history of prostate cancer in the United States, and an additional 241,740 cases will be diagnosed in 2012 [Siegel *et al.*, 2012].

Treatment options vary depending on cancer stage as well as patient comorbidity, age, and personal preferences. More than one-half (57%) of men aged younger than 65 years are currently treated with radical prostatectomy, either open, robot-assisted or laparoscopic. Patients aged 65 to 74 years commonly undergo radiation therapy (42%), although radical prostatectomy (33%) is also often used. Data show similar survival rates for patients with early stage

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disease who are treated with either of these methods. Active surveillance rather than immediate treatment is a reasonable and commonly recommended approach, especially for older men and those with favorable tumors and/or more serious comorbid conditions [Lu-Yao *et al.*, 2009; Shappley *et al.*, 2009]. Androgen deprivation therapy, chemotherapy, palliative bone-directed therapy (bisphosphonates, denosumab), radiation therapy, or a combination of these modalities is used to treat advanced and metastatic prostate cancer.

With regard to survival, currently more than 90% of all prostate cancers are diagnosed in the local or regional stages, for which the 5-year relative survival rate approaches 100%. Over the past 25 years, the 5-year relative survival rate for all stages combined has increased from 68.3% to 99.9%. The 10-year and 15-year relative survival rates are 97.8% and 91.4%, respectively [Siegel *et al.*, 2012].

Bladder cancer

It is estimated that there are 585,390 urinary bladder cancer survivors living in the United States, and an additional 73,510 cases will be diagnosed in 2012. Among patients with muscle-invasive disease, 4% undergo partial and 41% undergo total cystectomy. Approximately 27% of patients receive a combination of chemotherapy and high-dose radiation therapy without surgery. In appropriately selected patients, this bladder-sparing approach is as effective as cystectomy at preventing recurrence [Efstathiou *et al.*, 2012]. For advanced cancers that have not spread to other organs, patients may be offered chemotherapy alone (26%) or in combination with radiation therapy (11%) in an effort to shrink the tumor and permit salvage cystectomy.

For all disease stages combined, the 5-year relative survival rate is 78.1%. Survival declines to 71.4% at 10 years and 65.4% at 15 years after diagnosis. Patients with invasive tumors diagnosed at a localized stage have a 5-year survival rate of 70.7%; approximately 35% of cancers are detected at this early stage. For those with regional and distant disease, the 5-year survival rate is 34.6% and 5.4%, respectively [Siegel *et al.*, 2012]

Renal cancer

Renal cancer accounts for 2-3% of all adult malignancies with males more frequently affected (3:2 ratio) and the highest prevalence recorded in the sixth and seventh decade of life. The incidence and mortality of kidney cancer have continuously increased during the last 50 years in the USA and Western Europe [Pantuck *et al.*, 2001]. The incidence of renal cancer is increasing by around 2% per year, a fact that is mainly attributed to the abundant use of imaging studies and the resultant incidental diagnosis of, usually small, renal tumors [Ferlay *et al.*, 2007].

Currently one third of patients are diagnosed with locally invasive or metastatic disease while another 25% of patients will experience tumor recurrence following what was at the time considered curative radical nephrectomy [Gupta *et al.*, 2008; Athar and Gentile, 2008]. Renal cancer has a strong tendency to metastasize and has the worst cancer-specific mortality among urologic tumors since more than 40% of the patients with RCC die of the disease, opposite to the 20% mortality observed in prostate or bladder carcinoma [Athar and Gentile, 2008; Pascual and Borque, 2008]. Generally patients with metastatic RCC have on average 13 months of survival and the five-year survival rate is lower than 15% [Rini *et al.*, 2009].

Urinary tract obstruction

Upper tract obstruction

Upper urinary tract obstruction is a relatively common condition for practicing urologists. Although the etiology of obstruction when referring to the general population is usually benign, this proportion changes significantly towards malignancy when referring to elderly patients. Increases in the number of individuals diagnosed with cancer each year, largely due to aging and growth of the population, as well as improving survival rates, have led to an ever-increasing number of cancer survivors.

The constant evolutions in endourology have effectively facilitated minimally invasive management of upper-tract obstruction. In cases where malignancy is the cause of obstruction, however, the landscape significantly changes. Questions arise regarding the need and ethics for relieving the obstruction, the means to accomplish this, and the benefits and drawbacks of each technique regarding both their efficacy and their impact on the patients' quality of life in the face of malignancy.

Obstruction of the ureters caused by extrinsic compression from a primary tumor or retroperitoneal lymph nodes masses is not an unusual situation in the course of advanced pelvic malignancies. The majority of the cases are gynecologic or gastrointestinal pelvic and retroperitoneal malignancies, and the situation may be aggravated by periureteral fibrosis, a long-term adverse events of previous chemotherapy or radiation therapy. Upper-tract obstruction from advanced pelvic malignancy is usually an ominous sign of disease progression that translates into a median survival of less than one year [Radecka *et al.*, 2006]. The cause of obstruction may be invasioninfiltration of the ureters by tumor (cervical, bladder, prostate, or colorectal cancer), extrinsic compression by a retroperitoneal primary or metastatic neoplasia, or scarring, adhesions, and luminal ureteral strictures resulting from radiotherapy or chemotherapy. Obstruction may result from extrinsic ureteral compression caused by expansion of the retroperitoneal cavity from a retroperitoneal mass or encasement of the ureters with malignant lymph nodes.

In most instances, obstruction clinically manifests slowly with vague and nonspecific symptoms, dull flank pain or discomfort, feeling of fullness, or even lethargy. In some cases, urinary tract infection (UTIs) may be the initial symptom, more so in older individuals. Once obstructive uropathy is established in the setting of a malignant disease, it may progress to renal insufficiency with manifestations such as uremia, electrolyte imbalance, or life-threatening UTIs if the obstruction is not reversed.

The management of malignant ureteral obstruction poses ethical and practical dilemmas for the physician, the patient and his relatives. The first question to be answered should be: "What is the clinical gain and what may be the consequences of relieving the obstruction?" There are absolute as well as relative indications for reversing an obstruction. It goes without saying that obstruction should be relieved in the case of unremitting pain as well as in the case of febrile upper UTI irrespective of the disease progression or estimated survival time. In the case of life-threatening renal insufficiency from upper tract obstruction, the decision to deobstruct or not should be weighed against the prognosis of the individual, the impact of the scheduled intervention on quality of life, the available treatment options with curative intent and their possibilities of success, and, of course, patient preferences once all these issues have been explained and discussed [Sountoulides et al., 2010].

There is evidence that palliative urinary diversion and preventing death from progressive renal failure may result in a survival advantage [Shekarriz *et al.*, 1999; Wong *et al.*, 2007]. For patients with end-stage cancer, however, although palliative urinary diversion may prolong survival for a few weeks or months, this gain should be balanced against the anticipated quality of life after diversion. Given

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that the median survival for these patients usually does not exceed one year, prolonging survival by preventing death from uremia may come with the price of reduced quality of life because of pain, fatigue, or other sequelae of advanced metastatic disease [Emmert *et al.*, 1997; Russo, 2000]. Therefore, it is debatable whether urinary diversion by means of internal stent or nephrostomy catheter placement offers benefit for cancer patients with life-threatening comorbidities unless it facilitates or follows certain therapeutic anticancer treatment [Wilson *et al.*, 2005; Kouba *et al.*, 2008]. In any other case, the patient's right to a peaceful death from uremia when there is no hope for cure or palliation should be taken into account when concerns are raised regarding quality of life during those final days [Shekarriz *et al.*, 1999].

Still for the majority of cases, upper urinary tract decompression and maintenance of ureteral patency even as a palliative measure is the final decision. Options for upper tract decompression include percutaneous nephrostomy, retrograde stenting and open urinary diversion. With the advent of minimally invasive surgery a plethora of techniques have been introduced for the management of ureteral obstruction, including endoscopic intraureteral incision (endoureterotomy), retro- and trans-peritoneal laparoscopic cutaneous ureterostomy (LCU), placement of indwelling ureteral stents and percutaneous nephrostomy.

Ureteral stent or nephrostomy tube

For the last decades the two more favored options for decompression of an obstructed collecting system in cancer patients have been retrograde or antegrade insertion of an indwelling ureteral stent or placement of a percutaneous nephrostomy (PCN).

Although there has been extensive discussion of the risks and benefits of insertion of ureteral stents and placement of nephrostomy tubes, it is not clear which modality provides maximal benefit for which patients. The fact that there are no guidelines available for the management of malignant ureteral obstruction accounts for the certain disparity in practice patterns among urologists and medical oncologists, as was shown in a recent survey [Hyams and Shah, 2008].

Indications

A trial of retrograde stent placement is considered by many as first-line treatment option for patients with extrinsic ureteral obstruction of malignant origin. Retrograde



Figure 1 Nephrostomography in a patient with upper urinary tract obstruction from advanced bladder malignancy. Note that the contrast medium stops at the level of the distal ureter (red arrow).

ureteral stent insertion and nephrostomy catheter placement are performed under fluoroscopic guidance with patients under local anesthesia, monitored sedation, spinal, or general anesthesia, depending on the individual case. In case initial retrograde placement of a stent is successful, patients usually have periodic endoscopic stent exchange every 3 to 4 months [Sountoulides et al., 2010]. Retrograde stent placement might be the preferred initial approach in cases in which nephrostomy is anticipated as technically difficult because of extraordinary body habitus or in patients with a solitary functioning kidney due to the small but present risk of clinically important hemorrhage [Zagoria and Syer, 1999]. The presence of severe coagulopathy represents a relative contraindication to PCN [Ramchandani, et al., 2003]. One can also argue that ureteral stent change preserves renal function because it follows the normal retrograde route from the bladder to the collecting system. Also, from that aspect, it is less invasive than nephrostomy and probably better tolerated, suggesting

that it may be more advantageous than nephrostomy especially in view of the limited life expectancy of patients with advanced malignancies [Rosenberg *et al.*, 2005; Rosevear *et al.*, 2007].

Placement of a nephrostomy tube with or without a subsequent attempt at antegrade stent placement may be the first option in cases of distal ureteral obstruction from cervical, prostate, or colorectal cancer. PCN should also be the preferred option in cases of significant involvement of the bladder by a prostatic or bladder malignancy where attempts at identification of the ureteral orifices and stent placement are usually unsuccessful [Danilovic et al., 2005; Kanou et al., 2007] (Figure 1). Other contraindications to retrograde stent placement include gross bladder hemorrhage or difficulty in reaching the bladder because of previous surgery or anatomic anomalies [Danilovic et al., 2005; Uthappa and Cowan, 2005; Kanou et al., 2007]. PCN may also be more effective in relieving upper-tract obstruction in cases of extensive peritoneal carcinomatosis from gastrointestinal malignancies and even more so in cases where obstruction is complicated by pyonephrosis with thick purulent material filling the renal pelvis. In these cases a large bore nephrostomy tube provides better chances of drainage compared to internal stents (Figure 2). Drainage failure of ureteral stents in advanced pelvic carcinomatosis has been attributed to the absence of long-segment ureteral peristaltic movement because peritoneal carcinomatosis induces obstruction along the entire ureteral length [Park et al., 2002].

Efficacy

PCN placement for extrinsic ureteral compression has remarkable technical success rates (96% to 100%) compared with retrograde stent placement in relieving upper-tract obstruction [Pappas *et al.*, 2000; Ku *et al.*, 2004]. Regarding stents, there is a significant improvement in the success rates with retrograde stent insertion being technically successful in an average of 85% of cases, considering results from recent series [Rosenberg *et al.*, 2005; Kanou *et al.*, 2007; Chung *et al.*, 2004; Ku *et al.*, 2004].

Still, failure of ureteral stents to maintain a patent upper tract is a common but unpleasant reality for patients with malignant obstruction. There are certain parameters inherent to malignancies to be held responsible for the higher stent failure rate in this setting. Stent encrustation and tumor growth through the stent are usual causes of stent obstruction and failure, resulting in more frequent



Figure 2 Ultrasonographic picture of a dilated renal pelvis filled with thick purulent material. This was a case of pyonephrosis due to obstruction from an advanced bladder malignancy where a large bore nephrostomy tube was placed.

stent change or resolving to PCN [Park et al., 2002].

Quality of life after palliative urinary diversion

Despite the technical improvements in stents design and compatibility, neither nephrostomy tube placement nor internal stent placement are able to significantly alter median overall survival for patients with advanced cancer [Pappas et al., 2000; Wong et al., 2007]. Therefore the issue of quality of life and its relation to the type of deobstruction is gaining significance. One could argue that in the palliative setting, assessment of the quality of life or functional status of the patient is more appropriate and even more important than survival time per se. There is no doubt, however, that defining quality-of-life criteria relevant to palliative intervention for these patients is neither a clear nor an easy task. Very often, the functional and quality-oflife status of these patients is generally poor at the time of presentation secondary to preexisting conditions related to their malignancy. Therefore, the additional impact of any intervention that aims at relieving upper-tract obstruction and avoiding renal insufficiency on quality of life has to be carefully validated. There is a lack of standardized methods to assess quality of life in relation to palliative upper tract deobstruction resulting in different, sometimes arbitrary, definitions been used. When quality of life is addressed, one should take into account the benefits and advantages of each procedure-intervention compared with the underlying situation that necessitates the procedure. For instance, for a patient with progressive upper tract obstruction and established renal insufficiency from advanced untreatable malignancy with minimal pain, the ureteral stent or nephrostomy tube may actually worsen quality of life, while for the patient with intractable flank pain or febrile infection, tube or stent placement may be better tolerated and advantageous to quality of life.

Although the number of trials that have evaluated the issue of quality of life for patients who are undergoing palliative urinary diversion for malignancy is limited, there are still some conclusions to be drawn. Relevant to PCN, early results showed marked deterioration in quality of life for patients with malignant obstruction [Hoe *et al.*, 1993]. One study demonstrated that only 11 of 17 patients with a PCN had acceptable quality of life for two months or more [Emmert *et al.*, 1997].

Shekarriz and coworkers evaluated the performance

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status of patients with advanced malignancies following urinary diversion by either stent or nephrostomy. The authors used the modified Karnofsky performance scale in order to evaluate patients' ability to function as an indirect assessment tool of quality of life. The results showed that the overwhelming majority of patients remained on a poor performance status after diversion, irrespective of the means of diversion. Overall, patients were found to have spent almost half of their survival time after intervention in the hospital, while 15% never left the hospital after the procedure. A significant 86% were seriously bothered by cancer-related pain until the end, and only 14% were rendered free from pain after the procedure. In total, 68% had either minor (63%) or major (5%) procedure-related complications. Karnofsky scores revealed that performance status did not change for the largest portion of patients despite palliative diversion [Shekarriz et al., 1999].

Despite the high technical success rate of PCN, studies have shown a high incidence of complications that are associated with the long-term management of PCNs, resulting in inferior quality of life compared with internal stents. In recent studies, tube dislodgement or blockage occurs in 10% to 19% of patients with malignant obstruction, with the need for replacement and possible hospital stay adding to the compromised quality of life of these patients [Ku *et al.*, 2004; Kouba *et al.*, 2008]. Other problems that can contribute to poor quality of life after PCN are urinary leakage, skin excoriation and inflammation at the nephrostomy exit site [Radecka *et al.*, 2006].

On the other hand, there are reports demonstrating a positive effect of urinary diversion on quality of life with either nephrostomy or stent. Gasparini and associates reported an almost 1.5-year of average survival after diversion in a group of 22 patients. Seventy-seven per cent of patients were discharged home after the procedure and spent 86% of their remaining survival time at home [Gasparini *et al.*, 1991]. Kanou and colleagues found diversion by means of a stent or a nephrostomy catheter to have a meaningful effect on quality of life for approximately two-thirds of patients [Kanou *et al.*, 2007].

The issue of quality of life for cancer patients, however, is multifactorial, and in the absence of a validated qualityof-life assessment tool, there is a need for prospective trials that directly compare PCN with retrograde stent placement regarding complications and their impact on overall quality of life. It is clear that the consideration of advantages, drawbacks, and side effects between internal stent and PCN hardly means that these modalities are optimal for the management of malignant ureteral obstruction. If one has to picture the current trend of managing malignant ureteral obstruction, it would be that internal stent placement is the preferred management option for urologists and patients alike, provided that they are both aware that in some cases, the stent will fail and PCN will be necessary. However until the development of the optimal "tumor stent", urologists will continue to individualize their approach to the cancer patient with upper-tract obstruction toward a decision as to the optimal option for relieving the obstruction.

Metallic "tumor" stents

The introduction of metallic stents for the management of malignant ureteral obstruction aimed at addressing some of the problems and limitations encountered with the use of double-J stents. Double-J stents are not permanent stents and need to be changed every three months or even shorter in case of early occlusion from debris, tumor ingrowth or encrustations. However stent exchange may require hospitalization and anaesthesia; both pose certain risks for patients with malignancy. Also stent exchange may prove technically difficult, and can possibly fail or cause complications, with added morbidity and negative impact on the patients' quality of life.

Coiled metal stents—the resonance stent

Stent design, properties and technique of insertion

A new design for a metallic ureteric stent has been recently developed for the management of malignant ureteral obstruction in an attempt to overcome problems such as the low primary patency rate and the resultant need for additional placement or removal of stents as well as the high risk of migration especially and significant difficulty to remove. The ideal stent should be easily placed, maintain patency without additional interventions and for longer intervals between stent changes, and be easily removed.

The 6F Resonance[™] (Cook, Ireland) metal stent is a continuous unfenestrated metal coil with an inner safety wire welded to both closed, tapered ends. The Resonance is designed in the style of an indwelling full length ureteral stent with conventional pig-tail ends but no end holes. Improved patency rates guarantee a 1-year in-dwelling life span according to the manufacturer. It is constructed of MP35N[®] alloy, a composite of nonmagnetic nickel-cobalt-chromium-molybdenum possessing a combination of ultrahigh tensile strength and excellent resistance to

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Figure 3 Configuration of the coiled, unfenestrated Resonance[®] metallic stent.

corrosion. The unique properties of the nickel-cobaltchromium-molybdenum alloy material of the Resonance stent theoretically prevent hyperplastic tissue ingrowth and encrustation and improve the stent's biocompatibility. Its super elastic properties provide tremendous strength as well as flexibility, and it is compatible with a 1.5 T MRI scan [Borin *et al.*, 2006] (*Figure 3*).

The technique of insertion of the Resonance[™] (Cook, Ireland) stent differs from that for insertion of conventional ureteric stents as the stent can be placed in either an antegrade or a retrograde fashion. The absence of end-holes precludes the passage of the stent over a guide-wire, and the flexibility of the stent (and the resulting lack of rigidity) discourages the forcible pushing of the stent through a tight stricture. The stent is, therefore, introduced through an outer sheath.

For retrograde placement of the stent, during cystoscopy an introduction set similar to an 8/10F dilator is passed over a guidewire into the renal pelvis. As the metal stent is closed on both ends and cannot be placed over a guidewire it has to be passed through the 10F introducer sheath. The wire and inner catheter are removed, and the latter is used to help advance the stent proximally until the pigtail is deployed in the renal pelvis. The 10F sheath is then retracted with the inner catheter held in place until the distal pigtail is deployed in the bladder.

Experience with the Resonance stent

Experience with the insertion of Resonance stents in a series of patients with malignant ureteral obstruction was recently

reported from the U.K. Seventeen Resonance stents were antegradely placed in fifteen patients with various malignancies prior to adjuvant chemotherapy. Three of the seventeen stents had failed from the first day as was evident by nephrostograms and renal function deterioration. All three stents were placed in patients with bulky pelvic disease and all of them were subsequently maintained on external drainage by percutaneous nephrostomies. The rest of the stents were functioning properly with no evidence to suggest stent blockage during their follow-up period until the time of stent change, usually every 6-12 months, or death with the stent in situ. Encrustation was minimal in all cases where the stents were changed after some months [Wah *et al.*, 2007].

Liatsikos *et al.* recently evaluated the mid-term effectiveness (8.5 months of follow up) of the Resonance stents used in 25 patients with malignant ureteral obstruction. Technical success rate was 100% and all stents remained patent during follow up [Liatsikos *et al.*, 2010].

Recent studies with longer follow up have somewhat lessened the initial excitement about the efficacy of the Resonance stent. In the study from a referral center in Durham from a total of 37 stents placed in 25 patients with malignant ureteral obstruction, 12 (35%) were identified to fail. Progressive hydroureteronephrosis and increasing creatinine were the most common signs of stent failure. Patients with evidence of prostate cancer invading the bladder at stent placement were found to have a significantly increased risk of failure. According to authors' experience, the failure rates with metallic stents are similar to those historically observed with traditional polyurethane based stents in malignant ureteral obstruction [Goldsmith et al., 2012]. The same non-encouraging results were reached in the study by Gaved et al. in two of pediatric patients with extrinsic ureteral obstruction. The authors found the patency rates for the Resonance stents were much lower than those reported for adults [Gayed et al., 2013].

A Chinese retrospective study on 20 patients found the Resonance stent to demonstrate excellent patency rates in cases of both benign and malignant obstructions with the exception of radiotherapy patients (50% patency rate) [Li *et al.*, 2011]. Also the Resonance stent seems to be financially advantageous compared to traditional stent in the long-term according to a recent study [Taylor *et al.*, 2012].

Although the results of current studies on the efficacy of the Resonance stent are mixed [Rao *et al.*, 2011] there is evidence that the Resonance stent holds promise for the effective management of patients with malignant
obstruction of the upper urinary tract.

Lower urinary tract obstruction-bladder outlet obstruction (BOO)

In general, when examining the causes of BOO, it is important to consider that BOO results from a variety of etiologies, which may be either functional or anatomic. BOO often produces lower urinary tract symptoms (LUTS), although the degree of intensity of LUTS is highly variable and not predictive of either the presence nor the severity of BOO. Induced LUTS symptoms may be predominantly obstructive, irritative, or often a combination of both. Typically, obstructive symptoms include hesitancy, sensation of incomplete bladder emptying, reduced urinary stream, and post voiding urinary dribbling. Irritative complaints include urinary urgency, frequency of urination, occasional dysuria, and nocturia. Rarely are symptoms related to BOO isolated; often the individual experiencing LUTS presents with a variety of mixed symptoms of obstruction and irritation. BOO may also occur in the complete absence of symptoms and be first identified in the scenario of urinary retention or decompensation of the upper urinary tract [Dmochowski, 2005].

In the setting of malignancy, irritative LUTS and OAB symptoms in otherwise non-obstructed patients can result from therapies such as external beam radiation or brachytherapy of the prostate or bladder. In patients without infection these symptoms are treated with anticholinergics such as tolterodine, darifenacin, solifenacin, oxybutynin, fesoterodine, and trospium with or without the addition of an α -blocker. Although a theoretical risk of urinary retention exists with these medications, relevant studies suggested that this risk is no higher than that associated with placebo [Chapple, 2010].

With regards to obstructive LUTS, the exact incidence of urinary retention or severe BOO among men with advanced prostate cancer is not known, although the commonest adverse events encountered in the final year of life in men with advanced prostate cancer are those of LUTS. It is estimated that more than one fourth (25%) of men treated with androgen deprivation therapy for advanced prostate cancer will require a "channel TURP" at a mean of approximately two years after initiation of therapy. A relative study showed that the need for "channel TURP" is higher among men with a high Gleason sum and those presenting with retention in the group of patients with advanced PCa under androgen ablation therapy [Sehgal et al., 2005].

Management of BOO

Minimally invasive surgery and prostatic stents

Transurethral resection of the prostate (TURP) is currently the mainstay of minimally invasive surgery (MIS) for relieving BOO of any etiology. "Channel TURP" is the resection of visually obstructing tissue without extension to the prostatic capsule in a patient with metastatic or locally advanced disease to improve voiding symptoms. "Channel TURP" has been the most common surgical treatment for PCa patients associated with obstructive LUTS or urinary retention. A recent study showed an improvement in over three quarters of men with advanced prostate cancer who received an intervention including "channel TURP" or long-term urethral or suprapubic catheterization [Khafagy *et al.*, 2007].

The use of lasers to treat BOO secondary to BPH has been popularized during the last decades. Several different devices have been developed, including the neodymium:YAG (Nd:YAG), holmium:YAG and, more recently, the potassium titanyl-phosphate (KTP) laser for photoselective vaporization of the prostate (PVP). At present, there are publications available on PVP for patients with advanced prostate cancer demonstrating the efficacy and safety of PVP in those patients. For patients with PCa bothered by BOO or retention, PVP or GreenLight[®] laser prostatectomy is safe and provides relief from symptoms, with significant continuous improvement in IPSS, QoL score, Qmax, and PVR with minimal morbidity [Jin *et al.*, 2012; Cheng *et al.*, 2011; Chen *et al.*, 2013].

The concept of placing a stent within the prostatic urethra to relieve BOO secondary to BPH was introduced in the 80s. Subsequent development has led to the evolution of two broad categories of prostatic stents: permanent and temporary. Temporary metal stents are designed to sit freely within the prostatic urethra, making removal easier if required. Both permanent and temporary stents have been shown to reduce symptoms and improve urinary flow, but their use has been associated with high rates of complications, such as stent migration and encrustation. Stents also have a role in the management of bladder neck contracture or urethral stricture following radical prostatectomy or radiation therapy for PCa for patients unwilling or unable to undergo open reconstructive surgery, although their use is associated with high rates of incontinence [Breyer and McAninch, 2011; Erickson et al., 2011].

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Lately retrievable metallic prostate stents have been introduced for the management of obstruction in PCa patients. Initial experience with these stents has shown that they are easier to place and effective in patients with BOO from prostate cancer. Moreover they overcome the problem of stent migration as these stents can be easily removed under local anaesthesia [Song *et al.*, 2013].

Permanent or intermittent urethral catheterization

Patients with urinary retention should be offered the option of clean intermittent catheterization, ideally performed by patients themselves. This approach causes less urinary tract infection than an indwelling catheter and allows the patient to spend most of the day without a urethral catheter in place. Clean intermittent catheterization (CIC) can be done by clean (i.e., not sterile) technique. The decision to leave an indwelling catheter should only be taken when there is a clear indication. In advanced prostate cancer or any other cause of BOO long-term catheterization should be the last option and is usually reserved for cases of overflow incontinence after failed attempts at relieving BOO or for those patients unable or unwilling to undergo MIS or perform CIC. Long-term catheterization can become necessary in: (I) BOO, in patients who are unsuitable for surgical relief of BOO, have failed a trial without catheter and intermittent catheterization is not possible; (II) chronic retention, often as a result of neurological deficit or treatment where intermittent catheterization is not possible; (III) Debilitated, paralyzed or comatose patients in presence of skin breakdown and infected pressure ulcers; (IV) Cases where a patient insists on this form of management after discussion of the possible risks; (V) Intractable incontinence when all other measures have proven ineffective and catheterization enhances the patient's quality of life.

Practical considerations with indwelling catheters

The standard practice for either suprapubic or urethral indwelling catheters, commonly known as Foley catheters, involves monthly changes at home or at the office and requires certain precautions and personal hygiene care. The usual Foley catheter size used for bladder drainage is 16F or 18F and the retention balloon is filled with 5-10 mL of sterile water. A recent study showed that among the problems encountered with the long-term use of indwelling urethral or suprapubic catheters were in descending order: catheter leakage (bypassing of urine), urinary tract infection,

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catheter blockage, catheter-associated pain and accidental dislodgment of the catheter [Wilde *et al.*, 2013].

Incontinence episodes are caused by uninhibited bladder contractions provoked by the presence of the catheter itself and the inflated balloon. Incontinence episodes are best treated by simple measures involving deflating the balloon to just 5 mL of saline, changing or irrigating the catheter in case it is blocked, and oral or intravesical administration of anticholinergics to suppress spontaneous bladder contractions [Ersoz et al., 2010]. Increasing the balloon size to treat a urethral catheter that is leaking around the urethra is not recommended [Gibbs et al., 2007]. Pain at the urethral meatus and around the catheter entry site is more frequent in males and can be effectively controlled by the topical application of water-soluble lubricants and local anesthetics like EMLA. Certain patients with indwelling catheters have a tendency to drink less and are prone to the development of encrustations, bladder stone formation and problematic urine drainage through the catheter. In these cases the catheters can be irrigated with either plain normal saline or 30-50 mL of 0.25% acetic acid twice per day. Acetic acid due to its bacteriostatic properties supposedly minimizes catheter encrustation and reduces foul odor, although bladder irrigations with acetic acid or neomycin-polymyxin solutions showed no effect in terms of reducing urinary bacterial load and inflammation [Waites et al., 2006]. A wide variety of catheter washout policies have been suggested in order to prevent catheter blockage, however a recent review has showed that the evidence is too scant to conclude whether or not washouts are beneficial [Hagen et al., 2010].

Regarding the issue of UTIs in relation to indwelling catheters it is true that catheter-associated urinary tract infections are the most common nosocomial infections worldwide accounting for an estimated 25-40% of all nosocomial infections. Patients with indwelling catheters are at higher risk for the development of UTIs, from simple cystitis to severe life-threatening septic pyelonephritis. As with all foreign material-related infections the biofilm plays a central role in the pathogenesis of catheter-related UTIs [Al-Mohajer and Darouiche, 2013]. Catheter colonization from biofilm-producing bacteria as early as from the second week of catheterization is inevitable in all patients. Indwelling catheter patients have significant bacteriuria with Escherichia Coli (E.Coli) being the most frequently isolated uropathogen (70%), followed by Klebsiella pneumoniae and Pseudomonas aeruginosa. Diabetes is the most common predisposing factor associated with UTIs in catheterized patients [Niveditha et al., 2012].

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The complex characteristics of bacterial biofilms promote antibiotic resistance, leading to the emergence of resistant device-related infections most usually caused by Klebsiella pneumoniae or Staphylococcal biofilms, posing new challenges in their management [Singhai *et al.*, 2012]. The utilization of continuous antibiotic coverage for patients with indwelling catheters is not recommended as it might exacerbate bacterial resistance. The diagnosis of UTIs in such patients may prove difficult, given the lack of reliable diagnostic tests. On the other hand upper tract UTIs in frail and immunocompromised patients with a malignant disease require special attention as they may prove fatal.

Hematuria

Intractable hematuria can be a disastrous evolution for patients with advanced non-resectable disease involving the urinary tract. For the management of gross hematuria defining the etiology of bleeding is the most important determinant. Gross hematuria in the context of bladder cancer may have a variety of etiologies. The probable causes can be sloughing tumoral mass, radiation cystitis, cyclophosphamide-induced hemorrhagic cystitis (CIHC), and also other sources of bleeding such as the prostate.

Since there are neither available guidelines nor welldesigned studies comparing the available options, a treatment algorithm should be based on individualized scenarios and clinical experience, bringing also into account the patient's preferences.

Despite various treatment options, management of intractable hematuria in patients with inoperable bladder cancer remains a challenging task. Patients with advanced cancer and hematuria should initially be screened for coagulopathy and if clot evacuation and epsilonaminocaproic acid treatment fail to control the bleeding, intravesical treatments should be considered. Bladder irrigation with 1% to 2% alum (potassium or ammonium aluminum sulfate) or 1% silver nitrate can be effective [Goel *et al.*, 1985]. If renal insufficiency is present or bladder lesions allow a significant amount of alum to enter the vascular system, serum aluminum levels should be monitored. Patients can usually tolerate bladder instillations with these agents and so anesthesia is not usually required.

The majority of publications on alum instillation comprise the etiologic spectrum of sloughing tumoral mass, radiation cystitis, and CIHC. The reported response rate was around 80% with sparse reports of complications such as ureteral fibrosis and tuberculosis-like reactions [Braam *et al.*, 1986]. Yet, six cases of aluminum toxicity and death were reported, all harboring a component of renal insufficiency. Hence, in the cases of concomitant renal insufficiency, alum instillations should be avoided and alternative measures are to be sought. Otherwise, alum instillation seems a very effective and inexpensive method with the least morbidity.

Formalin instillations are effective in controlling hematuria with a response rate of 90% with consecutive instillations, however they have been associated with a plethora of serious complications such as reduced bladder capacity with severe LUTS, retroperitoneal fibrosis and renal failure [Ghahestani and Shakhssalim, 2009]. The presence of reflux should first be ruled out with a preoperative cystogram. Then if no reflux is present, formalin, at 1% to 4% concentration, is instilled passively until half the bladder capacity is reached, left for 20 to 30 minutes and afterwards the bladder is continuously irrigated with normal saline [Giannakopoulos et al., 1997]. The procedure is extremely painful so general or regional anesthesia is required. Overall, current recommendations are against the use of formalin if other measures are available with the following exceptions: (I) if a previous combined approach or urinary diversion has been used to evade the potential complications of formalin instillation; and (II) in cases of radiation cystitis if severe fibrosis of the bladder is already present, surgical handling of the abdomen is difficult and other measures have failed [Ghahestani and Shakhssalim, 2009].

Hemorrhagic cystitis with severe hematuria can result from intravenous administration of chemotherapeutic drugs, particularly the alkylating agents ifosfamide and cyclophosphamide. Acrolein is the main molecule responsible for this side-effect and mesna (2-mercaptoethane sulfonate) is the commonly used preventive agent. Mesna binds acrolein and prevent its direct contact with the urothelium. The standard protocol used for prevention of chemotherapyinduced HC with three doses of mesna does not completely prevent bladder damage as 67-100% of patients present with cystoscopic or microscopic alterations in bladder mucosa such as edema and hemorrhage [Lima *et al.*, 2007]. The administration of mesna in combination with dexamethasone has also been shown to result in the remission of hematuria following systemic chemotherapy [Vieira *et al.*, 2003].

Hyperbaric oxygenation has been reported to be effective in cases of radiation cystitis and CIHC. Overall, 108 patients with radiation cystitis were assigned for hyperbaric oxygenation with a response rate of 85%. The role of hyperbaric oxygenation in cases of CIHC, with or without mesna, remains controversial in spite of promising studies on animals [Hughes *et al.*, 1998], considering that this modality is expensive and needs at least 20 sessions of treatment.

Another treatment option commonly used to control bleeding and pain is external radiation. Palliative radiation therapy (RT) is an established tool in the management of symptoms caused by malignancies. RT is effective at palliating both locally advanced and metastatic cancer, including related symptoms of pain, bleeding, or obstruction. With regard to bladder cancer there is some evidence of the benefit of palliative RT for the control of urinary symptoms and hematuria. In one study, up to 59% of patients with advanced bladder cancer had resolution of hematuria and 73% had reduction in pain after treatment [Srinivasan et al., 1994]. In another study, complete palliation of locally advanced bladder cancer was seen in 43% of patients [Salminen, 1992]. Although bladder and bowel complications are not infrequent, radiation therapy is generally well tolerated.

Transarterial embolization (TAE) is a viable alternative to be considered for intractable hematuria from advanced pelvic tumors with initial response rates exceeding 80% and overall permanent control of hematuria in more than half of the cases [Liguori *et al.*, 2010; El-Assmy and Mohsen, 2007]. The approach is bilateral, the catheter should be advanced distally to the origin of the superior gluteal artery and the artery embolized with unresorbable particles. TAE is a less-invasive method with minimal complications, low cost and less anesthesia requirements [Liguori *et al.*, 2010].

Intra-arterial chemoperfusion with mitoxantrone is an alternative option for patients with intractable bladder hemorrhage with results equivalent to intraarterial embolization therapy (ET). Due to the delayed effect in CP, ET should be used in patients with life-threatening bleeding [Textor *et al.*, 2000].

Palliative cystectomy with some form of urinary diversion remains as the last resort and should only be considered in patients with good performance status if all other options have failed or are not feasible or available because it is the most invasive treatment associated with the greatest morbidity. Although, by definition, achieving a free surgical margin with a curative intent may be impossible in most of these patients, a rough ablative procedure may be inevitable. One must keep in mind that many cases previously thought to be inoperable are now suitable candidates for the potentially curative surgery after neoadjuvant chemotherapy.

At the end of the day, evidence suggests that interventional

radiology and alum instillation are suitable alternative options for patients who, after critical consideration, cannot be treated by irrigation, transurethral resection or palliative cystectomy [Abt *et al.*, 2013].

Prevention and management of bone-related events

Patients with prostate cancer are at a higher risk for the development of bone metastases emphasizing the need for tools that may assist in identifying patients who may be most in need of palliative therapeutic intervention. Despite the fact that castration-resistant prostate cancer that has spread to the bones represents an incurable disease state, the concerted efforts of a multidisciplinary team can provide meaningful treatment benefits. Awareness of risk factors for bone metastases and skeletal related events like pain and fractures may enable urologists to identify skeletal health issues before they result in potentially disabling morbidity.

The skeleton is one of the most prominent sites of prostate cancer metastasis. Among those with advanced disease 68% of prostate cancer patients will develop bone metastases [Gralow et al., 2009]. Bone metastases are characterized by increased bone turnover and altered balance between osteogenesis and osteolysis. However apart from the disease, prostate cancer treatment itself may cause a reduction in bone density resulting in osteopenia and subsequent osteoporosis. Androgen deprivation therapy for advanced prostate cancer is well known to accelerate bone loss due to enhanced catabolism leading to severe osteopenia and osteoporosis. Osteoporosis in turn increases the risk of bone pain and fractures, both associated with reduced quality of life, particularly among the elderly survivors [Tipples and Robinson, 2011]. Prostate cancer patients treated with either surgical (bilateral orchiectomy) or pharmaceutical (LHRH-antiandrogens) castration experience significant bone loss as early as one year post-treatment [Smith, 2003]. Also according to a large study on patients with prostate cancer surviving at least five years after diagnosis 19.4% of men treated with androgen deprivation therapy experienced a fracture, compared with 12.6% of men who did not receive such treatment [Shahinian et al., 2005].

Bisphosphonates

The class of compounds known as bisphosphonates have generated interest as therapeutic agents for prostate cancer cases with bone involvement since evidence exists that they

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Figure 4 Picture of an osteonecrotic jaw lesion in a patient with metastatic prostate cancer under zoledronic acid. Note the non-healing extraction (black arrow) socket of nine months' duration in the lower right mandible of the patient.

reduce the risk of fracture among postmenopausal women with osteoporosis. Bisphosphonates have also been shown to be effective in reducing bone complications in patients with osteolytic bone metastases from multiple myeloma and breast cancer. It was initially felt that prostate cancer, which usually causes osteoblastic metastases, would not be responsive to bisphosphonates because these agents primarily inhibit osteoclast function. However, subsequent research revealed that bone resorption in metastatic prostate cancer is very high, reflecting substantial osteoclastic activity. Therefore, there was biologic rationale for the use of bisphosphonates in prostate cancer to treat both the metastases and the ongoing bone loss due to androgen deprivation [Body, 2003]. Among the initial studies that had examined the effects of bisphosphonates in preventing bone loss, Smith et al. reported that a third-generation amino-bisphosphonate, zoledronic acid, used intravenously every three months in men with non-metastatic PCa under medical castration, was associated with an increase in bone mineral density at one year [Smith et al., 2003].

The presence of bone metastases in patients with advanced disease is related to long-term skeletal complications such as pain, bone loss and fractures. These patients should be considered for bisphosphonate therapy if not otherwise contraindicated. To date, the most safe and effective regimen in the class of bisphosphonates in treating such patients is zoledronic acid [Saad *et al.*, 2003]. Zoledronic acid 4 mg, or



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Figure 5 Axial CT scan showing an osteosclerotic process (green arrow) in the right part of the jaw with extensive periosteal reaction.

3 mg for patients with impaired renal function, is administered as a 15-minute i.v. infusion every 3-4 weeks, with minimal side effects such as flu-like symptoms and a small risk of hypocalcemia [Hanamura et al., 2010]. Bisphosphonate-induced osteonecrosis of the jaw (Figures 4,5) in patients treated for metastatic prostate cancer represents a recently recognized adverse effect of bisphosphonates [Bantis et al., 2011]. The benefits derived from bisphosphonates must be weighed against the risk of osteonecrosis of the jaw which however can be minimized by lowering the dose, adhering to recommendations regarding dental hygiene and avoidance of dental interventions during treatment with zoledronic acid [Kyrgidis et al., 2012]. Treatment should be reserved for patients with prostate cancer who have osteoporosis and it may be considered in patients with osteopenia and/or additional risk factors [Srinivas and Colocci, 2006].

Denosumab

Recently, the United States Food and Drug Administration (FDA) approved denosumab, a fully human monoclonal antibody, for the prevention of skeletal-related events (SREs) in patients with bone metastases from solid tumors. Denosumab is a targeted RANK-ligand inhibitor, which is a key mediator of osteoclast formation, function and survival. Denosumab use was associated with increased bone

mineral density at multiple skeletal sites in women receiving aromatase-inhibitor therapy for breast cancer. Similarly, in postmenopausal women with low bone mass, denosumab was associated with increased bone mineral density at all measured skeletal sites and with decreased levels of markers of bone turnover [Miller et al., 2008]. Denosumab is administered as a monthly subcutaneous injection for the management of skeletal related events in PCa patients. In a double-blind, multicenter study with 734 men receiving androgen-deprivation therapy for prostate cancer, a significant increase in bone mineral density was seen with denosumab at all measured skeletal sites, including the lumbar spine, hip, and radius. Also denosumab was associated with significant decreases, compared to placebo, in the cumulative incidence of new vertebral fractures at 12, 24, and 36 months [Smith et al., 2009]. Recent evidence suggests that denosumab may be superior to zoledronic acid for the prevention of skeletal-related events in patients with metastatic, castration-resistant PCa [Omlin and de Bono, 2012; Fizazi et al., 2011]. However overall, survival and progression-free survival were similarly unaffected by zoledronic acid and denosumab. In conclusion, patients with bone metastases from PCa will benefit from zoledronic acid and denosumab although evidence is insufficient to prove a greater efficacy of one agent over the other until more definite evidence is available [Iranikhah et al., 2012].

The role of nuclear medicine in the management of bone lesions

Pain associated with bone metastases is a common clinical problem that contributes to patient morbidity and reduced quality of life. Therapeutic strategies for pain palliation include analgesics (non-steroidal anti-inflammatory drugs, opiates), hormones, chemotherapy, radiotherapy, local surgery, local anesthesia and radionuclide therapy. Moderate, localized skeletal symptoms are usually controlled by conventional or opioid analgesics and singlefraction external-beam radiotherapy is reserved for cases of resilient pain [Thapa *et al.*, 2011].

This approach however becomes less useful in the context of disseminated skeletal metastases where although wide field hemi-body radiotherapy is an effective treatment option, potential benefits are often outweighed by significant bone marrow suppression and gastrointestinal toxicity. Pain palliation in these patients can be effectively achieved with the systemic administration (internal radiotherapy) of bone-seeking radiopharmaceuticals,

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since the relatively selective tumor targeting reduces the potential marrow toxicity. Palliative radionuclide therapy has been used successfully for more than 30 years. At present, radionuclides such as Strontium-89 (Sr-89) and Samarium-153 (Sm-153) are recommended for periodic use in cancer patients presenting with multiple uncontrolled painful sites of bone metastases in which the use of multiple or single fields of external beam radiation is not possible [Strigari *et al.*, 2007].

Strontium 89 is a calcium analogue, which is deposited by osteoblasts near metastatic tumor sites. Shallow penetrating low-energy beta particles are emitted, thus limiting damage to surrounding tissues. Although pain may initially increase, 80% of patients will eventually have reduction in pain with 10% showing complete relief lasting from 3 to 6 months [Robinson *et al.*, 1995].

186Re-hydroxyethylidene diphosphonate (HEDP) is a potentially useful radiopharmaceutical for metastatic prostate cancer to bone, having significant advantageous characteristics. To start with, bone marrow toxicity is limited and reversible, which makes repetitive treatment safe. Studies have shown encouraging results for palliative therapy using 186Re-HEDP, with an overall response rate of 70% in painful bone metastases (*Figures 6*, 7). It is also effective for the palliation of painful bone metastases from various tumors and the good results tend to last longer if patients are treated early in the course of their disease [Kolesnikov-Gauthier *et al.*, 2000].

This radioisotope however is not equally efficient and therefore not indicated for urgent conditions, such as spinal cord compression, since several weeks of treatment are required for treatment benefit to become apparent. Sufficient bone marrow reserves must be present before treatment in order to minimize the risk of bone marrow suppression. Other possible side effects of treatment include anemia, pancytopenia, and pneumonitis. Samarium Sm-153 lexidronam is a similar radiopharmaceutical that has been shown to be effective in treating bone pain from metastatic prostate cancer [Sartor *et al.*, 2004].

Paraneoplastic syndromes (PNSs) in urological malignancies

Introduction and incidence

PNSs are defined as a plethora of symptoms and clinical signs occurring in cancer patients and involving systemic effects taking place remotely from the tumor. These



Figure 6 Whole body scintigraphy of a patient with prostate cancer. The intense 99mTc-labeled HEDP uptake in the region of both knees (orange arrows-especially on the right) indicates bony metastases.

symptoms are not related either to its local repercussion or distant spread and are not caused by infection, nutritional deficiency or treatment [Sacco *et al.*, 2009]. Recognition of a PNS is clinically important as it can lead to the diagnosis of a previously undetected neoplasm or more often can be used as a surrogate "tumor marker" of disease progression or remission as it follows the clinical course of the causative malignancy. The most prominent PNSs associated with urological malignancies and especially renal cancer will be discussed in more detail.



Part III

Figure 7 Whole body scintigraphy of the same patient with 99mTc-labeled HEDP two weeks after 186Re administration for bone pain palliation. The images show slight improvement in the area of knees.

Paraneoplastic hypercalcemia

Hypercalcemia of malignancy (HM) is the most common endocrine PNS and accounts for approximately 30% of all hypercalcemia cases. Parathormone-releasing peptide (PTHrP) production leading to HM is a well-described paraneoplastic phenomenon which may be seen in as many as 20% of patients with cancer, usually small cell carcinomas of breast, lung, and genitourinary tract [Trias *et al.*, 2001].

HM is the most common PNS among patients with

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renal cell carcinoma (RCC). Of those with hypercalcemia and RCC, approximately 75% have high-stage lesions and 50% harbor bone metastasis, although neither the presence nor the degree of hypercalcemia have been shown to significantly correlate with tumor grade or survival [Chasan *et al.*, 1989; Ding *et al.*, 2012b].

The clinical picture of HM can be very polymorphic with some patients showing nonspecific symptoms such as asthenia, headache, lack of appetite, nausea, vomiting, constipation, somnolence, polyuria-polydipsia (due to nephrogenic diabetes insipidus), and others exhibiting a more severe and specific clinical presentation such as acute confusional or lethargic state or even coma associated with very high serum calcium (Ca⁺⁺>12 mg/dL). When calcemia exceeds 18 mg/dL, shock and death occur [Sacco *et al.*, 2009]. The usual laboratory pattern is that of an elevated total and ionized calcium in the absence of other causes (bone metastases), low PTH values (PTH may be over the lowest value of the reference interval), and high levels of phosphates. Measurement of PTHrP can be helpful in the diagnosis of an otherwise unexplained hypercalcemia.

HM cases do not usually require pharmacologic treatment since physiological homeostatic mechanisms and volume repletion either orally or i.v. can usually maintain calcium levels under safety limits. If necessary, drugs which inhibit osteoclasts and interrupt the vicious cycle of bone resorption (bisphosphonates, denosumab) or favor calcium fixation in the bone (calcitonin) can be employed. The addition of corticosteroids or diuretics to hydration and i.v. bisphosphonates has not been established, although some patients will require diuresis if they develop clinical volume overload [Turner *et al.*, 2007].

In refractory cases, calcitonin, EDTA (ethylenediaminetetraacetic acid) or plicamycin (mithramycin), an agent that decreases serum calcium concentrations by inhibiting RNA synthesis in osteoclasts, may be employed although the use of these agents is limited by difficulties in administration and side-effects (e.g., several daily s.c. injections for calcitonin and prolonged myelosuppression from mithramycin) [Turner *et al.*, 2007]. For the extreme case of very high levels of calcemia the use of hemodialysis may become necessary.

Paraneoplastic leukocytosis

Paraneoplastic leukocytosis is common in cancers and has been described for RCC and urothelial carcinomas of the bladder and pelvis [Turalic *et al.*, 2006; Lin *et al.*, 2007]. It has been attributed to tumor production of granulocyte colony-stimulating factor (G-CSF) which in turn promotes the development of mature neutrophils from hematopoietic progenitor cells [Sacco *et al.*, 2009]. The diagnostic evidence includes marked leukocytosis with predominant mature neutrophils, elevated serum G-CSF, positive immunohistochemical staining of tumor cells with anti-G-CSF antibody, leukocytosis and elevated serum G-CSF that reverses following tumor excision.

Constitutional symptoms

Constitutional symptoms are usually, but not exclusively, associated with the presence of RCC since it is estimated that 10-40% of patients with RCC will develop a PNS [Sacco et al., 2009]. Most PNS associated with localized or at least surgically resectable RCC are definitively treated with nephrectomy. Pyrexia, anemia, weight loss, and fatigue can be the first symptoms of RCC in up to one third of cases. Unexplained fever is found in 20-30% of RCC and is the sole presenting complaint in approximately 2% of patients. These and other constitutional symptoms in advanced RCC are thought to be mediated by cytokines such as TNF- β , IL-6, IL-1, interferons and prostaglandins. Anemia can occur for various reasons and is observed in about 20% of RCC patients. Poor nutritional status and the presence of a chronic disease are two main reasons for the anemia that, however, has been also related to tumor production of Interleukin-6 (IL-6) and iron-binding proteins, such as ferritin and lactoferrin [Loughlin et al., 1987; Nieken, 1995]. It is important to clinically evaluate the patient for signs of microscopic or macroscopic haematuria or alternative sites of bleeding, as well as potential iron, vitamin B12 or folate deficiency, before attributing their anemia to PNSs. The management of anaemia with administration of erythropoietin (EPO) results in an increase of 1-2 g/dL in haemoglobin over a 6-12 weeks' course. For patients in need for more rapid increase in haemoglobin treating physicians should consider red-cell transfusion [Turner et al., 2007].

One of the commonest PNSs associated with RCC is cancer *anorexia-cachexia syndrome (CACS)*, which can manifest as anorexia or dysgeusia (altered sensation of taste and foul-smelling breath), malaise, night sweats, involuntary weight loss and poor performance. In a recent study cachexia as well as polycythemia and hypercalcemia have been correlated to vascular endothelial growth factor (VEGF) expression [Ding *et al.*, 2013]. CACS should be

suspected if a patient has involuntary weight loss of more than 5% of pre-illness weight over a 2- to 6-month period. A recent study showed that among patients with at least one PNS, cachexia, the occurrence of a varicocele and pyrexia were related to advanced RCC stage [Ding *et al.*, 2013]. The etiology and management of cancer-related cachexia are discussed in more detail in another chapter of this book.

Once non-neoplastic causes of constitutional symptoms in patients with RCC have been ruled out, nephrectomy is the most effective treatment. Palliative treatment regimens consist of either a low-dose corticosteroid (hydrocortisone, 20 mg twice a day), or progesterone, 800 mg/d, however responses are usually transient. If symptoms persist after nephrectomy, metastatic disease is usually present and prognosis is dismal [Ok *et al.*, 2005].

Polycythemia and abnormal EPO production

Paraneoplastic polycythemia by cancerous overproduction of EPO is generally rare, but not infrequently seen in patients with renal cell carcinoma (RCC) where it involves 1-8% of patients [Sacco *et al.*, 2009]. Elevated red blood cell concentrations are thought to be mediated by EPO, a glycoprotein produced by peritubular renal interstitial cells that promote red blood cell production in the bone marrow. The majority of clear cell RCC displays a strong activation of the Hypoxia-inducible Factor (HIF), the transcription factor regulating EPO. The frequency of EPO gene expression in RCC is therefore much higher than the prevalence of clinical polycythemia [Wiesener *et al.*, 2007].

Excessive EPO production occurs in the tumor cells themselves, although perineoplastic cells may also contribute, secondary to local tumor compression and resultant tissue hypoxia [Nielsen *et al.*, 1988]. In cases of localized disease, EPO levels normalize following nephrectomy, whereas they remain elevated or rise again in those with metastatic disease or late tumor recurrence [Murphy *et al.*, 1970].

Stauffer's syndrome

Non-metastatic hepatic dysfunction in patients suffering from renal cell carcinoma, known as Stauffer's syndrome, is seen in 3-20% of RCC patients. The syndrome is characterized by generalized hepatitis with lymphocytic infiltration, hepatocellular degeneration and elevations in liver enzymes in the absence of hepatic metastasis and jaundice, although cases of reversible cholestatic jaundice without evidence of hepatic disease have also been reported. [Morla *et al.*, 2006; Tomadoni *et al.*, 2010].

The pathogenesis is unclear. Some believe that the renal tumor secretes hepatotoxins or lysosomal enzymes that stimulate hepatic cathepsins or phosphatases, which leads to hepatocellular injury; others suggest that tumor-secreted hepatotoxins lead to hepatocyte injury with subsequent activation of the immune system. The aberrant tumor production of interleukin-6, known to stimulate hepatic protein production, may also play a role [Sacco *et al.*, 2009]. Clinically, patients may present with hepatosplenomegaly, fever, and weight loss. Stauffer's syndrome may precede other manifestations of RCC and is characterized by elevated alkaline phosphatase, transaminases, erythrocyte sedimentation rate, gamma-glutamyl transferase and prothrombin time [Tomadoni *et al.*, 2010].

Summary

In the face of advanced and non-curable disease physicians and patients should have an honest conversation about personal goals, life priorities, and available resources for palliation of symptoms. Palliative care should be a standard part of every urologist's practice as urologists are dealing with a variety of malignancies with limited options for cure like in advanced renal cancer or long survival time after potentially curative interventions like in prostate cancer. There is a clear need to control a variety of symptoms related to either therapy or the disease itself in order to optimize the quality of life for these patients. Newer technologies and targeted drugs specifically at molecules that mediate adverse effects of cancer will probably provide a series of future opportunities to improve patients' wellbeing, even in the absence of cure. The physician's role in the absence of hope for cure is to also encourage the patient to transform the goal of living longer to improving the quality of remaining life.

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Introduction

Cough is among the most common complaints for which patients seek medical attention. Although cough is a protective mechanism, chronic and uncontrollable cough is among the most debilitating symptoms found in palliative care patients. Chronic cough has a substantial adverse impact on quality of life [French et al., 1998; Kuzniar et al., 2007]. A distinction exists between cough and the closely related defense expiratory reflex, which does not result in a cough [Widdicombe, 2006]. A cough sound allows the clinician to distinguish cough from other symptoms, such as throat-clearing and sneezing; cough usually presents with a series of coughs known as a cough bout. In some patients there may be relatively long periods (5-30 minutes) of continued constant cough bouts before there is any significant dry cough-free period (sometimes referred to as a "coughing fit"). During these periods, patients are generally unable to eat, drink, concentrate, or effectively communicate. Cough is recognized as a defense reflex mechanism, since it clears the larynx, trachea, and large bronchi of secretions such as mucus, noxious substances, foreign particles, and infectious organisms. The first Editorial of COUGH in 2008 marked the blossoming of research and educational efforts in the field of cough. Furthermore, 2005 also marked the start of an annual international conference devoted to cough.

Cough can be divided into acute self-limiting cough, lasting (by definition) less than 3 weeks, or chronic persistent cough, which usually lasts for more than 8 weeks. Some types of cough can last for an intermediate period of 3-8 weeks, which may be referred to as subacute cough. Acute cough is usually the result of an upper respiratory-tract viral infection that clears within 2 weeks in two-thirds of people [Chung and Pavord, 2008]; however, a post-infectious cough may linger for 6-8 weeks in many patients.

Epidemiology of cough

The epidemiology of cough is uncertain due in part to the fact that despite its debilitating feature many people do not seek medical attention for this symptom. The prevalence of cough in many communities in Europe and the USA reported through questionnaire surveys is 9-33% of the population, including young children [Lundback *et al.*, 1991; Cullinan *et al.*, 1993; Ludviksdottir *et al.*, 1996; Cerveri *et al.*, 2003; Carter *et al.*, 2006; Ford *et al.*, 2006]. However, in patients with lung cancer, the prevalence of cough is significantly higher. Seven large studies involving over 9,000 patients with lung cancer have reported that the prevalence of cough at diagnosis ranges from 24.9% to 84% [Hopwood and Stephens, 1995; Martins and Pereira, 1999; Hernandez *et al.*, 2006; Lovgren *et al.*, 2008].

Fujimura sent a screening survey to 29,085 randomly selected individuals and a more detailed survey to the first 1,000 individuals with cough who agreed to participate and provided consent [Fujimura, 2012]. The prevalence of cough among the general population was 10.2%. There was no difference in cough frequency between males and females or across age groups. The prevalence of prolonged or chronic cough (cough lasting \geq 3 weeks) was 35.8% and the duration of cough increased with age. Women were more troubled by cough than men were. "Feeling ashamed to cough in front of other people" (49.0%) and "causing trouble to other people" (42.8%) were the main reasons for feeling troubled by cough. More than 60% of surveyed individuals were not receiving care and 44.0% had no plans to visit a medical facility [Fujimura, 2012].

Desalu and colleagues conducted a cross sectional study among subjects aged >18 years from May 2009 to October 2009 in Ilorin, Nigeria [Desalu *et al.*, 2011]. The prevalence of acute cough was 3.8%, subacute 1.7% and chronic cough was 1.1%. Majority of subjects with acute cough [16 (88.9%)], subacute cough [8 (100%)] and

chronic cough [3 (60%)], were yet to consult a doctor [Desalu *et al.*, 2011].

Bende and Millqvist set out to determine the prevalence of chronic cough in relation to upper airway symptoms, in a cross-sectional, population-based epidemiological study [Bende and Millqvist, 2012]. In total, 1,387 volunteers (73% of the sample) were investigated. The overall prevalence of self-reported chronic cough was 6.3% [95% confidence interval (CI): 5.0-7.6%]. Female gender, age, height, BMI, and smoking were significantly related to cough. Furthermore, nasal blockage, nasal secretion, sneezing, asthma, odor and cold air sensitivity, and aspirin intolerance also related to cough with statistical significance, indicating a close connection between chronic cough and upper airway symptoms [Bende and Millqvist, 2012].

Cough pathophysiology

The cough reflex arc is constituted by:

- (I) Afferent pathway: sensory nerve fibers (branches of the vagus nerve) located in the ciliated epithelium of the upper airways (pulmonary, auricular, pharyngeal, superior laryngeal, gastric) and cardiac and esophageal branches from the diaphragm. The afferent impulses go to the medulla diffusely;
- (II) Central pathway (cough center): a central coordinating region for coughing is located in the upper brain stem and pons;
- (III) Efferent pathway: impulses from the cough center travel via the vagus, phrenic, and spinal motor nerves to diaphragm, abdominal wall and muscles. The nucleus retroambigualis, by phrenic and other spinal motor nerves, sends impulses to the inspiratory and expiratory muscles; and the nucleus ambiguus, by the laryngeal branches of the vagus nerve [Polverino *et al.*, 2012].

At least three broad classes of airway afferent nerves are included in the cough reflex are:

- (I) Rapidly Adapting Receptors (RAR);
- (II) Slowly Adapting Stretch Receptors (SARs);
- (III) C-Fibers.

The mechanical events of a cough can be divided into three phases [McCool, 2006]:

- (I) Inspiratory phase: inhalation, which generates the volume necessary for an effective cough;
- (II) Compression phase: closure of the larynx combined with contraction of muscles of chest wall, diaphragm, and abdominal wall (e.g., forced expiratory effort

against a closed glottis) resulting in a rapid rise in intrathoracic pressure;

(III) Expiratory or expulsive phase: the glottis opens, resulting in high expiratory airflow and the coughing sound. Large airway compression occurs. The high flows dislodge mucus from the airways and allow removal from the tracheobronchial tree.

These three phases are the basis for one of the two possible definitions of cough recommended by a European Respiratory Society (ERS) Task Force [Morice *et al.*, 2007a]. The other definition of cough is "a forced expiratory maneuver, usually against a closed glottis and associated with a characteristic sound".

During vigorous coughing, intrathoracic pressures may reach 300 mmHg and expiratory velocities approach 800 kilometers per hour [Ford et al., 2007]. While these pressures and velocities are responsible for the beneficial effects of cough on mucus clearance, they are also responsible for many of the complications of cough, including exhaustion, cough-induced syncope, cough-induced pneumothorax/ pneumomediastinum/pneumopericardium (with subcutaneous emphysema), insomnia, headache, dizziness, musculoskeletal pain, hoarseness, excessive sweating, urinary incontinence [Irwin et al., 2006]. Cough-induced rib fractures are another painful and potentially serious complication of chronic cough. Fractures often involve multiple ribs, particularly ribs five through seven [Polverino et al., 2012]. Additionally, cough may lead to severe pain exacerbation of painful osseous bone metastases, or patients with herniated nucleus pulposus and symptoms of acute cervical, thoracic, or lumbosacral radiculopathy.

Vagal innervation of the airways

Airway afferent nerve fibers originate in the nodose and jugular ganglia and are carried via the vagus nerve, where they terminate both in and under the airway epithelium [Grace *et al.*, 2012]. Airway afferents are stimulated by irritants or inflammatory mediators (often via activation of G-protein-coupled receptors, e.g., bradykinin B2 and prostanoid EP3 receptors) and subsequently open ion channels, (e.g., TRPA1 or TRPV1). Information is then carried along the vagus nerve to the solitary tract nucleus (NTS), located in the medulla. Here, the nerves synapse, and second-order neurons relay the message to a respiratory pattern generator within the CNS, activating efferent motor neurons and leading to cough [Grace *et al.*, 2012].

This suggests that supramedullary pathways are important in the conscious regulation of cough. Similar to pain, descending inhibitory pathways may be able to modulate the cough reflex [Sessle *et al.*, 1981].

The role of transient receptor potential (TRP) channels in cough

Several members of the TRP super family of ion channels are expressed on sensory neurons [Nasra and Belvisi, 2009]. Recently, ion channels of the TRP class, TRPA1 and TRPV1, have been implicated in the afferent sensory loop of the cough reflex and in the heightened cough sensitivity seen in disease [Lalloo *et al.*, 1995; Groneberg *et al.*, 2004; Andre *et al.*, 2009; Birrell *et al.*, 2009]. Preclinical models have established that TRPV1 antagonists are effective in inhibiting capsaicin and citric acid-induced cough in guinea pigs [Lalloo *et al.*, 1995; Trevisani *et al.*, 2004]. A role for the TRPA1 receptor as a tussive mediator was only recently confirmed in humans and guinea pigs [Andre *et al.*, 2009; Birrell *et al.*, 2009], and no TRPA1 inhibitors have yet progressed to clinical trials.

Canning and Mori utilized a microinjection strategy to precisely localize microinjection of glutamate receptor antagonists that nearly abolished cough evoked from the trachea and larynx in anesthetized guinea pigs while having no effect on basal respiratory rate and little or no effect on reflexes attributed to activating other afferent nerve subtypes [Canning and Mori, 2010]. Comparable microinjections in adjacent brainstem locations (0.5-2 mm distal) were without effect on coughing. Subsequent transganglionic and dual tracing studies confirmed that the central terminations of the cough receptors and their primary relay neurons are found bilaterally within nucleus tractus solitarius (nTS), lateral to the commissural subnucleus and perhaps in the medial subnuclei. These synapses possess the physiological characteristics of a cough gate [Canning and Mori, 2010].

G protein-couples inwardly rectifying K^* (GIRK) channels in cough

Antitussive agents are an extremely heterogenous group that posses many actions, however, Takahama and colleagues proposed that centrally acting antitussives may all act by inhibiting GIRK Channels coupled to the 5-HT_{1A} receptor [Ishibashi *et al.*, 2000; Takahama, 2012].

Potential mechanisms in cough sensitization

Airway inflammation and direct neuronal damage can

sensitize cough nerve terminals in the airway mucosa with resultant hypersensitization of excitatory fibers [Undem *et al.*, 2002]. Javorkova *et al.* [Javorkova *et al.*, 2006] found that patients who had received lung irradiation had heightened cough reflex sensitivities, perhaps due to peripheral C-fiber damage which may cause loss of inhibitory cough fibers rather than sensitization of excitatory fibers leading to cough. Heightened cough reflex sensitivity could be a reflection of either of these processes.

There are three broad mechanisms by which sensitization of the afferent pathways involved in cough may occur and which therefore may be relevant to the treatment of cough [Young and Smith, 2011].

- (I) Peripheral sensitization;
- (II) Central sensitization;
- (III) Impaired inhibition.

Peripherally acting antitussive agents

Leukotriene receptor antagonists

There is some evidence that the anti-inflammatory leukotriene receptor antagonists, montelukast and zafirlukast may reduce cough in patients with cough-variant asthma.

In a blinded cross-over study, patients with cough-variant asthma reported an improvement in cough symptoms whilst taking zafirlukast, with an associated reduction in cough reflex sensitivity [Dicpinigaitis *et al.*, 2002]. Additionally, an open-label study suggested montelukast, improved subjectively rated cough symptoms in cough-variant asthma [Kawai *et al.*, 2008; Young and Smith, 2011].

Lidocaine is a non-selective voltage-gated sodium channel blocker, widely used as a local anesthetic. Nebulized lidocaine is licensed for the treatment of cough in palliative care in the UK but not in the US and routinely applied topically to reduce coughing during fiber-optic bronchoscopy.

TRPM8 agonists

Menthol has long been used in the treatment of cough (lozenges and inhalations) and was subsequently found to activate TRPM8, a ligand-gated ion channel present on sensory afferent fibers encoding a wide-range of cold stimuli [McKemy, 2005]. There have been no studies of the use of inhaled menthol in pathological cough, but compared to placebo, menthol inhibited citric acid induced cough in healthy subjects [Morice *et al.*, 1994; Young and Smith, 2011].

Neurokinin (NK) receptor antagonists

Although NK receptor antagonists revealed a reduction in

cough response in preclinical studies [Girard *et al.*, 1995; Daoui *et al.*, 1998], in humans they failed to show any effects on cough in male asthmatic patients (NK1 antagonism) [Fahy *et al.*, 2005] or cough reflex sensitivity in healthy volunteers (NK3 antagonism) [Young and Smith, 2011].

Pre-synaptic mechanisms: inhibition of glutamate release

Gabapentin and Pregabalin are antiepileptic drugs which bind to and inhibit the pre-synaptic $\alpha 2\delta$ subunit of voltage gated calcium channels, subsequently inhibiting the release of glutamate into the central synapse [Taylor, 2009].

Baclofen binds to the pre-synaptic GABA B receptor, a G protein coupled receptor that activates various intra-cellular pathways leading to the inhibition of voltage-gated calcium channels. In animals, the antitussive effect of baclofen is reversed by intra-cerebroventricular administration of a selective GABA B antagonist, suggesting a central mode of action [Bolser *et al.*, 1994]. A placebo controlled cross-over study of just 2 patients with intractable cough demonstrated improvements with baclofen accompanied by a reduction in cough reflex sensitivity to capsaicin [Dicpinigaitis and Rauf, 1998; Young and Smith, 2011].

Post-synaptic mechanisms: the NMDA receptor

Critical to the initiation and maintenance of central sensitization is an upregulation of the N-methyl-D-aspartate receptor [Woolf and Thompson, 1991], located on the postsynaptic cell and activated by the excitatory neurotransmitter glutamate. Dextromethorphan, a component of many overthe-counter cough medications, is a low-affinity NMDA receptor antagonist [Dicpinigaitis, 2009], shown to reduce objective cough frequency in a series of studies in adults with colds, although the effect was small (13% reduction in cough frequency) [Pavesi et al., 2001]. Few studies have investigated dextromethorphan in chronic coughing, but in one study of patients with chronic bronchitis, 60 mg dextromethorphan significantly reduced objective cough frequency compared to placebo [Aylward et al., 1984], but 30 mg seem to be ineffective [Ruhle et al., 1984]. Additionally, ketamine, another NMDA-receptor antagonist, has been shown to suppress the coughing associated with fentanyl use at induction of anesthesia [Yeh et al., 2007].

Dextromethorphan inhibits cough when microinjected centrally into the nTS in animal models [Canning, 2009]. However, dextromethorphan is also a sigma-1 receptor agonist; this non-opioid receptor is found in high concentrations in the nTS [Alonso *et al.*, 2000] and may account for antitussive activity [Brown *et al.*, 2009; Young and Smith, 2011].

Etiologies potentially contributing to cough

Published guidelines on the management of chronic cough [Morice *et al.*, 2006; Pratter *et al.*, 2006] recommend the investigation and systematic treatment of a triad of underlying triggers—asthma, gastro-esophageal reflux disease (GERD) and post-nasal drip syndrome (PNDS); since these three comprise the majority of etiologies for chronic cough.

Laryngeal sensory neuropathy has been identified as the cause of chronic cough in 18 of 26 patients with acute onset of cough that was often associated with laryngospasm or throat clearing [Lee and Woo, 2005]. Other etiologies of cough may include: irritation of the external auditory meatus, chronic infections (e.g., bronchiectasis, tuberculosis, HIV associated disease, cystic fibrosis), endobronchial statues, aortic aneurysm, and pulmonary embolus.

Lesions that compress the upper airway, including arteriovenous malformations and retrotracheal masses, may present with chronic cough [Park *et al.*, 1998; McLaughlin *et al.*, 1999]. Cough can also be a symptom of tracheobronchomalacia, which results from loss of rigid support of the large airways and inspiratory collapse, and is usually seen in conjunction with obstructive lung disease in patients with a history of cigarette smoking [Waldron 1990]. Community studies have shown that active smoking is associated with a 2-fold to 3-fold increase and passive smoking with a 13-fold to 16-fold increase in the prevalence of cough and other respiratory symptoms [Janson *et al.*, 2001; Larsson *et al.*, 2003].

Infiltrating airway wall cancer, laryngopharygeal reflux, chronic bronchitis, eosinophilic bronchitis, infection (e.g., whooping cough)/post-infectious cough, granulomas (e.g., sarcoidosis or tuberculosis), compression of the airways from extrinsic masses, interstitial lung disease, pneumonia/ aspiration pneumonia, lung abscess, foreign body aspiration, allergic rhinitis, and congestive heart failure may be associated with cough [Margarino *et al.*, 1998; Scotti *et al.*, 1988].

In up to 25% of cases, the cause of cough remains unclear after extensive investigations [Birring *et al.*, 2007]. Sleep disruption is common in patients with cough and is often the reason why they seek medical attention. Sleep suppresses cough and the biological mechanisms for this action are poorly understood. Cough has been reported as a presenting symptom of obstructive sleep apnea [Birring *et al.*,

2007]. It is uncommon for healthy people to cough at night; however, approximately 50% of patients with chronic cough report sleep disruption due to cough. Cough frequency is much lower at night than during the day. There is reduced exposure to tussive stimuli at night and decreased cough reflex sensitivity. Cough is more difficult to induce in REM sleep compared to slow-wave sleep [Lee and Birring, 2010]. In addition to obstructive sleep apnea, tonsillar enlargement and environmental fungi have also recently been described as causes of chronic cough [Birring, 2011]. Patients with an idiopathic chronic cough are predominantly female, have an onset of cough around the menopause and have a high prevalence of organ specific autoimmune disease, particularly hypothyroidism. The presence of bronchoalveolar lymphocytosis suggests there is homing of inflammatory cells from primary sites of autoimmune inflammation to the lungs. A heightened cough reflex is a key feature of most patients with chronic cough and has led some investigators to suggest that chronic cough be recognized as a unique entity called Cough Hypersensitivity Syndrome (CHS) [Birring, 2011], which would be associated with a hypersensitive cough response to tussive stimuli such as capsaicin or citric acid [Chung, 2011].

Drug-induced cough

There are mane medications that may promote a distressing cough that generally sibsides after the medication is discontinued. Of interest is that although opioids may be utilized to treat chronic cough, certain opioids (e.g., fentanyl, sufentanil, remifentanil) when administered rapidly intravenously may lead to acute cough. Administering the opioid in a slow gradual step-wise manner [Kim *et al.*, 2012] or by giving a small priming dose [Gu *et al.*, 2012] may reduce this phenomenon. Additionally, pretreatment with pentazocine [Ai *et al.*, 2010], clonidine [Horng *et al.*, 2007], midazolam [Agarwal *et al.*, 2003], dexmedetomidine [He *et al.*, 2012; Sun and Huang, 2012], ketamine [Sato *et al.*, 1998], dextro methorphan [Mukherjee *et al.*, 2011], or the combination of midazolam and dexmedetomidine [Yu *et al.*, 2012] may reduce opioid-induced cough.

Angiotensin converting enzyme (ACE) inhibitors

Angiotensin converting enzyme inhibitors cause dry nocturnal cough in about 2-33% [Chung and Pavord, 2008] of people. There is a poor dose response relationship and it normally occurs within the first week of treatment—but onset can sometimes be delayed for up to six months. In addition, although most cases subside after four weeks, a significant proportion of cases can take up to three months to resolve after stopping the drug [Dicpinigaitis, 2006].

Wyskida and colleagues performed a prospective observational study involving 10,380 patients treated with ramipril for a period of no longer than 8 weeks, consisting of 3 visits: baseline, first follow-up (after 4-8 weeks) and second follow-up visit (after 4-8 weeks of cessation of ramipril, conducted only for evaluating coughing patients) [Wyskida *et al.*, 2012]. The incidence of ramipril-related cough was 7.1%. They concluded that female sex, cigarette smoking, COPD, asthma, and previous history of tuberculosis increase the risk of ramipril-related cough. Furthermore, the later the cough occurs during treatment, the less often the drug is the causative agent and the cough and also less likely to disappear after discontinuation of ramipril [Wyskida *et al.*, 2012].

Angiotensin 2 receptor (A2R) blockers

Angiotensin 2 receptor blockers are commonly used as a first substitute when ACE inhibitor cough appears, though they have a similar side effect profile to ACE inhibitors. However, cough can still occur with A2R blockers but is typically three to four times less common [Matchar *et al.*, 2008; Yusuf *et al.*, 2008].

β-blockers

Cough may be the initial manifestation of drug-related airway hyperresponsiveness or bronchoconstriction that is described with β -blockers; associated wheeze and dyspnoea may occur. β -blockers (including eye drops) cause bronchoconstriction via bronchial β 2 receptor blockade [Medford, 2012].

Non-steroidal anti-inflammatory drugs (NSAIDs)

Aspirin and NSAIDs cause bronchoconstriction in 5% of people with asthma by generating cysteinyl leukotriene and inhibiting cyclooxygenase-1 (COX-1). Symptoms may occur within 30 minutes to 3 hours of ingestion and be associated with facial flushing and nasal and upper airway symptoms [Medford *et al.*, 2012].

Calcium antagonists

Calcium antagonists relax the lower oesophageal sphincter

pressure and in dose-dependent fashion impair oesophageal clearance and cause reflux cough (amongst other symptoms). In studies of reflux-related symptoms, verapamil and amlodipine were reported as causing more reflux symptoms than diltiazem [Hughes *et al.*, 2007]. Reflux cough may also be aggravated by other drugs including nitrates via similar effects on lower oesophageal sphincter pressure [Medord, 2012].

Among other medications reported to potentially lead to cough are proton-pump inhibitors (e.g., omeprazole, pantoprazole) [Howaizi and Delafosse, 2003; Reiche *et al.*, 2010] and topiramate [Maggioni *et al.*, 2010; Tosun *et al.*, 2012]. Patients with chronic cough being treated with statin therapy should discontinue their statin. Psaila and colleagues described the second case in the literature of lone cough associated with statin therapy necessitating treatment discontinuation followed by complete resolution of symptoms [Psaila *et al.*, 2012].

Cough assessment

Cough VAS are 100 mm linear scales on which patients indicate the severity of cough. Cough VAS is also highly responsive when used as an outcome measure in clinical studies of patients with a chronic cough [Brightling et al., 2000; Birring et al., 2003; Birring et al., 2004]. There are three recently developed self-completed cough specific quality-of-life questionnaires that can be used to facilitate communication with patients and establish information on the range of problems affecting them [French et al., 2002; Birring et al., 2003; Baiardini et al., 2005]. The Leicester Cough Questionnaire (LCQ) and the Cough Specific Quality of Life Questionnaire (CQLQ) are well validated, repeatable and have good responsiveness [Birring et al., 2003]. The LCQ developed in the United Kingdom is brief, easy to administer and comprises 19 items divided into three domains: physical, psychological and social (with a sevenpoint Likert response scale). The minimal important clinical difference (MICD) for the LCQ is 1.3 [Raj et al., 2009]. The LCQ can be downloaded from the following link: (http:// thorax.bmjjournals.com/cgi/content/full/58/4/339). The CQLQ is a 28-item questionnaire that has been developed and tested in North America [French et al., 2002]. The items are divided into six domains: physical complaints, extreme physical complaints, psychosocial issues, emotional wellbeing, personal safety fears and functional abilities.

The CQLQ has 28 items in six domains [French *et al.*, 2002]. Responsiveness to treatment has been shown in a group of patients with cough that was successfully treated

and the LCQ score has been shown to correlate with cough visual analogue scores [Birring *et al.*, 2003], and the cough frequency assessed by a sound-based cough monitor (cough counts) [Birring *et al.*, 2006; Pavord and Chung, 2008].

Lee and colleagues conducted a study to determine whether short duration recordings accurately reflect 24-hour cough frequency and to investigate their responsiveness [Lee *et al.*, 2012]. 4-hour cough frequency was responsive to improvements in cough severity following trials of therapy. 4-hour cough frequency correlates highly with 24-hour cough frequency recordings and relates equally well with subjective measures in chronic cough [Lee *et al.*, 2012].

A Cochrane Systematic review; "Interventions for Cough in Cancer" [Molassiotis *et al.*, 2010a] and "Clinical Expert Guidelines for the Management of Cough in Lung Cancer" [Molassiotis *et al.*, 2010b] both published in 2010, as well as a review by Wee and colleagues [Wee *et al.*, 2012] (published 2 years later) reveal that the evidence base for the use of antitussive therapy in patients with lung cancer is extremely poor due in partly to a lack of validated cough assessment tools being utilized and heterogenous patient groups [Harle *et al.*, 2012].

Palliation of cough

The palliation of cough depends on the suspected pathophysiologic mechanisms/etologies largely contributing to a specific individual patient's cough. Therapies should be tailored to target the major pathways/processes playing a role in promoting a specific patient's cough.

If PNDS-induced cough is suspected, antihistamine/ decongestant combination should be started. If there is suspicion that a patient has PNDS as a result of chronic sinusitis, there may be a role for antibiotics in addition to antihistamine/decongestant therapy. Incomplete cough resolution after an adequate trial of PNDS therapy should not be discounted because chronic cough often results from multiple conditions simultaneously [Irwin *et al.*, 1998; Irwin and Madison, 2000]. Rather, a second empirical trial can be added to the partially effective one [Peck and Mintz, 2006].

Macedo and colleagues examined the effect of specific topical treatment of rhinosinusitis on cough in patients presenting with a chronic cough associated with a postnasal drip or 'nasal catarrh' [Macedo *et al.*, 2009]. In an open study, they were treated with fluticasone nasules (400 mcg once daily), ipratropium bromide (42 mcg three times daily) and azelastine nasal spray (140 mcg twice daily) for 28 days, after which they were re-assessed. Eighteen out of 21 patients completed the study. All patients reported having the presence

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of mucus in the throat. Mean cough score improved posttreatment (P<0.05), but there was no significant change in capsaicin cough sensitivity or nasal catarrh questionnaire score. The above treatment targeted towards rhinosinusitis accompanying PND syndrome and chronic cough led to an improvement in cough [Macedo *et al.*, 2009].

Some patients with asthma might have a bronchodilatorresponsive, corticosteroid-resistant cough, but this pattern of treatment response has not been clearly documented. The clinical condition of eosinophilic bronchitis is characterized by a troublesome cough without other symptoms of asthma or bronchial hyper-responsiveness. Test results suggesting the presence of eosinophilic airway inflammation, such as a raised induced sputum eosinophil count [Carney et al., 1997; Brightling and Pavord, 2000; Brightling et al., 2000] or increased exhaled nitric oxide concentration [Chatkin et al., 1999], are associated with the success of corticosteroid therapy; they are helpful in distinguishing between cough due to eosinophilic airway disease and non-eosinophilic cough. In the absence of these tests, proposed guidelines recommend a carefully controlled 2-week trial of oral prednisolone 30 mg daily [Pavord and Chung, 2008].

Tiotropium has been shown to inhibit cough reflex sensitivity to capsaicin in patients with acute viral upper respiratory tract infection [Dicpinigaitis *et al.*, 2008]. Although bronchodilation by tiotropium may reduce the number of cough events as well, the authors concluded that the antitussive effect of tiotropium may occur through other mechanisms like suppression of cough receptor sensitivity by e.g., regulation of excessive mucus secretion.

Takemura *et al.* prospectively observed the effect of montelukast (10 mg) daily for 4 weeks in 23 consecutive nonsmoking adults with anti-inflammatory treatmentnaive cough variant asthma (CVA) [Takemura *et al.*, 2012]. Montelukast significantly decreased the cough VAS (P=0.0008), sputum eosinophil count (P=0.013) and cough sensitivity (C2: P=0.007; C5: P=0.039), whereas pulmonary function, airway responsiveness and sputum mediator levels remained unchanged. Multivariate analysis showed that a better response to montelukast was associated solely with younger age (P=0.032). They concluded that the antitussive effect of montelukast in CVA may be attributed to the attenuation of eosinophilic inflammation rather than its bronchodilatory properties [Takemura *et al.*, 2012].

A meta-analysis of six small randomized controlled trials of proton-pump inhibitor therapy showed very small effects of treatment on cough severity in adults with chronic cough [Chang *et al.*, 2006], questioning the importance of acid reflux in cough. Potentially the link between reflux and cough is more dependent on the volume of reflux than on its acidity, and therapeutic strategies that reduce reflux volume by addressing gastro-oesophageal sphincter function might be more effective. The discrepancy between the high frequency of GERD in asthmatic patients and the ineffective reflux therapy outcomes in these patients suggests that GERD may cause injury and/or promote cough through other mechanisms, such as pepsinogen, pepsin, bile salts, or other components of reflux materials, instead of the acid [Saber and Ghanei, 2012]. Baclofen may be worthwhile trying for GERD-related cough unresponsive to PPIs.

Nonpharmacologic approaches to cough palliation

Treatment with ACE inhibitors and exposure to cigarette smoke are the most important potential aggravating factors [Pavord and Chung, 2008]. Removal of these or other factors (e.g., environmental irritants) is often associated with a substantial improvement in cough. Persistence of cough after withdrawal of ACE inhibitors raises the possibility of another cause of cough, such as asthma, the onset of which has been linked to the use of ACE inhibitors [Lunde *et al.*, 1994].

Vertigan and colleagues [Vertigan *et al.*, 2006] have shown, in a randomized placebo-controlled trial, that speech therapy improved chronic cough. Similar benefits were noted in an uncontrolled study of outpatient physiotherapy [Carney *et al.*, 1997].

The perception of the magnitude of the urge to cough (UTC) seems to be influenced by signals or sensations arising from exercising limb and thoracic muscles and/or by higher nervous (cortical) mechanisms. The results indicate that the adjustments brought into action by exercise-induced or voluntary isocapnic hyperpnea exert inhibitory influences on the sensory and cognitive components of fog-induced cough (perhaps via desensitization of the cough reflex) [Lavorini *et al.*, 2010]. Biofeedback and cognitive coping may be beneficial in the treatment of pediatric habit cough [Labbé, 2006].

Pharmacologic approaches to cough palliation

The findings of the 2006 ACCP evidence-based clinical practice guidelines suggest that suppressant therapy is most effective when used for the short-term reduction of coughing. Relatively few drugs are effective as cough suppressants [Bolser, 2006].

Smith and colleagues performed a Cochrane Review to assess the effects of oral over the counter (OTC) cough preparations for acute cough in children and adults. Twenty-six trials (18 in adults, eight in children) involving 4,037 people (3,421 adults and 616 children) were included [Smith *et al.*, 2012]. They concluded that there is no good evidence for or against the effectiveness of OTC medicines in acute cough [Smith *et al.*, 2012]. Higher quality evidence is needed to determine the effectiveness of self care treatments for acute cough [Smith *et al.*, 2012].

Oduwole *et al.* published a Cochrane Review of honey for acute cough in children over 2 years old [Oduwole *et al.*, 2012]. They included two RCTs of high risk of bias involving 265 children, comparing the effects of honey with dextromethorphan, diphenhydramine and 'no treatment' on symptomatic relief of cough using the 7-point Likert scale. They concluded that honey may be better than 'no treatment' and diphenhydramine in the symptomatic relief of cough but not better than dextromethorphan. There was no strong evidence for or against the use of honey [Oduwole *et al.*, 2012].

Cohen and colleagues conducted a double-blind, randomized, placebo-controlled study to compare the effects of a single nocturnal dose of 3 honey products (eucalyptus honey, citrus honey, or labiatae honey) to placebo (silan date extract) on nocturnal cough and difficulty sleeping associated with childhood upper respiratory tract infections (URIs) [Cohen *et al.*, 2012]. Parents rated the honey products higher than the silan date extract for symptomatic relief of their children's nocturnal cough and sleep difficulty due to URI. Honey may be a preferable treatment for cough and sleep difficulty associated with childhood URI [Cohen *et al.*, 2012].

Paul *et al.* published a randomized placebo-controlled, double-blind study of honey; or dextromethorphan, or no treatment for upper respiratory infections (URIs) in children [Paul *et al.*, 2007]. Honey was better than no treatment for nocturnal cough frequency in children with URIs. Dextromethorphan was not found to be particularly useful [Paul *et al.*, 2007].

Opioids

Opioids have long been advocated for the suppression of cough [Chung, 2005; Chung 2003]. However, there are few trial data to support this recommendation. Although small, single-dose studies of codeine in chronic bronchitis have shown some benefit [Sevelius and Colmore, 1966; Sevelius *et al.*, 1971; Aylward *et al.*, 1984], a recent trial suggested

an effect similar to that of placebo [Smith *et al.*, 2006]. The effect of opioids in intractable chronic cough has not been studied in large multi-center well designed studies.

Codeine is probably the most commonly prescribed opioidderived antitussive agent. As with other opioids, it mainly acts centrally on the cough network in the brainstem, but might also inhibit peripheral activation of cough receptors. The use of a recent randomized and double-blinded trial using a validated ambulatory cough monitor to objectively measure cough frequency, failed to demonstrate an effect of codeine over placebo in cough associated with COPD [Smith *et al.*, 2006]. A study of cough reflex sensitivity to citric acid in healthy subjects also found morphine to be a more powerful cough suppressant than codeine, but with an increased incidence of side-effects such as sedation [Fuller *et al.*, 1988].

Patients recruited from the Hull Cough Clinic were enrolled into a randomized double-blind placebo-controlled study using 4 weeks of slow-release morphine sulfate and a corresponding period of matched placebo. An open-labeled extension of the core study allowed dose escalation to 10 mg twice daily. Cough was assessed using the Leicester Cough Questionnaire, daily symptom diary, and citric acid cough challenge [Morice et al., 2007b]. Twenty-seven patients completed the core study. A significant improvement of 3.2 points over baseline was noted on the Leicester Cough Questionnaire (P<0.01). A rapid and highly significant reduction by 40% in daily cough scores was noted among patients on slow-release morphine sulfate (P<0.01). Objective testing of the cough reflex using citric acid cough challenge tests did not show any significant changes. Eighteen patients continued into the extension study. Two-thirds of these patients opted to increase the morphine to 10 mg twice daily. At the end of 3 months, there was a similar improvement in cough between the 5- and 10-mg groups [Morice et al., 2007b]. Morice et al. concluded that morphine sulfate is an effective antitussive in intractable chronic cough at the doses of 5 to 10 mg twice daily [Morice et al., 2007b].

The use of morphine and diamorphine has been restricted to severe distressing cough in malignant disease, in which cough is often associated with pain and distress. There is evidence of the effectiveness of a slow-release formulation of morphine in a population with distressing, unexplained cough [Morice *et al.*, 2007b].

Alpha-2 delta ligands A

Ryan and colleagues conducted a randomized, doubleblind, placebo-controlled trial of gabapentin for refractory

chronic cough. Adult patients with refractory chronic cough (>8 weeks' duration) without respiratory disease or infection were randomly assigned to receive gabapentin (maximum tolerable daily dose of 1,800 mg) or placebo for 10 weeks. The primary endpoint was change in cough-specific quality of life [Leicester cough questionnaire (LCQ) score] from baseline to 8 weeks of treatment, analyzed by intention to treat [Ryan *et al.*, 2012].

Sixty-two patients were randomly assigned to gabapentin (n=32) or placebo (n=30) and ten patients withdrew before the study end. Gabapentin significantly improved cough-specific quality of life compared with placebo (between-group difference in LCQ score during treatment period 1.80, 95% CI, 0.56-3.04; P=0.004; number needed to treat of 3.58). Side-effects occurred in ten patients (31%) given gabapentin (the most common being nausea and fatigue) and three (10%) given placebo [Ryan *et al.*, 2012]. The treatment of refractory chronic cough with gabapentin is both effective and well tolerated. These positive effects suggest that central reflex sensitization is a relevant mechanism in refractory chronic cough [Ryan *et al.*, 2012].

GABA B receptor agonists

GABA B receptor agonist therapy reduces the frequency of transient lower esophageal sphincter relaxations (TLESR; the major cause of reflux) in animals and in patients with GERD (thus, reducing GERD). However, GABA B receptor agonists have also been shown to possess antitussive effects in patients and in animals independent of their effects on TLESR, suggesting that lesogaberan may be a promising treatment for chronic cough [Canning *et al.*, 2012].

Lesogaberan dose-dependently inhibited citric acid evoked coughing in guinea pigs [Canning *et al.*, 2012]. Comparable effects of the GABA B receptor agonists baclofen and 3-aminopropylphosphinic acid (3-APPiA) on cough were also observed. Baclofen produced obvious signs of sedation and respiratory depression. By contrast, both lesogaberan and 3-APPiA (both inactivated centrally by GABA transporters and therefore essentially peripherallyrestricted agents), were devoid of sedative effects and did not alter respiratory rate [Canning *et al.*, 2012].

GABA B receptor agonists in addition to their being used in the treatment of pain, overactive bladder, hiccups, tetanus/ spasticity, and headache [Müller *et al.*, 1986; Meythaler *et al.*, 2001; Enna and McCarson, 2006; Miyazato *et al.*, 2008] have also been evaluated for their effects on airways hyperresponsiveness, GERD and cough [Dicpinigaitis *et al.*, 2000; Lidmus *et al.*, 2000; Lehmann, 2009; Boeckxstaens *et al.*, 2010]. Xu *et al.* published on the successful resolution of refractory chronic cough induced by gastroesophageal reflux and unresponsive to proton pump inhibitor therapy with treatment of baclofen [Xu *et al.*, 2012].

Miscellaneous antitussive agents

There are many agents which may potentially possess antitussive qualities, but have not been tested in large well-designed trials or perhaps not studied well at all. Nevertheless, it is conceivable that these agents may be worthwhile to use in a therapeutic trial in certain patients who are refractory to traditional antitussive therapy.

Dextromethorphan may have some effect on cough associated with upper respiratory tract infections, although any effects on cough frequency were small and of uncertain clinical relevance [Pavesi *et al.*, 2001; Grattan *et al.*, 1995].

Low dose amitriptyline was found to be superior to codeine/guaifenesin based on subjective ratings of cough and quality of life scores in a randomized, un-blinded study of patients with post-viral cough [Jeyakumar *et al.*, 2006]. In a prospective cohort study of patients with idiopathic chronic cough, amitriptyline improved symptoms over 3 weeks but treatment was not compared to placebo [Bastian *et al.*, 2006; Young and Smith, 2011].

Anecdotal case reports/case series exist for the treatment of cough with paroxetine [Hamel *et al.*, 2000; Zylicz and Krajnik, 2004]. This potential beneficial effect may be due to paroxetine's actions on the 5-HT_{1A} receptor.

Chronic cough has been treated with lidocaine delivered by aerosol [Howard et al., 1977] or nebulizer [Chong et al., 2005], although good evidence of the effectiveness and safety of this approach is absent. Lim and colleagues performed a retrospective study of adults who received a prescription and nurse education for nebulized lidocaine for chronic cough between 2002 and 2007 [Lim et al., 2012]. Of 165 eligible patients, 99 (60%) responded to a mailed survey with phone follow-up. Responders were a median age of 62 years (range, 29-87 years), 77 (79%) were female, and 80 (82%) were white. The median duration of cough was 5 years before treatment with nebulized lidocaine. Of the patients who used nebulized lidocaine (93% of survey responders), 43% reported an adverse event, but none of these events were considered significant and no event required an emergency visit, hospitalization, or antibiotic therapy for aspiration pneumonia. In long-term, twice or thrice daily use with normal liver function, nebulized lidocaine should theoretically not accumulate in the serum

because the serum half-life of lidocaine is about 90 minutes. The most common adverse effects were unpleasant taste and throat or mouth irritation. These results are in agreement with clinical studies of nebulized lidocaine as long-term (12-month) therapy for asthma in children and adults. These studies have not reported notable adverse reactions even with total daily doses ranging from 160 to 640 mg [Hunt *et al.*, 1996; Decco *et al.*, 1999]. The mean (SD) of the pretreatment cough severity score was 8.4 (1.6) and posttreatment was 5.9 (3.4) (P&clt; 0.001). Of the patients reporting improvement in cough symptoms (49%), 80% reported improvement within the first 2 weeks [Lim *et al.*, 2012].

Future potential antitussive agents

Future potential antitussive agents may include: peripheral mu opioid agonists [Choudry *et al.*, 1991], peripheral delta opioid agonists [Kotzer *et al.*, 2000], transient receptor potential vanilloid receptor-1 antagonists [Lalloo *et al.*, 1995; Trevisani *et al.*, 2004], bradykinin B2 receptor antagonists [Featherstone *et al.*, 1996; Fox *et al.*, 1996], tachykinin receptor antagonists [Fahy *et al.*, 1995; Girard *et al.*, 1995; Hay *et al.*, 2002], cannabinoid CB2 agonists [Patel *et al.*, 2003], and voltagegated K⁺ (Kv) channel openers-large-conductive calcium activated (ca) channels (e.g., NS-1619) [Fox *et al.*, 1997], or ATP-sensitive potassium (KATP) channels (e.g., pinacidil) [Mortia and Kamei, 2000].

Summary

Intractable chronic cough can be among the most debilitating of symptoms to palliative care patients. There are many factors that may contribute to chronic cough. The better that clinicians can determine the major "cough generators" in an individual patient, the better chance that providers may be able to target therapy to match individual patient pathophysiology. Current treatment strategies appear to be suboptimal to effectively alleviate cough for many patients. Future antitussive strategies seem promising but their value remains to be seen.

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Delirium

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Introduction

Delirium, a frequent syndrome in patients with advanced illness, is characterized by inattention and acute cognitive dysfunction. Delirium may be hypoactive, mixed, or hyperactive. Clinical features vary and the patient may be withdrawn, non communicative, overtly psychotic, or hyperactive [Lawlor and Bruera, 2002]. Key features of delirium include the acute onset and fluctuating clinical course, which help distinguish delirium from depression and dementia [Fong *et al.*, 2009].

Delirium is a sign of poor prognosis in advanced illness. Patients with advanced cancer who develop delirium have shorter median survival (21 d) than those without delirium (39 d) [Caraceni *et al.*, 2000]. Delirium also portends a poor prognosis in critically ill patients, especially those who require mechanical ventilation [Fong *et al.*, 2009].

Tools specific to delirium are available to decrease the risk of underdiagnosis [Pae *et al.*, 2008]. Treatment of delirium may be pharmacologic or nonpharmacologic. Preventive measures are advocated but unproven. Delirium frequently is reversible (50%) [Lawlor *et al.*, 2000]. The purpose of this chapter is to review the epidemiology, pathophysiology, and treatment of delirium.

Epidemiology

Delirium occurs in 1% to 2% people in the community setting and 14% to 24% people admitted to a general hospital [Fong *et al.*, 2009]. The frequency of delirium during a hospital stay is 56% and may be higher in patients receiving postoperative, intensive, subacute, or palliative care [Fong *et al.*, 2009]. Elderly patients aged >65 years are susceptible to developing delirium; the frequency of delirium is 15% to 53% in elderly postoperative patients [Inouye, 2006] and higher in elderly patients admitted to an intensive care unit [Pisani *et al.*, 2003]. The prevalence of delirium in hospitalized patients with advanced cancer is 28% to 48%, and delirium may be present in almost all patients during the hours or days before death [Coyle *et al.*, 1990].

Etiology

Several factors may predispose to delirium, and other acute processes may cause delirium (*Tables 1,2*) [Burns *et al.*, 2004]. In the elderly, dementia is an important risk factor for delirium. Delirium and dementia often are associated with each other, and patients with both conditions may have decreased cerebral blood flow or metabolism, increased inflammation, or cholinergic deficiency [Van Gool *et al.*, 2010]. Patients who have cancer with central nervous system involvement also are at high risk for developing delirium [Caraceni and Simonetti, 2009]. Systemic end organ damage is another nonmodifiable condition that may predispose to delirium [Fong *et al.*, 2009].

Pathophysiology

The pathophysiology of delirium is complex and not well understood. Toxicity from drugs, inflammation, and acute stressors may disrupt neurotransmission and cause delirium. There may be cholinergic deficiency in patients who have delirium [Hshieh *et al.*, 2008], and anticholinergic drugs commonly cause delirium in hospitalized patients [Han *et al.*, 2001]. Other neurotransmitters are linked to

Table 1 Conditions predisposing to delirium
Conditions predisposing to delirium
Delirium
Depression
Cerebrovascular accident
Dehydration
Hip fracture
Alcoholism
Immobility
Adapted from [Fong et al. 2009]

the development of delirium, including elevated levels of dopamine or imbalances between the dopaminergic and cholinergic systems [Trzepacz, 2000]. Drugs that treat the dopaminergic/cholinergic imbalance in Parkinson's disease may cause delirium, and dopamine antagonists such as haloperidol are very useful in treating delirium [Young *et al.*, 1997].

The production of proinflammatory cytokines may be an important cause of delirium [Rudolph *et al.*, 2008; MacLullich *et al.*, 2008]. Peripherally secreted cytokines may affect neural cells such as microglia and cause inflammation in the brain [Dilger and Johnson, 2008]. Inflammatory cytokines may affect the synthesis or release of acetylcholine, dopamine, norepinephrine, and serotonin, and this may change neuronal function [Dunn *et al.*, 1999] and directly cause neural injury [Jonker *et al.*, 1982]. Cytokine levels are elevated in patients who have delirium [de Rooij *et al.*, 2007]. Furthermore, low-grade inflammation in the presence of the chronic neurodegenerative changes associated with dementia can cause delirium.

Elevations of cortisol associated with emotional stress may precipitate or sustain delirium [Trzepacz and Van der Mast, 2002]. Steroids may impair cognitive function and occasionally cause psychosis. In addition, elevated cortisol levels have been observed in patients with postoperative delirium [Kudoh *et al.*, 2005]. Furthermore, abnormal suppression in the dexamethasone suppression test has been noted in some patients with delirium [Robertsson *et al.*, 2001].

Metabolic and ischemic insults to the brain may cause delirium. Hypoxemia, hypoglycemia, and metabolic derangements may cause direct neuronal injury; this may cause neuronal energy deprivation, altered production of neurotransmitters, and altered propagation of nerve

Table 2 Acute conditions that cause delirium
Acute conditions that cause delirium
Opioids
Infection
Hypoxemia
Metabolic abnormalities
Sepsis
Pain
Surgery
Physical restraint
High number of hospital procedures
Intensive care unit admission
Bladder catheter use
Anemia
Duration of cardiopulmonary bypass
Adapted from [Fong et al., 2009].

impulses across neural networks that are important for attention and cognition [Trzepacz and Van der Mast, 2002].

Clinical features

Delirium usually has a rapid onset and fluctuating course, often worsening in the evening. Impairments may be very subtle, and delirium is often underdiagnosed. There may be impaired consciousness and disordered attention. The patient may be distracted easily and may have difficulty concentrating. Impairments in judgment, abstract thinking, and memory are present. The sleep wake cycle commonly is abnormal and inverted, and speech may be affected.

The three subtypes of delirium include hyperactive, hypoactive, and mixed delirium, depending on levels of psychomotor activity and arousal [Trzepacz and Van der Mast, 2002]. The agitated patient may constantly yell, move about in bed, try to get up, and tear out intravenous lines. Patients may constantly repeat verbal statements. Hallucinations commonly occur with hypoactive or hyperactive delirium [Centeno *et al.*, 2004]. Hospice patients (50%) may experience hallucinations during the final weeks of life [Centeno *et al.*, 2004]. Although hyperactive delirium is common, most patients with delirium have hypoactive or mixed (hyperactive and hypoactive) subtypes [Stagno *et al.*, 2004]. Hypoactive delirium may be difficult to identify because patients may be quiet, withdrawn, and minimally communicative. However, in these patients,

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further observation may reveal inattention and disorganized thinking.

Physical examination may reveal factors that predispose to delirium, such as infection, neurologic deficits, urinary retention, and fecal impaction. Depending on the goals of care, further evaluation may include blood tests or imaging studies. The extent of evaluation may depend on disease trajectory and wishes of the patient or guardian.

Drugs that may contribute to the development of delirium include opioids, benzodiazepines, and other psychoactive drugs. Opioids may contribute to delirium when they are given to a patient without previous history of opioid use or when the dosage is rapidly increased. In a prospective study of 216 consecutive patients admitted to an intensive care unit, fentanyl and morphine were strongly associated with the development of delirium regardless of dosage [Dubois *et al.*, 2001]. Signs of opioid-induced delirium include myoclonus or hyperalgesia. Drugs with strong anticholinergic properties may cause delirium, including anticholinergics, benzodiazepines, steroids, nonsteroidal anti-inflammatory drugs, some antibiotics (quinolones and cephalosporins), antiparkinsonian drugs, and some cancer chemotherapeutic agents.

Elderly patients with poor pain control may develop delirium [Morrison *et al.*, 2003]. In a study of 113 nursing home residents, individuals with greater cognitive impairment had been prescribed fewer analgesics than those with low cognitive impairment [Closs *et al.*, 2004].

Alcohol withdrawal is important in the differential diagnosis of delirium. Infections such as urinary tract infection, aspiration and bacterial pneumonia, and infected decubitus ulcer may cause delirium. Metabolic causes of delirium include hyponatremia, hypercalcemia, hepatic insufficiency, and renal failure. Furthermore, delirium in patients with cancer may be caused by central nervous system and leptomeningeal involvement.

The Confusion Assessment Method (CAM) is a useful tool that uses an algorithm to identify and diagnose delirium [Inouye *et al.*, 1990]. The CAM evaluates features of delirium such as acute onset or fluctuation of symptoms, inattention, disorganized thinking, and altered consciousness [Inouye *et al.*, 1990]. The CAM has high sensitivity, specificity, and interrater reliability for trained interviewers [Inouye *et al.*, 1990]. However, training of practitioners is important for the successful application of CAM. Nurses using the CAM may not always recognize delirium, especially in patients with hypoactive delirium, vision impairment, older age (\geq 80 y), and dementia [Inouye *et al.*, 2001]. Other tools may quantify the severity of delirium, such as the 10-item Memorial Delirium Assessment Scale [Breitbart *et al.*, 1997] and the Delirium Rating Scale-Revised-98 (DRS-R98) [Meagher *et al.*, 2008].

Preventive measures

Nonpharmacologic approaches

Nonpharmacologic and pharmacologic prevention strategies may minimize the incidence of delirium. The Hospital Elder Life Program (HELP) is a nonpharmacologic strategy that uses delirium prevention strategies to improve overall quality of hospital care [Inouve et al., 2006]. This program focuses on maintaining orientation to surroundings; meeting basic needs such as nutrition, fluids, and sleep; encouraging mobility within the limitations of the patient's physical condition; assessing for sensory impairments; and providing visual and hearing adaptations for sensory impairments. In a controlled trial, HELP was associated with decreased frequency of delirium (HELP, 9.9%; usual care, 15.0%; matched odds ratio, 0.60; 95% confidence interval, 0.39 to 0.92); the HELP interventions decreased the number of delirium episodes and days of delirium in hospitalized elderly individuals [Inouye et al., 1999].

Other nonpharmacologic approaches use multifactorial interventions and educational strategies for health care staff [Inouye *et al.*, 1999]. Physical activity improvements are important in the nonpharmacologic approach to delirium. In a controlled trial in the elderly, patients treated with home rehabilitation after acute hospitalization had a lower risk of developing delirium and greater patient satisfaction than patients treated in the inpatient hospital setting [Caplan *et al.*, 2006].

In advanced cancer patients, supportive measures such as gentle hydration may be effective in preventing delirium. A Canadian palliative care unit lowered the incidence of delirium by adopting a policy of vigorous hydration [Bruera *et al.*, 1995]. In a randomized, controlled, double blind trial [Bruera *et al.*, 2005] that evaluated the effects of parenteral hydration (1,000 versus 100 mL/d) on symptoms such as sedation, fatigue, hallucinations, and myoclonus, most (83%) patients who received 1,000 mL/d had improvements in myoclonus and sedation; most patients were on opioids and they may have benefited from increased elimination of active opioid metabolites. This study showed a large placebo effect, and 59% patients who received placebo had improved symptoms after <36 hours.

Pharmacologic prevention

Prophylactic pharmacologic treatment of delirium has been evaluated. Haloperidol may reduce the incidence of delirium in the postoperative patient [Kaneko et al., 1999], but this effect was not confirmed in a larger study [Kalisvaart et al., 2005]. Cholinesterase inhibitors have been evaluated in randomized, controlled clinical trials but have not shown prevention of postoperative delirium. However, these studies were limited because of small sample size and low statistical power [Liptzin et al., 2005]. Although case reports and an open label study have suggested promising results with anticholinergic therapy for prevention [Novan et al., 2003; Slatkin et al., 2001] additional randomized, controlled studies are necessary before definitive recommendations can be made [Bourne et al., 2008]. Other strategies are being evaluated that minimize the use of opioids or benzodiazepines by using alternative agents such as gabapentin [Leung et al., 2006] or dexmedetomidine [Levanen and Makela, 1995].

Supportive and environmental measures

Nonpharmacologic supportive measures can be useful in preventing delirium [Inouye *et al.*, 2003]. Patients recovering from delirium have reported that several interventions may increase a sense of control during delirium including clear communication, reorientation, a visible clock, and the presence of a family relative [Schofield, 1997]. Additional measures that may help reorient patients include a quiet and comfortable private room, comfortable ambient temperature, adequate lighting, and a clearly visible sign providing the patient's location and date. Delirium also may be lessened by reducing environmental stimulation from external noise, staff, equipment, and visitors.

Communication is improved when patients have their glasses, hearing aids, and dentures and when communication is clear and simple. It is helpful to include repeated verbal reminders of the day, time, location, and identity of key individuals such as treatment team members and relatives. Orientation may be improved by having family members bring familiar objects from the patient's home to the hospital room. It also may be helpful for the patient to maintain activity as tolerated and participate in self care and treatment plans. Physical therapists may help patients with ambulation in the room and hallways. The nonambulatory patient can participate in range of motion exercises and position changes in bed. Although studies are limited in the palliative care population, these measures likely may benefit the patient.

Family support

The presence of delirium may cause marked distress to the patient and family [Morita *et al.*, 2004]. Family members may view delirium as a sign of suffering and pain [Del Fabbro *et al.*, 2006]. After recovering from delirium, most patients (53.5%) reported that delusions were the most important predictor of distress, and hypoactive delirium may be as distressing as hyperactive delirium [Spiller and Keen, 2006]. The family may be supported with explanations about delirium including frequency in advanced illness, potential causes, and likelihood of reversibility.

Pharmacologic treatment

Neuroleptic drugs

Neuroleptic agents are the primary drugs for treating delirium. They are effective in patients with hyperactive or hypoactive delirium [Breitbart *et al.*, 1996]. Despite the lack of studies comparing different agents, haloperidol is considered the best drug for treating delirium. Haloperidol is the drug of choice because it has minimal active metabolites or anticholinergic effects, causes limited sedation or hypotension, and may be given by various routes [Prommer, 2012]. Intravenous administration causes less extrapyramidal adverse reactions than other routes in patients with delirium. Total intravenous doses <2 mg/day are unlikely to prolong the QT interval [Prommer, 2012].

Several dosing strategies for haloperidol have been recommended. Some experts have advocated aggressive titration of symptoms, such as agitation and hallucinations, with haloperidol (dose: 0.5 to 1 mg; route: oral, intravenous, intramuscular, or subcutaneous) administered hourly according to the clinical response [Breitbart and Strout, 2000]. Some guidelines have recommended stratification of dosing based on the severity of delirium and response to the initial dose [Hogan *et al.*, 2006]. These guidelines have recommended that patients with mild-to-moderate delirium receive haloperidol at low doses initially (0.5 mg oral, two to three times daily), with titration according to clinical response. However, these recommendations have not been evaluated in a clinical trial.

Other recommendations have suggested that parenteral haloperidol be used in patients with severe delirium,

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with age being the guide for the initial dose. These recommendations have suggested higher parenteral doses (1 to 2 mg) in younger patients and lower doses (0.25 to 0.5 mg) in patients aged ≥ 60 years; the dose is repeated after one to two hours as needed, until decreased agitation is observed [Lipowski, 1987]. In a study that examined aggressive titration of haloperidol for the treatment of cancer-related delirium, a titration protocol (30 minute intervals) included doses given according to route availability (initial, 0.5 mg intramuscular or intravenous or 0.75 mg oral for 3 doses; subsequent doses as needed: 1 mg intramuscular or intravenous or 1.5 mg oral for 3 doses, then 2 mg intramuscular or intravenous or 3 mg oral for 3 doses, then 5 mg intramuscular or intravenous for 3 doses) [Akechi et al., 1996]. With this dosing protocol, patients required an average total 6 mg/day to control delirium (range, 5 to 11 mg/d), and many patients required <5 mg on the first day to achieve control of target symptoms such as agitation. The total dose of haloperidol on subsequent days was based on the total dose of the previous day. This regimen suggested that aggressive titration of drugs may be very important in the effective treatment of delirium. Other factors may affect haloperidol dosing in delirium, and health care professional distress may cause increased doses given [Hui et al., 2010].

Atypical antipsychotic drugs

Atypical antipsychotic drugs such as risperidone and olanzapine have been evaluated for treating delirium [Passik and Cooper, 1999]. The advantages of these drugs include fewer extrapyramidal adverse reactions because of decreased interaction with dopamine D2 receptors, and fewer drug interactions. Disadvantages of these atypical antipsychotic drugs include the high cost and limited (oral) route of administration. All atypical antipsychotic drugs are serotonin 5-HT2A antagonists. Risperidone may improve cognition in delirious patients [Mittal *et al.*, 2004]. In a double blind trial, there were no differences between risperidone and haloperidol in adverse reactions or Memorial Delirium Assessment Scale scores [Han and Kim, 2004].

Olanzapine is as effective as haloperidol [Skrobik *et al.*, 2004]. In patients with delirium in the intensive care unit, enteral olanzapine and enteral haloperidol had equal efficacy in treating delirium, but olanzapine had fewer extrapyramidal adverse reactions than haloperidol [Skrobik *et al.*, 2004]. Olanzapine also is an effective agent

for treating cancer-related delirium [Breitbart *et al.*, 2002]. Risk factors for a poor response to olanzapine in cancer patients with delirium include patient age >70 years, history of dementia, central nervous system metastases, hypoxia, hypoactive delirium, and delirium of severe intensity (Memorial Delirium Assessment Scale score \geq 23). Olanazapine has been given by the subcutaneous route [Elsayem *et al.*, 2010].

Aripiprazole is an atypical antipsychotic drug that has partial D2 receptor agonism [Alao and Moskowirz, 2006]. Aripiprazole was effective in an open label trial for the treatment of delirium [Boettger *et al.*, 2011].

Benzodiazepines

Benzodiazepines are the primary drugs for the treatment of delirium associated with alcohol withdrawal [Del Fabbro *et al.*, 2006]. However, benzodiazepines may cause paradoxical agitation [Hall and Zisook, 2012]. In hospitalized patients with delirium and acquired immunodeficiency syndrome, lorazepam is ineffective and may cause increased cognitive impairment [Breitbart *et al.*, 1996].

Other drugs

Psychostimulant drugs such as methylphenidate may be useful in treating hypoactive delirium. In patients with hypoactive delirium, methylphenidate may improve Mini-Mental Status Examination scores and psychomotor activities [Gagnon *et al.*, 2005].

Summary

Delirium is an important clinical syndrome that may cause major distress for the patient with advanced illness and family. Both nonpharmacologic and pharmacologic approaches are important in the prevention and treatment of delirium.

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Introduction

Dementia, due to neurodegenerative disease associated with aging, is a progressive and largely irreversible clinical syndrome characterized by a widespread impairment of mental function, with some or all of the following features: memory loss, language impairment, disorientation, change in personality, difficulties with activities of daily living, selfneglect and behavior that is out of character (for example, aggression, sleep disturbance or sexual disinhibition) [National Institute for Health and Clinical Excellence, 2006]. The overwhelming percentage of people with dementia of aging have Alzheimer's disease (AD), while smaller numbers are caused by Frontotemporal Disease, Lewy Body Dementia or Stroke (vascular dementia). The term dementia in this chapter refers to AD as the common example. The number of people living with dementia will almost double every 20 years, to 42.3 million in 2020 and 81.1 million in 2040. Although the expert consensus was for a higher prevalence of dementia in developed regions than developing regions, it is China and its developing western-Pacific neighbors that have the highest number of people with dementia (6 million), followed by western Europe with 4.9 million, and North America with 3.4 million [Ferri et al., 2005]. An estimated 5.2 million Americans of all ages have AD in 2013. One in nine people age 65 and older (11%) has AD. About one third of people age 85 and older (32%) have AD. Of those with AD, an estimated 4% are under age 65, 13% are 65 to 74, 44% are 75 to 84, and 38% are 85 or older [Alzheimer's Association, 2013], and the median length of survival from diagnosis to death is eight years [Davies and Higginson, 2004], but it may be shorter in other types of dementia. For example, in Frontotemporal dementia, additional Parkinsonism also predicts shorter course. The prognosis for a patient may range from two to over 15 years [Lloyd-Williams, 1996] with the end-stage of the illness lasting as long as two or even three years [Shuster,

2000]. Furthermore, the number of patients with dementia is estimated to double over the next 50 years [Byrne, *et al.*, 2006].

Challenges

The disease course that dementia usually follows is one of prolonged and progressive disability [Murray et al., 2005; Murtagh et al., 2004]. The fact that dementia, at times, is not seen as a palliative illness is probably because of the long period of time that often elapses between detection of the illness and death [Albinsson and Strang, 2002]. The level of baseline function is often low as the disease primarily affects older people who will have already accumulated much other comorbidity. This is in contrast to cancer which usually follows an initial slow overall decline from a high level of function, followed by a relatively rapid decline in function at the end of life, and a fairly predictable terminal phase where there is time to anticipate palliative care needs and plan for end-of-life care [Murray et al., 2005; Lachs and Pillemer, 2004]. Failure to recognize dementia as a terminal illness often impacts end-of-life care provided to dementia patients [Mitchell et al., 2004a].

Palliative care can alleviate suffering and provide highquality end-of-life care to dementia patients. Yet, despite similar levels of palliative-care need, dementia patients are substantially less likely to be referred for palliative care and are prescribed fewer palliative-care medications than terminally ill cancer patients [Mitchell *et al.*, 2004a]. At the end of life, dementia sufferers are frequently hospitalized [Mitchell *et al.*, 2009; Lamberg *et al.*, 2005] and commonly experience burdensome, invasive medical interventions, including tube feeding, laboratory tests, and restraints [Mitchell *et al.*, 2004a] and suffer from poor pain management [Teno *et al.*, 2001; Won *et al.*, 1999].

For every patient (suffering from dementia) there will

be at least one carer (caregiver) who will face complex and challenging problems as the disease progresses: aggressive behavior, restlessness and wandering, incontinence, delusions and hallucinations, reduced mobility and feeding problems. Palliative care aimed at older people frequently raises ethical issues about the boundaries between curative, palliative and useless care [Wary, 2003]. The decision to withdraw or withhold is much more difficult than the decision to commence or continue treatment [Hinkka et al., 2002]. The main barrier to extending specialist palliative care services to older, non-cancer patients relates to clinicians' reluctance and/or inability to predict palliative status and time-to-death [Coventry et al., 2005]. However, a protracted dying process is costly and older people are increasing in numbers continually [Von Genten and Twaddle 1996; Evers et al., 2002; Aminoff and Adunsky, 2004]. Dementia patients are also unlikely to have spiritual needs assessed before death [Sampson et al., 2006a].

Furthermore, communication difficulties and a lack of advance directives, such as "do not resuscitate" orders [Bayer, 2006] lead to a poor understanding of the needs and wishes of dementia patients. Currently, end-of-life care is predominantly provided to dementia patients by care homes, or to a lesser extent by informal caregivers in their own home [Smith *et al.*, 2000]. Complex treatment and social-care needs of dementia may mean that traditional palliative-care settings, such as hospices, are not appropriate or adequately equipped to provide care needs to dementia patients. These challenges are further compounded by difficulty in predicting prognosis of the terminal phase of dementia. Dementia is therefore associated with complex needs [Bayer, 2006; Hughes *et al.*, 2005].

On the brighter side, the recognition of the need for good quality end-of-life or palliative care has increased over recent years [Department of Health 2000; 2003]. Dementia is now recognized as a progressive terminal illness for which there is currently no cure [Shuster, 2000; Lloyd-Williams and Payne, 2002; Burgess, 2004] but its progression varies. Although the term 'palliative care' was originally applied only to the terminally ill, it has now been broadened to include those who have a life-threatening illness not amenable to curative treatment and who are not necessarily imminently dying and may thus have a prognosis of months to years [National Council for Palliative Care, 2007]. Given the increasing prevalence of people dying with dementia, palliative care for these older people is extremely relevant [Roger, 2006]. A systematic review of UK trials investigating the efficacy of palliative care for older people with dementia concluded that there is now 'equivocal evidence of the efficacy for a palliative model of care in dementia' [Sampson et al., 2006b]. Furthermore, a palliative care approach is favored by formal and informal (unpaid) caregivers and the current World Health Organization definition of palliative care extends to incorporate non-malignant life-limiting disease as [Hughes et al., 2005; Davies and Higginson, 2004]: "...an approach that improves the quality of life of patients and their families facing the problems associated with life threatening illness... by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual".

Pharmacological palliative treatment of cognitive and behavioral and psychological symptoms of dementia (BPSD)

Treatment of cognitive symptoms

There are four currently available Food and Drug Administration (FDA) approved medications for the treatment of dementia. Three are cholinesterase inhibitors: donepezil, rivastigmine, and galantamine; the fourth is memantine, an N-methyl-D-aspartate (NMDA) receptor noncompetitive antagonist [Yiannopoulou and Papageorgiou, 2012].

Anticholinestrases

Results from randomized, controlled trials involving patients with moderate-to-severe [Feldman *et al.*, 2001; Tariot *et al.*, 2001] or severe [Feldman *et al.*, 2005; Winblad *et al.*, 2006; Black *et al.*, 2007; Homma *et al.*, 2008] AD suggest that cholinesterase inhibitors are associated with modest improvements in cognition and function, and these drugs are approved by the Food and FDA in the United States for the treatment of severe AD.

Donepezil, a cholinesterase inhibitor, for the treatment of AD, showed improvements in cognitive test scores and in the ability to perform daily activities, and subsequent trials indicated that the drug had efficacy over the course of one to two years [Birks and Harvey, 2006]. Donepezil previously was approved in 5- and 10-mg tablet strengths, with a maximum daily dose of 10 mg (later FDA also approved Exelon patch 13.3 mg). On July 27, 2010—The US FDA has approved donepezil HCl 23-mg tablets for the oncedaily treatment of moderate to severe AD, in patients who have been established on 10 mg for at least three months. The FDA's action was based on data from a head-to-head clinical study (n=1,467) showing that patients randomly

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assigned to receive the 23-mg dose achieved significant improvements in cognition at 24 weeks compared with those who continued on 10 mg. Benefits were quantified using mean changes from baseline in Severe Impairment Battery score, which is a validated clinical instrument used to rate selective aspects of cognition, including elements of memory, language, orientation, attention, praxis, visuospatial ability, construction, and social interaction on a scale of 0 to 100, where lower scores indicate greater impairment. The most commonly reported adverse events with the 23-mg donepezil dose (rate $\geq 5\%$ and higher than with the 10-mg dose) included nausea (11.8% vs. 3.4%), vomiting (9.2% vs. 2.5%), diarrhea (8.3% vs. 5.3%), and anorexia (5.3% vs. 1.7%). Weight loss was also reported (4.7% vs. 2.5%), with 8.4% of patients on the 23-mg dose losing 7% or more of their body weight by study end (vs. 4.9% for the 10-mg dose). Discontinuations were markedly more common in the 23-mg group (18.6% vs. 7.9%) and were primarily driven by cases of vomiting, diarrhea, nausea, and dizziness during the first month of treatment. The FDA warns that cholinesterase inhibitors such as donepezil may have vagotonic effects on the sinoatrial and atrioventricular nodes, leading to bradycardia or heart block in patients with and without underlying cardiac conduction abnormalities; syncopal episodes have been reported. Because increased cholinergic activity can increase gastric acid secretion, patients should be monitored closely for symptoms of active or occult gastrointestinal bleeding, particularly those with a history of ulcer disease or receiving concomitant treatment with nonsteroidal anti-inflammatory drugs [Medscape, 2010]. About half of the patients who are prescribed cholinesterase inhibitors, however, discontinue them within a year, apparently because of a perceived lack of efficacy and adverse effects such as anorexia, weight loss, agitation, bradycardia, and syncope [Gill et al., 2009].

N-methyl-D-asparate (NMDA) antagonistmemantine

The FDA approved memantine, for treatment of moderate to severe AD. Memantine—NMDA antagonist—is thought to work by blocking the action of the glutamate. Although memantine helps treat the symptoms of AD in some patients, there is no evidence that it modifies the underlying pathology of the disease. The most frequently reported adverse events were dizziness (7%), headache (6%), and constipation (6%) [FDA News, 2003]. Evidence of the efficacy of memantine has been shown primarily in patients with moderate or severe AD [Areosa *et al.*, 2005].

Anticholinesterases (e.g., donepezil) and NMDA antagonist (e.g., memantine) combination, and medical decision making

The findings of a study showing that combination therapy with memantine and a cholinesterase inhibitor was more effective than treatment with a cholinesterase inhibitor alone [Tariot *et al.*, 2004] have not been replicated [Porsteinsson *et al.*, 2008]. As the patients continue to worsen, it is difficult to determine whether they are benefiting from them [Herrmann *et al.*, 2011]. There is very limited evidence to guide the difficult decision regarding continuation or discontinuation of treatment when the disease progresses, but continued treatment is associated with an increase in adverse outcomes, including syncope, the need for insertion of permanent pacemakers, and hip fractures [Gill *et al.*, 2009].

In the United Kingdom, where decisions about medication coverage are made by the National Health Service (NHS), physicians have three guidelines-based choices when their patients who are being treated with donepezil reach a moderately severe level of cognitive impairment and it is uncertain whether the drug is helping or harming: continue donepezil, discontinue it, or switch to memantine, a NMDA-receptor antagonist that is specifically indicated for the treatment of moderate-to-severe AD in both the United Kingdom and the United States. The NHS does not approve the addition of memantine to a cholinesterase inhibitor. In contrast, U.S. physicians typically add memantine to ongoing donepezil treatment, frequently when patients are still mildly impaired, without waiting for their condition to worsen from moderate-tosevere (the indication for which the drug is approved by the FDA) [Schneider, 2012].

Recently a large scale, randomized, placebo-controlled, Donepezil and Memantine in Moderate to Severe Alzheimer's Disease (DOMINO) trial [Howard *et al.*, 2012], showed that over the one-year follow-up period, continuing donepezil, as compared with discontinuing it, was associated with better scores on measures of cognitive ability and activities of daily living; adding memantine at the time donepezil was discontinued was better than not adding memantine; and adding memantine while continuing donepezil was not better than continuing donepezil alone. Although memantine appears to be helpful for the treatment of moderate-to-severe AD when used alone [McShane *et al.*, 2006] or when replacing donepezil [Howard *et al.*, 2012] the results of the DOMINO trial do not support the typical use in the United States, and an FDA-approved use, as add-on therapy to established donepezil treatment. In contrast to the benefits observed in a six-month U.S. trial [Tariot *et al.*, 2004], in the longer DOMINO trial, adding memantine to donepezil, as compared with continuing donepezil alone, was not associated with better cognition or function [Schneider, 2012]. Many physicians use ADL/IADLs for the clinical decision making about when to stop these medications. For example, when none or few are left, and at that time in progression, swallowing pills medications has become problematic. It is a good time to discontinue them as well as all the other unneeded medications (e.g., vitamins, statins, aspirin).

Results with donepezil in the DOMINO trial may not apply to the other marketed cholinesterase inhibitors, galantamine and rivastigmine, since the pharmacokinetic characteristics, mechanisms of cholinesterase inhibition, and other actions of these drugs differ from those of donepezil [Darreh-Shori and Soininen, 2010].

Treatment of behavioral and psychological symptoms of dementia (BPSD)

Noncognitive symptoms such as agitation or psychosis are among the most distressing manifestations of dementia [Ropacki and Jeste, 2005]. BPSD occur at some point in the course of the illness in up to 90% of patients with AD, although there is marked interindividual variability [Lyketsos *et al.*, 2002]. The most common BPSD include mood changes, psychosis, personality changes, anxiety, agitation, aberrant motor behavior, and neurovegetative disturbances including alterations in sleep patterns and appetite [Mega *et al.*, 1996]. The presence of BPSD has been associated with an increased cost of direct care [Murman *et al.*, 2002]. It has been observed that agitation can be related to depression in the first stages of the disease or to other symptoms such as delusions in more advanced stages [Benoit *et al.*, 2003; Cohen-Mansfield and Libin, 2005].

Treatment of depressive symptoms

Depression is a highly prevalent psychological disorder in palliative care settings and is associated with a reduced quality of life for patients and substantial costs to the health care system [Stiefel *et al.*, 2001; Qaseem *et al.*, 2008]. Factors associated with depression in this population include increased frequency and intensity of physical symptoms, lower general well-being, increased mortality and a hastened desire to die [Lloyd-Williams *et al.*, 2004; Delgado-Guay *et al.*, 2009; Smith *et al.*, 2003; O'Mahony *et al.*, 2005]. Despite awareness of the high prevalence of depression in this population, rates of detection and treatment are reported to be comparatively low, with only 50% of depressed patients being recognized as depressed and subsequently referred for treatment [Irwin *et al.*, 2008; Wilson *et al.*, 2007] While depression left unaddressed can seriously impact on patients' quality of life, recent evidence supports the efficacy of both pharmacological and psychological treatments in this setting [Rayner *et al.*, 2011; Price and Hotopf, 2009].

Older adults have among the highest rates of suicide for all age groups in the United States. Depressive symptoms and suicidal ideation are most likely to be reported to a primary care physician than to any other health care professional. In order to accurately assess suicidal ideation in older adults, the issue must be addressed directly by the primary care provider since older adults are less likely to report suicidal ideation spontaneously but are likely to be honest when asked [Heisel *et al.*, 2010; Cohen *et al.*, 2010]. It is also important to keep in mind that up to 50% of caregivers of older adults experience depressive symptoms as well [Ellison *et al.*, 2012].

Despite the fact that patients and providers may be reluctant to start antidepressant medications in older patients, these therapies have been shown to be safe and effective for older adults. Of older patients treated with antidepressants 50-65% will improve as a consequence of treatment [Mottram et al., 2006; Pinguart et al., 2006]. Serotonergic deficits are strongly associated with impulsecontrol disorders and aggression [Lesch and Merschdorf, 2000]. Similarly, agitation and aggression may be linked to serotonergic dysregulation observed in patients with Dementia of Alzheimer's Type [Sweet et al., 2001; Mintzer et al., 1998]. The selective serotonin reuptake inhibitors (SSRIs) are typically chosen as first line therapy because of their low side effect profile. As with all medication initiation in older adults, it is best to start at the lowest possible dose and titrate up slowly to an effective dose while monitoring for side effects and potential drug interactions. If the patient has not shown signs of improvement after four weeks on a therapeutic dose it is likely that medication will not be effective in controlling symptoms and another treatment plan should be undertaken. It is always reasonable to get a geriatric psychiatry or geriatrician consult if there are questions about response to treatment [Downing et al., 2013]. Although there is no comparable database on the safety of SSRIs in patients with dementia, SSRIs have been associated with a risk of hyponatremia, bleeding, and suicide attempts in older depressed patients [Dalton et al., 2006; Fabian et al., 2004; Juurlink et al., 2006].

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Treatment of psychotic symptoms

Psychotic symptoms such as hallucinations, delusions, and persistent misinterpretations are well-known comorbid features of AD, with a prevalence of around 40% [Ropacki and Jeste, 2005]. Psychotic symptoms have a tendency to persist throughout time [Ropacki and Jeste, 2005; Devanand *et al.*, 1997], and when they disappear, they reappear within one year in 95% of cases [Levy *et al.*, 1996]. Delusions and hallucinations do not behave in the same manner with respect to their temporal evolution; whereas delusions are persistent, hallucinations tend to terminate in a few months [Ballard and Howard, 2006].

The psychosis of AD (PoAD) is a process different from that of psychosis in schizophrenia in adults [Leroi et al., 2003]. Both functional and structural changes in the frontal, parietal, and temporal areas have been associated with certain psychotic symptoms [Bruen et al., 2008]. It is suggested that the presence of psychotic symptoms may not be caused by specific brain areas dysfunction (for example, increased dopamine activity in mesolimbic area as seen in schizophrenia), but due to a functional disequilibrium between different brain regions: interhemispheric or anterioreposterior. Other noncognitive symptoms, such as irritability, might be risk factors or first symptoms of PoAD, [Wilkosz et al., 2007]. Other studies based on neurochemical data point to dopaminergic deficits in dementia casting doubt about the rationale for using D2-blocking agents in these patients [Colloby et al., 2004].

The occurrence of psychosis during the course of dementia contributes to earlier institutionalization, faster cognitive and functional impairment, and increased caregiver's burden. Psychotic symptoms tend to decrease the quality of life of both the patient and the caregiver [Bassiony and Lyketsos, 2003; Scarmeas *et al.*, 2005]; and are often associated with other disruptive behaviors such as agitation and aggression [Rapoport *et al.*, 2001; Mizrahi *et al.*, 2006].

Psychopharmacology of psychosis of AD is very challenging. Among psychotropic medications, only antipsychotic agents show superiority over placebo for the treatment of psychosis and agitation-aggression in patients with dementia, although they are associated with only low-to-moderate efficacy [Schneider *et al.*, 2006; Maher *et al.*, 2011; Sultzer *et al.*, 2008]. Side effects of antipsychotic drugs include sedation, extrapyramidal signs, tardive dyskinesia, weight gain, and the metabolic syndrome [Jeste *et al.*, 2000; Zheng *et al.*, 2009]. An analysis combining data from 17 short-term trials involving patients with dementia showed that mortality among patients receiving antipsychotic medications was, on average, 1.6 to 1.7 times as high as that among patients receiving placebo. This finding led the FDA to require a black-box warning for these medications [Schneider *et al.*, 2005]. Some observational studies conducted in nursing homes have not shown increased mortality with the use of antipsychotic drugs in patients with dementia [Raivio *et al.*, 2007; Simoni-Wastila *et al.*, 2009; Chan *et al.*, 2011].

Even if antipsychotic drugs are effective, they are often discontinued because of concern about adverse effects and because of federal regulations that urge early discontinuation of antipsychotic drugs after three to six months of treatment [Shorr et al., 1994]. With some exceptions, [Horwitz et al., 1995; Ruths et al., 2004; Ballard et al., 2008] most trials of the discontinuation of antipsychotic drugs in patients with dementia [Fitz and Mallya, 1992; Avorn et al., 1992; Thapa et al., 1994; Bridges-Parlet et al., 1997; Cohen-Mansfield et al., 1999; Ballard et al., 2004] have not shown the reemergence of psychosis or agitation. Recent studies suggest that patients with psychosis or agitationaggression who have a sustained response to antipsychotic treatment for four to eight months have a significantly increased risk of relapse for at least four months after discontinuation. This finding should be weighed against the risk of adverse effects with continued antipsychotic treatment [Devanand et al., 2012].

Declercq and colleagues conducted an exhaustive review of literature studying the use of antipsychotic medication in dementia. They concluded that literature is skeptical about the use of antipsychotic agents to treat neuropsychiatric symptoms (NPS) in dementia. Their effectiveness is limited and there is concern about adverse effects, including higher mortality. Physicians, nurses and families of older people with dementia are often reluctant to try to stop antipsychotics, fearing deterioration of NPS. Strategies to reduce antipsychotic use have been proposed, but a systematic review of interventions aimed at withdrawal of antipsychotic agents in older people with dementia has not yet been performed. Many older people with Alzheimer's dementia and NPS can be withdrawn from chronic antipsychotic medication without detrimental effects on their behavior. However, people whose agitation or psychosis had previously responded well to antipsychotic treatment found an increased risk of relapse or shorter time to relapse after discontinuation. People with more severe NPS at baseline could benefit from continuing their antipsychotic medication. In these people, withdrawal might not be recommended. It is not known if there are beneficial

effects of withdrawal on intellectual processes, quality of life or ability to carry out daily tasks, or if the risk of harmful events is reduced by drug withdrawal. More research is needed to identify people for whom withdrawal is not indicated and risk of relapse should be weighed against the risk of adverse events with long-term antipsychotic treatment [Declercq *et al.*, 2013].

Ethical considerations

Communication, personalized care planning and advanced directives

Quality care at end-of-life is highly individual and should be achieved through a process of shared decision-making and clear communication that acknowledges the values and preferences of patients and their families. One of the key issues with dementia is that unless communication is initiated in the early stages of the disease, loss of cognitive function makes taking individual's views into consideration difficult, if not impossible, which in turn increases the emotional burden on carers [Steinhauser et al., 2000]. The time devoted to discussing advanced directives was associated with greater satisfaction with care for people with advanced dementia. In addition to formal advanced directives, there is also some evidence that advance care planning in general may help to address not only the needs of patients but those of family members [Engel et al., 2006]. The study of the attitude of physicians, nurses and relatives towards medical end-of-life decisions found that relatives attached more importance to advanced directives than physicians and concluded that end-of-life decisions should be communicated more openly [Rurup et al., 2006]. Currently, however, a conversation with patients and families about advanced care planning appears to occur late, if at all [Mast et al., 2004]. The advanced communication among patients, families and physicians facilitates informed decision-making on the basis of the patient's preference rather than on the basis of physicians' attitudes and values [Hinkka et al., 2004]. The need for improved, timely and appropriate communication has been, therefore, a key theme throughout the literature with many authors placing significant importance on its role and value in effective end-of-life planning for dementia [Ahronheim et al., 1996; Maguire et al., 1996; McCarthy et al., 1997; Morrison and Siu, 2000; Volicer, 2001; 2003; Hinkka et al., 2002; Lloyd-Williams and Payne, 2002; Michel et al., 2002].

Place of care

In a retrospective nationwide survey conducted to consider the characteristics of care in different settings for patients with terminal dementia across USA, of families whose relatives had died within a 12-month period, it was found that the end-of-life experience of individuals with dementia differed according to care settings. For example, if the patient was cared for at home during the last 90 days patient experienced fewer symptoms than those cared for in other areas [Volicer et al., 2003]. Other authors found that the majority of patients (up to 95%) end-up requiring 24-h care either in long-stay hospital wards or in nursing homes [Luchins and Hanrahan, 1993; Ahronheim et al., 2000]. Most patients with advanced dementia are treated in nursing homes, but when acute illness supervenes, they are often transferred to hospitals, where they are at risk of receiving invasive or uncomfortable non-palliative interventions [Ahronheim et al., 1996]. For example, even though the immediate cause of death recorded by autopsy in dementia patients was pneumonia [McCarthy et al., 1997], the hospitalization for pneumonia does not seem to improve outcome in nursing home patients and death and functional deterioration had been reported to be more frequent in hospitalized patients than in patients treated in nursing homes. It is perhaps with this in mind, consideration should be given to the most appropriate place in which to provide palliative care [Fried et al., 1997]. One way to achieve this is if hospitals with expertise in care at the end-of-life share their knowledge with the referring nursing homes to share the principles of best practice [Campbell and Guzman, 2004]. The gaps in professional knowledge, skills and expertise, provide an opportunity to cross-fertilize the fields of dementia care for the benefit of all concerned [Burgess, 2004]. Hospital palliative care teams, through offering specialist advice, can improve the care of many non-cancer patients [Kite et al., 1999].

Medical interventions

In a large comparative quantitative study of patients with dementia and cancer, it was found that the most frequent symptoms reported for dementia patients in the last year of life were: mental confusion (83%), urinary incontinence (72%), pain (64%), low mood (61%), constipation (59%) and loss of appetite (57%). Although the number of reported symptoms dementia and cancer patients experienced was similar, there were differences between the two groups with respect to the frequency of the symptoms, with dementia patients experiencing symptoms for longer [McCarthy *et al.*,

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1997]. There is significant evidence of older people with end-stage dementia having poor pain control, feeding tubes inserted [Sachs et al., 2004] and inappropriate treatments such as restraints and laboratory tests [Mitchell et al., 2004a]. During the previous six months of patients' life with and without dementia, use of systemic antibiotics was prevalent in the treatment of patients with end-stage dementia (53%) [Evers et al., 2002] despite the limited utility and associated discomfort [Morrison and Siu, 2000]. The possible reasons for the high prevalence of antibiotic treatment include a lack of advance directives, inadequate training of physicians in discussing end-of-life decisions and prognostic uncertainty about the course of the disease [Evers et al., 2002]. These findings confirm the aggressive nature of treatment of dementia sufferers reported in other studies [Fabiszewski et al., 1990]. There is much debate, therefore, concerning the appropriateness of medical interventions for dementia patients, with substantial evidence that an aggressive medical approach is of limited efficacy [Ahronheim et al., 1996; Lloyd-Williams, 1996; Morrison and Siu, 2000; Volicer, 2001; Evers et al., 2002; Hinkka et al., 2002; Sampson et al., 2006b]. Endstage dementia has been associated with a poor prognosis and a limited life expectancy, which are not improved by invasive procedures [Morrison and Siu, 2000; Evers et al., 2002].

The futility and discomfort of aggressive treatments, combined with the under-recognition and under-treatment of pain and other symptoms among patients with severe dementia, supports the use of palliative care approaches for this patient group [Evers et al., 2002]. Knowing that we cannot cure or arrest the progression of most dementias, palliative care or providing comfort and good quality-oflife for individuals with this diagnosis should be therefore the treatment priority [Head, 2003]. Several studies have emphasized the need for implementing good palliative care for patients with dementia and that palliation of symptoms leads to improved comfort and quality of life [Fabiszewski et al., 1990; Luchins and Hanrahan, 1993]. One example is the Liverpool Care Pathway, which focuses on the specific needs of each patient and their family, to ensure that symptoms are assessed, managed and monitored systematically in accordance with evidence-based guidelines [Ellershaw and Wilkinson, 2003].

Prognostic indicators of 6-month mortality in dementia patients

Individual prognostic indicators and prognosticator scales

Prognostication is a complex and challenging task that relies

primarily on clinical judgment [Von Genten and Twaddle, 1996; Coventry et al., 2005]. Identified prognosticators of sixmonth mortality varied greatly between studies. However, at least one factor relating to nutrition, nourishment, and/ or eating habits was identified as a significant prognostic indicator in all studies, including decreased appetite [Luchins et al., 1997], insufficient food intake [Mitchell et al., 2004b; 2010], malnutrition [Zvi Aminoff 2008; Aminoff and Adunsky, 2006], and weight loss [Marsh et al., 2000; Mitchell 2010; Schonwetter et al., 2003]. Anorexia was strongly and significantly associated with increased mortality within six months in multiple studies [Zvi Aminoff, 2008; Aminoff and Adunsky, 2006; Schonwetter et al., 2003] and dry mouth, which impairs the ability to swallow, was found to be significantly associated with nearly doubled risk of mortality [Schonwetter et al., 2003].

Increased risk score on a dementia rating scale, such as the FAST, Mitchell Novel Risk Score (MDS/Mitchell score), and the Advanced Dementia Prognostic Tool (ADEPT) scales was a commonly identified risk factor in majority of the literature [Zvi Aminoff, 2008; Aminoff and Adunsky, 2006; Luchins *et al.*, 1997; Marsh, *et al.*, 2000; Mitchell *et al.*, 2004b; 2010]. Mini-Suffering State Examination (MSSE) scale might be particularly associated with increased mortality within six months [Zvi Aminoff, 2008; Aminoff and Adunsky, 2006].

The presence of one or more comorbid conditions, including cancer and heart failure, was also identified as a significant prognosticator in majority of the literature [Zvi Aminoff, 2008; Aminoff and Adunsky, 2006; Luchins et al., 1997; Mitchell et al., 2004b; 2010; Schonwetter et al., 2003]. Furthermore, comorbidities were especially indicative of decline if more than one was present [Luchins et al., 1997; Mitchell et al., 2004b; Schonwetter et al., 2003]. Unstable medical condition [Zvi Aminoff, 2008; Aminoff and Adunsky, 2006; Mitchell et al., 2004b; 2010] and impaired mobility are also significant prognosticators [Luchins et al., 1997; Marsh, et al., 2000; Mitchell et al., 2004b; 2010]. A majority of the literature also identified measures of functional or cognitive impairment as a significant prognostic indicator for six-month mortality; [Zvi Aminoff, 2008; Aminoff and Adunsky, 2006; Luchins et al., 1997; Marsh et al., 2000; Mitchell et al., 2004b; 2010; Schonwetter et al., 2003]. Decreased activities of daily living scores were strongly and significantly associated with increased mortality. A definition of "not awake most of the day" was also identified as an associated risk factor [Mitchell et al., 2004b]

Other prognostic markers identified in the literature

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included speech and language deficits [Luchins *et al.*, 1997; Marsh, *et al.*, 2000], hematological indices (hemoglobin, cholesterol, and total protein levels) and signs of suffering (screams and pain). Finally, the type of dementia was not found to be a significant indicator of six-month mortality for end-stage patients in any of the studies [Zvi Aminoff, 2008; Aminoff and Adunsky, 2006].

Current dementia mortality prognosticator guidelines

In the United States, where five of the studies included in this review were set, access to end-of-life care in the hospice setting is restricted to patients with a medically demonstrated prognosis of six months or less [National Council for Palliative Care, 2005].

Current National Hospice Palliative Care Organization (NHPCO) guidelines for assessing the eligibility of endstage dementia patients for hospice care via Medicare benefits require: (I) sufficient dementia severity and (II) the occurrence of medical complications. Dementia severity is assessed using the FAST scale, and patients qualify for hospice admission when dementia severity surpasses stage 7c [National Hospice Organization, 1996]. In contrast, in the United Kingdom, the Gold Standards Framework (GSF) does not promote the development of care focused on time remaining but instead promotes planning and anticipation of worst-case scenarios in order to promote care driven by patient preferences. The GSF prognostic guidelines (which are widely used but have not been prospectively validated) aim to identify patients in the last 6-12 months of life, with the ABCD register classifying prognosis on a scale of years, months, weeks, or days, and this status is reviewed monthly [National Gold Standards, 2012].

While most studies supported inclusion of a measure of dementia severity as a six-month prognosticator of mortality [Zvi Aminoff, 2008; Aminoff and Adunsky, 2006; Luchins *et al.*, 1997; Marsh *et al.*, 2000; Mitchell *et al.*, 2004b; 2010a], there was no consensus on the best scale to use. With one exception [Luchins *et al.*, 1997] all the studies in this review found that the FAST 7c criterion currently used in the United States was not a reliable predictor of six-month mortality [Zvi Aminoff, 2008; Aminoff and Adunsky, 2006, Marsh *et al.*, 2000; Mitchell *et al.*, 2004b; 2010; Schonwetter *et al.*, 2003]. One limitation of the FAST scale is that it assumes an ordinal disease progression and therefore excludes all dementia patients whose disease progression is nonlinear [Luchins *et al.*, 1997]. Particularly, this may exclude patients with comorbidities, who may skip stages as a result of secondary illnesses Schonwetter *et al.*, 2003]. Furthermore, FAST may not be valid for patients with non-Alzheimer dementia [Reisberg *et al.*, 1996]. The ADEPT scale was found to perform moderately as a prognosticator for six-month mortality, with high interrater reliability, good calibration, modest discrimination, and high sensitivity (>90%), although low specificity (30%). Furthermore, when compared to the ADEPT scale, the US Medicare hospice eligibility guidelines were found to have poor discrimination [Mitchell *et al.*, 2010]. The MSSE scale was found to be particularly associated with increased mortality within six months, and studies have reported MMSE to have high specificity, but low sensitivity, especially with non-Alzheimer dementias [Zvi Aminoff, 2008; Meulen *et al.*, 2004].

The findings also support the inclusion of a nutritional prognosticator into current guidelines. Anorexia was the most commonly cited prognosticator in the nutrition, nourishment, and eating category [Zvi Aminoff, 2008; Aminoff and Adunsky, 2006; Schonwetter et al., 2003]. However, anorexia may actually be a general risk factor for mortality, not specific to advanced dementia. Although the FAST scale used in current NHPCO prognosticator guidelines includes assessment of weight loss, which indirectly considers nutritional variables, the development of a separate prognostic scale for the assessment of nutritional variables in addition to a functional scale may increase prognosticator sensitivity. Since the methods used to assess nutrition varied widely between the studiesranging between assessment of daily food consumption [Mitchell et al., 2004b; 2010], weight loss Schonwetter et al., 2003], and malnutrition [Aminoff and Adunsky, 2006]future studies should compare the prognostic value of these measures of nutrition to determine the most clinically relevant nutritional prognostic indicator.

Some prognosticators that may prove useful, such as speech and language deficiencies, hematological indices, and signs of suffering, were not consistently evaluated throughout the literature. Therefore, it is difficult to determine their usefulness as potential prognosticators. Future studies should consider including these measures to conclusively evaluate their prognostic value.

Generalization of identified prognosticators

When establishing prognostic criteria that affect the level of care universally available to patients, special consideration needs to be taken to ensure that findings are translatable to

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all groups. Most of the studies are set in institutionalized care, whether hospice or other with one exception [Luchins et al., 1997], which included one cohort, set in home hospice care. None of the studies, to our knowledge examined cohorts based in community settings. While focusing on institutionalized care is practical in the context of assessing governmental standards that are only applied to medical and long-term care institutions, researchers must not ignore the reality of patients who continue to live in their own homes in the community, which may be very different from that in the medical or institutional care settings. The progression of disease may differ in a community setting, and palliative care may begin earlier and last longer than in the medical setting. Furthermore, to our knowledge there are no studies comparing findings across health-care systems (private as in USA vs. universal as in Canada and United Kingdom) [Brown et al., 2013].

End of life and cause of death

Cachexia/dehydration, cardiovascular disorders, and acute pulmonary diseases such as pneumonia were the most important immediate causes of death in the studied sample of Dutch nursing home patients with dementia. Dementia was not listed as an immediate cause of death. Comparing causes of death of patients who survive until the final phase of dementia with those who die before reaching that phase, cachexia/dehydration appeared a more frequent cause of death of patients who survived to the final phase (53.2% vs. 32.2%). Furthermore, survival to the final phase of dementia was an independent predictor of cachexia/ dehydration as a cause of death.

In Dutch practice, explicit communication on hastening of death is possible without fear of litigation [Bosshard G et al., 2005; van der Steen et al., 2005]. Dutch residents with severe dementia and pneumonia are rarely hospitalized or treated with rehydration therapy, are more frequently treated with simple oral antibiotics, and antibiotics are more frequently withheld compared with US residents [Mehr et al., 2003; van der Steen et al., 2004]. Despite higher rates of dehydration and insufficient fluid intake, feeding tubes are rare in Dutch practice while commonly provided to US patients with severe dementia [Mehr et al., 2003; van der Steen et al., 2004. Of demented US nursing home patients, 16.7% was tube-fed [Mitchell and Kiely, 2001], and care at the end of life in general is more aggressive in the US [Mitchell et al., 2004a; Lamberg et al., 2005]. Different practice is related to different organization of care, with Dutch nursing home physicians

being on-staff and specially trained in complex medical-ethical dilemmas, palliative care, and moral problems, providing ample opportunity for starting with advance care planning upon admission [Hoek *et al.*, 2001; Pasman *et al.*, 2004].

Caregiver health

The number of family members providing informal unpaid (i.e., non-professional or family) caregiving to individuals with dementia continues to increase [National Alliance for Caregiving and AARP, 2004]. The length of time an informal caregiver spends caring for the patient is significant. According to the National Alliance for Caregiving and AARP [2004], the average caregiver serves in their caregiving capacity for 4.3 years. Caregivers of people with AD and other dementias provide more hours of help, on average, than caregivers of other older people and serve in their caregiving role for longer periods of time [Ornstein et al., 2013]. While these informal (unpaid) caregivers provide a critical service to family members in lieu of formal sources of long-term care, they often suffer from chronic stress which results in negative consequences for the caregiver's mental and physical health [Aneshensel et al., 1995; Pinquart and Sorensen, 2003]. Family members of palliative care patients also represent a high-risk group for psychiatric disorders, [Pitcheathly and Maguire, 2003] vet research indicates they too often do not receive the support needed from professional care services [Proot et al., 2003].

Existing dementia caregiving research points to the critical role of timing in understanding the stress process and informal caregiver outcomes. For example, age of onset of dementia is inversely associated with time to nursing home placement [Stern *et al.*, 1997]. In addition, low resilience early in the caregiving career was associated with relinquishing the caregiver role at three years follow-up, suggesting that the caregiver's experience earlier in the patient's illness may be predictive of later outcomes [Gaugler *et al.*, 2007]. Together, these findings suggest that challenges that occur early in the caregiving career when signs of illness first appear may have lasting impact for the caregivers over the course of the patient's illness.

Although cognitive decline is considered the clinical hallmark of dementia, an extensive body of literature suggests that BPSD are particularly burdensome to caregivers and may eventually lead to decisions to institutionalize patients [Black and Almeida, 2004]. Severe behavioral symptoms early in caregiving were independent predictors of increased burden and depression over three years regardless of later BPSD development [Gaugler *et al.*, 2005]. Although the literature is not consistent as to which individual behavioral symptoms result in most depressive symptoms for caregivers [Ornstein and Gaugler, 2012], the negative impact of patient's aggression and agitation on caregivers is well documented [Covinsky *et al.*, 2003].

Future directions

Designing and testing interventions that promote highquality, goal-directed care across health care settings will be a cornerstone for future research in advanced dementia. An example of such a study would be an RCT (randomized clinical trial) of an intervention to avoid unwanted hospitalizations of nursing home residents with advanced dementia whose goals of care are primarily comfort. Interventions that reduce disparities in the quality of care provided to patients with advanced dementia who are of various ethnic and racial backgrounds are also needed. Clinical trials in advanced dementia, while essential, will not be straightforward to conduct; interventions are often complex, settings are not well suited to research (for example, nursing homes), and outcomes are challenging to define and measure. Nonetheless, the success of prior RCTs that faced similar challenges demonstrates that these hurdles can be overcome [Hanson et al., 2011; Loeb et al., 2006; Volandes et al., 2009; Loeb et al., 2005].

Health policy research is essential to move advanced dementia care forward. A primary goal of this research should be to identify policies that incentivize cost-effective and evidence-based care without comprising the quality of palliative care provided to these vulnerable patients. The Patient Protection and Affordable Care Act presents a timely opportunity for demonstration projects that evaluate alternative financial structures to reduce unwarranted and unwanted hospitalizations for nursing home residents with advanced dementia, such as bundled payments or capitated programs, similar to the Program of All Inclusive Care for the Elderly (which integrates Medicare and Medicaid financing for frail elderly patients) [Ouslander and Berenson, 2011]. Expanding access to the Medicare hospice benefit and broad-based palliative care programs is a key part of the equation. For example, prior work clearly shows that the six-month hospice eligibility guidelines are problematic [Mitchell et al., 2010]. Thus, research that explores novel approaches to enroll dementia patients into hospice is warranted. Comparative effectiveness research that evaluates different strategies to treat common complications (such as

pneumonia) would also inform policy [Mitchell et al., 2012].

Another area relates to development of new technologies, which so far has primarily addressed the use of assistive devices for physical disability, typically in younger adults, and not the cognitive, functional, and behavioral sequelae of dementia. A host of cognitive aids, environmental sensors, video and audio technologies, and advanced integrated sensor systems are under development to monitor the health, safety, and well-being of cognitively and/or functionally impaired persons [LoPresti et al., 2004; Pew and van Hemel, 2004]. These technologies with continued research will find applications in dementia care. It has been estimated that a one-month delay in nursing home placement of all Americans older than 65 years would reduce healthcare expenditures by \$1.2 billion annually [Johnson et al., 2000]. Remote mobile health monitoring, is predicted to be the next major wave in the reform of healthcare delivery systems, and honors the oft-stated preference of the elderly to remain independent for as long as possible, even in the face of increasing disability [Dishman et al., 2004].

Summary

Dementia is a terminal illness with protracted course. The treatment modalities change with the stage of the disease. This is further complicated with tremendous caregiver burden, complex ethical issues and difficult prognostication of six month mortality. There is lack of evidence of the efficacy of high end costly treatment interventions. Providing patient and family with education and support at every stage of the disease is very valuable. Understanding of the fact that dementia is a terminal illness and applying the principles of palliative care help make rational decisions throughout the course of the illness. This is as much as an art as it is a science.

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Encephalopathy

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Introduction

Encephalopathy is a general or global brain malfunction in the setting of systemic disorder and in the absence of primary structural brain disease. The systemic disorders that bring about such cerebral dysfunction are diverse, ranging from failure of organs other than the nervous system, to electrolyte imbalances, to life-threatening infections, to exposure and buildup of toxic substances, and many more. Encephalopathy typically arises in an acute fashion, although subacute and chronic variants have been reported. Most cases are reversed once the precipitating noxious agent or disease process is resolved.

Managing encephalopathy poses multiple challenges to the clinician. Prompt diagnosis is not readily accomplished owing to the disease's diverse presentation and broad differential diagnosis. The instigating condition may not always be amenable to effective treatment. It carries substantial impact on prognosis, and bears implications extending beyond the patient. This chapter will discuss the clinical characteristics of encephalopathy in adults, detail its specific causes, and describe management strategies. Since patients suffering from encephalopathy are those with serious illnesses and often critically ill, the need for high quality palliative care is recognized and will be highlighted in this chapter.

Delirium vs. encephalopathy

The term encephalopathy is often associated, even used interchangeably, with conditions such as altered mental status, delirium, and acute confusional state. Literally meaning "disease of the brain", encephalopathy is an important and more encompassing disease entity that deserves clinical distinction. Not to be considered synonymous with delirium,

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encephalopathy is the clinical manifestations of widespread failure of cerebral metabolism often due to an underlying systemic cause [Lipowski, 1990]. Whereas delirium is characterized by acute onset inattention, disorganized behavior, and disturbances in cognition and consciousness occurring in a fluctuating manner, the manifestations of encephalopathy extend beyond deranged consciousness and awareness. A wide array of focal neurologic signs, including seizures, may be seen, therefore making delirium a mere, albeit compulsory, component of encephalopathy [Zampieri *et al.*, 2011]. To further differentiate the two conditions in terms of coding, delirium is classified as a mental disorder or as a symptom, while encephalopathy is a specific neurologic diagnosis that identifies toxic and metabolic states affecting the brain [Pinson, 2010].

Epidemiology

Of the myriad causes of encephalopathy in adults, the forms that are associated with sepsis and hepatic failure are frequently encountered in practice. Usually seen in intensive care unit (ICU) patients, sepsis-associated encephalopathy occurs in up to 70% of patients with severe systemic infection [Gofton and Young, 2012]. Hepatic encephalopathy, in turn, occurs in about 60% to 80% of patients with cirrhosis [Bajaj, 2010]. Data pertaining to the incidence of other causes of encephalopathy have not been as widely reported.

It is worth mentioning that delirium is quite prevalent in both critically and terminally ill patients. One can surmise that delirium in these subsets of patients may actually be a component of encephalopathy given the severity of systemic impairments that they are burdened with. Pertinent incidence 466

Metabolic- and	Hypoxia-Ischemia
endocrine-related	Hypercapnia
	Hypoglycemia
	Hyperglycemia
	Hypothyroidism
	Hyperthyroidism
	Wernicke's
Related to electrolyte disturbance	Hyponatremia
	Hypernatremia
	Hypocalcemia
	Hypercalcemia
	Hypomagnesemia
Related to organ failure and other systemic diseases	Hepatic
	Uremic
	Autoimmune
	Paraneoplastic
	Hypertensive
	Pancreatic
Infection-related	Sepsis-associated
	Human immunodeficiency virus (HIV)
	Other viruses and bacteria
Drug- and toxin-related	Chemotherapy
	Other drugs
	Metals
	Industrial agents
	Pesticides
	Carbon monoxide

estimates of delirium in various clinical scenarios are as follows: 80% of mechanically ventilated patients in an ICU [Pun and Ely, 2007], 60% to 80% of patients in a medical ICU [Ely et al., 2001], 10% to 31% in medical inpatients [Siddiqi et al., 2006], 37% to 46% in the general surgical population [Dyer et al., 1995], and 26% to 44% of cancer patients admitted to hospital or hospice [Centeno et al., 2004].

Mechanisms of brain dysfunction

A common pathway leading to brain dysfunction is disruption of the ascending reticular activating system (ARAS), which regulates arousal, sleep-wake transition, and attention. This key structure consists of multiple pathways ascending from the mesopontine tegmentum to the basal In the case of drug-induced encephalopathy, particularly the type associated with chemotherapeutic agents, the risk increases when the blood brain barrier is either overwhelmed by a high systemic dose or intracarotid infusion, or bypassed by intrathecal administration [Hildebrand, 2006]. Additional risk factors include: frequent chemotherapy administration and concurrent radiotherapy, which is typically seen with methotrexate [Verstappen et al., 2003].

et al., 1996]. Patients with existing liver disease, such as cirrhosis, develop hepatic encephalopathy when faced with stressful circumstances such as infection, dehydration, surgery,

The blood brain barrier protects the central nervous system (CNS) from harmful effects of drugs and toxins.

electrolyte disturbance, and hemorrhage.

As delirium is intimately linked with encephalopathy, the two entities share several common risk factors as described by Maldonado [Maldonado, 2008]. These are: age greater than 75 years, severe illness (infections, hypotension, hypoxia, malnutrition, and metabolic disorders), and exogenous substances (polypharmacy, psychoactive medications, substance abuse and withdrawal, heavy metal poisoning, and toxins).

Encephalopathy

forebrain, thalamus, and cerebral cortex. Any one of the Table 1 Causes of encephalopathy specific causes of encephalopathy in adults listed in Table 1 can interfere with the ARAS and/or its projections resulting in an impaired mental state. The exact mechanism leading to encephalopathy is unknown, but several pathophysiologic processes have been proposed. Neurons, due to their high lipid content and high metabolism, are susceptible to damage and destruction during hypoxic-ischemic states and by toxins and drug metabolites. Electrolyte disturbance, metabolic substrate excess and deficiency, and excitatory and inhibitory neurotransmitter imbalance can all derange the local neuronal environment resulting in brain malfunction. Systemic illnesses, as exemplified by sepsis, can attack the brain through multiple adverse mechanisms, such as direct cellular damage, mitochondrial and endothelial dysfunction, derangement of calcium homeostasis, and compromised cerebral blood flow. **Risk factors** In general, the risk for developing encephalopathy increases as the severity of underlying illness escalates. In sepsis-associated encephalopathy, for instance, known risk factors include: worsening renal failure, increasing bilirubin level, need for mechanical ventilation, and increasing Acute Physiology and Chronic Health Evaluation II (APACHE II) score [Eidelman

Clinical features

Signs and symptoms

Although the presentation of patients with encephalopathy is often diverse, the one manifestation that is constant is altered mental status. Early symptoms to watch out for include: disturbance in arousal or the degree of sensory stimulation necessary for the patient to appropriately respond to clinician questioning. About a quarter of patients will either be hyperaroused or hypoaroused, and half will fluctuate between the two states [Posner *et al.*, 2007]. Disorientation, visual or combined visual and auditory hallucinations, sleep/wake cycle alteration, and disturbance in attention and concentration are also noted early on. The delirium symptoms subsequently worsen and deteriorate into stupor and coma as the degree of cerebral dysfunction worsens.

Aside from deficits in awareness and cognition, other neurological deficits are usually present in encephalopathy. Focal weakness is not uncommonly appreciated with metabolic encephalopathy [Posner *et al.*, 2007]. Frontal release signs or primitive reflexes (e.g., suck, snout, palmomental, and palmar grasp reflexes) may be elicited. Cerebellar injury due to toxins can manifest with ataxia and poor balance. Cortical blindness may arise from exposure to mercury, interferon and vincristine [Dobbs, 2011]. Bilateral trigeminal palsies are seen in trichloroethylene encephalopathy, and peripheral neuropathy may accompany both lead and arsenic encephalopathy. Seizures, either focal or generalized, may occur in toxic and metabolic encephalopathies, and differ from that found in structural brain disease in that the focus typically migrates from episode to episode.

Other prominent findings on neurological examination are tremors, asterixis, and myoclonus. The tremor seen in metabolic encephalopathy is characterized as coarse, irregular, usually absent at rest, first noted in the fingers of the outstretched hand, and may eventually spread to the face, tongue, and lower extremities. Asterixis, or palmar flapping movement of the outstretched hands, is classically seen in hepatic encephalopathy, but may also be elicited in other forms of metabolic encephalopathy, as well as in sepsis-associated encephalopathy. Multifocal myoclonus (sudden, nonrhythmic twitching of muscles in different parts of the body) is usually associated with encephalopathy caused by uremia and hyperglycemia.

Outside of the neurological examination, looking for signs and symptoms of an underlying illness precipitating encephalopathy may lead to prompter diagnosis. Signs of chronic liver disease, such as clubbing, palmar erythema, jaundice, ascites, spider angiomata, caput medusa (i.e., engorged periumbilical veins), gynecomastia, and testicular atrophy, support a diagnosis of hepatic encephalopathy in a patient presenting with altered mental status. Bluish gum discoloration may accompany mental status derangement in lead encephalopathy, as do Mees lines (i.e., white lines running across the width of fingernails and toenails) seen in some metallic (e.g., arsenic and thallium) and chemotherapy intoxication, and gastrointestinal symptoms in lead as well as arsenic poisoning. Autonomic signs, such as hypertension, hypotension, tachycardia and fever, as well as respiratory abnormalities, such as Cheyne-Stokes respiration (i.e., pattern of deeper and faster breathing followed by periods of apnea), are frequently noted in the setting of severe systemic disease. Hypertension is the most prominent nonneurologic finding in posterior reversible encephalopathy syndrome (PRES).

The neurologic manifestations of the various causes of encephalopathy are further elaborated in the specific sections below.

Neuroimaging and electroencephalogram (EEG)

Neuroimaging, such as computed tomography (CT) and magnetic resonance imaging (MRI), is primarily utilized to exclude other causes, mainly structural brain disease, of altered awareness and cognition. The most common finding among patients with toxic and metabolic encephalopathy is brain edema. In the case of PRES, white matter edema along with hyperintense lesions on T2/FLAIR usually in the parieto-occipital region, are crucial diagnostic clues.

The electroencephalogram (EEG) has greater utility in the management of acute encephalopathy compared to neuroimaging. The usual pattern seen is a non-epileptiform disturbance, such as slowing of background activity with or without presence of triphasic waves and frontal intermittent rhythmic delta activity. Specific EEG patterns have been linked to differing outcomes among patients with encephalopathy and will be discussed in the next section.

Differential diagnosis

Due to its wide-ranging presentation, chief of which is altered mental status, the differential diagnosis for encephalopathy is quite broad. A caveat worth mentioning is that encephalopathy in a critically ill patient can result from different causes, which can be intertwined, worsened or masked by each other. Consider a patient with underlying liver disease who develops a severe infection and subsequent renal failure. When consciousness falters and other neurologic symptoms become apparent, the precipitant of encephalopathy for this challenging case can either lie in the intersection of or be one of the following: hepatic, uremic, sepsis-associated. It is therefore incumbent upon the clinician to obtain and perform a thorough history and physical examination, focused on the chronology of manifestations and supported by laboratory findings, in order to ascertain the true cause or causes of encephalopathy and institute the most appropriate treatment.

A foremost aspect of differentiation is deranged mental status due to structural brain disease (e.g., brain tumor or infarct) as opposed to a metabolic cause. Neuroimaging can often facilitate this task with ease, but several clinical features can be considered. Patients with metabolic encephalopathy exhibit diffuse motor signs, such as tremors, multifocal myoclonus and bilateral asterixis, and generally slow EEG [Posner *et al.*, 2007]. In contrast, focal and unilateral signs are seen in structural disease. In addition, patients with metabolic brain disease do not assume the typical rostral-caudal deterioration and regionally restricted defects displayed by patients with structural disease.

Psychogenic diseases need to be distinguished from encephalopathy. Patients suffering from severe depression, anxiety, mania, and psychosis may present with deranged awareness. They are differentiated from encephalopathy by the absence of abnormal reflexes and involuntary movements, ability to remain oriented or retain new information, and normal EEG pattern.

Other important diseases that serve as differential diagnosis for acute encephalopathy include CNS infections (e.g., meningitis and encephalitis), CNS neoplasms (i.e., primary and metastatic), CNS vasculitis, multiple sclerosis, acute disseminated encephalomyelitis, sarcoidosis, neuropsychiatric systemic lupus erythematosus, nonconvulsive status epilepticus, alcohol withdrawal, drug withdrawal (e.g., benzodiazepines), and air embolism. Autoimmune encephalopathy presents with either rapidly progressive or chronic progressive cognitive decline [Flanagan and Caselli, 2011]. The former can be mistaken for Creutzfeldt-Jakob disease, and the latter for Alzheimer's disease and frontotemporal dementia.

Management

General considerations

The history, physical, and neurological examination remain

the best tool to determine the exact cause of encephalopathy that the clinician is faced with. Laboratory tests are necessary to confirm specific etiologies such as encephalopathies related to electrolyte disturbances, hyperglycemia or hypoglycemia, thyroid dysfunction, hepatic and renal failure, autoimmune and paraneoplastic conditions, and toxins, especially metals. Cerebrospinal fluid studies may be helpful in excluding an infection or neoplasm. As mentioned above, the purpose of neuroimaging is to identify other causes of altered mentation. EEG, on the other hand, is done not only to detect the characteristic pattern associated with encephalopathy, but also to rule out seizure disorder, especially nonconvulsive status epilepticus, as a cause of impaired consciousness.

The primary therapeutic objective is to treat the underlying cause of encephalopathy. This may entail correcting the particular electrolyte abnormality, treating the inciting infection, managing hepatic and renal failure, stopping the offending drug, ridding the body of a certain toxin, and replacing deficient metabolic substrates. Management strategies specific to the cause of encephalopathy are detailed below.

Prognosis

While most forms of encephalopathy are reversible following effective treatment of the underlying cause, some forms may bring forth a poor prognosis. A recent international multicenter study done by Salluh et al. revealed that delirium was associated with both increased ICU and hospital mortality and hospital length of stay [Salluh et al., 2010]. Sepsis-associated encephalopathy carries a similarly poor prognosis. It has been estimated that mortality is approximately 70% in patients with severe sepsis-associated encephalopathy and is due to multiorgan failure rather than neurological complications [Gofton and Young, 2012]. An important study by Eidelman et al. linked mortality from sepsis-associated encephalopathy to the Glasgow Coma Score (GCS) [Eidelman et al., 1996]. Patients with a GCS of 15 had 16% mortality, while patients' mortality with a score of less than eight jumped to 63%. Another relevant study done by Sutter et al. examined the correlation between EEG pattern and outcomes in 154 patients with acute encephalopathy. The investigators determined that the presence of a theta/ delta pattern was associated with unfavorable outcome (i.e., Glasgow Outcome Score 1-3), patterns with triphasic waves were linked to high odds for death, and those containing frontal intermittent delta activity were associated with favorable outcomes (i.e., Glasgow Outcome Score >3) and

high odds of being discharged home [Sutter et al., 2013].

Regarding the other types of encephalopathy, the seminal study by Levy and colleagues revealed that only 13% of 210 patients were able to regain independent function within the first year following hypoxic-ischemic encephalopathy [Levy *et al.*, 1985]. The poor prognostic factors that the investigators identified were absent pupillary light reflexes and motor responses, and non-orienting as well as non-roving conjugate spontaneous eye movements. Hypoglycemic encephalopathy is likewise associated with a high mortality, which was 46% in one study [Witsch *et al.*, 2012]. Hospitalized patients suffering from overt hepatic encephalopathy have a 3.9-fold increased risk of dying [Chacko and Sigal, 2013].

Palliative care

Larson and Curtis detailed a need for good-quality palliative care in patients suffering from end-stage liver disease due to their symptom burden and risk of death [Larson and Curtis, 2006]. This need similarly applies to most types of encephalopathy, especially as the clinical course progresses to the point of non-reversibility. There is a call for optimal management of symptoms that may be present, such as pain, nausea, dyspnea, and agitation. More importantly, intimate discussions about goals of care and end-of-life issues will have to be anticipated.

Encephalopathy impairs the patient's ability to communicate. The clinician is, therefore, compelled to recruit trusted friends and family members to actively participate in the patient's care. Apart from impaired cognition, patients with encephalopathy will subsequently lose their independence and further deteriorate in health; hence, caregivers will inevitably play a vital role. A relationship built on trust and openness involving the clinician, patient, and caregivers is essential in providing the most appropriate care throughout the course of both the encephalopathy and underlying illness.

It is prudent to foresee the patient eventually losing decision-making capacity, therefore, advance care planning in the form of completing a living will and assigning a durable power of attorney for healthcare needs to be pursued as early in the disease trajectory as possible. In addition, the clinician has to be adept at breaking bad news, providing prognostic information, refocusing hope, and advocating for de-escalation of care, including changing code status to Do Not Resuscitate (DNR) when life expectancy becomes severely limited.

Specific causes of encephalopathy

Metabolic- or endocrine-related

Hypoxia-ischemia

Critical loss of oxygen and blood flow to the brain results in neuronal necrosis, cytotoxic edema, and release of harmful agents, such as lactic acid, glutamate, proteases, nucleases, and nitric oxide [Greer, 2006]. The clinical circumstances that may lead to this detrimental deficiency are as follows: (I) global reduction in cerebral blood flow (myocardial infarction, ventricular arrhythmia, aortic dissection, hemorrhage, and shock); (II) hypoxia from suffocation (drowning, strangulation, aspiration, and tracheal obstruction or compression); (III) diseases that cause respiratory muscle paralysis (Guillaine-Barre syndrome, amyotropic lateralizing sclerosis, and myasthenia gravis); and (IV) non-ischemic hypoxia from carbon monoxide poisoning (see below) [Samuels, 2009]. It is interesting to note that the specific brain insult, whether hypoxic or ischemic, is often complementary and non-distinguishable; therefore, the term "hypoxic-ischemic" is usually applied.

In mild cases, inattentiveness, poor judgment, and incoordination are observed. In most cases, however, coma ensues and recovery, which is dependent on the duration of hypoperfusion, varies from full recovery, to some degree of cognitive impairment, to a persistent vegetative state. Cases of delayed postanoxic encephalopathy have been described, and are generally characterized by complete recovery followed by a relapse of neurologic deficits, confusion, and agitation [Custodio and Basford, 2004]. Induced hypothermia is the widely accepted intervention done to prevent poor neurological outcome. Other controversial strategies include: thrombolysis, induced hypertension, and the use of neuroprotective agents, such as barbiturates, calcium channel blockers, benzodiazepines, and immunosuppressants [Greer, 2006].

Hypercapnia

Hypercapnic encephalopathy is the end result of persistent respiratory acidosis, elevated carbon dioxide levels (PaCO₂), and reduced oxygen levels (PaO₂). Conditions that give rise to hypercapnia include: chronic obstructive pulmonary disease (COPD), fibrotic lung disease, neuromuscular weakness, and impaired central respiratory center. Clinical manifestations consist of headaches, intermittent drowsiness, inattentiveness, papilledema, asterixis, confusion, stupor, and coma.

The goals of treatment are close monitoring, adequate management of the precipitating condition, airway

protection, and positive pressure ventilation to correct gas exchange and deranged mental status. Conventional mechanical ventilation remains the "gold standard" strategy for providing positive pressure ventilation. The role of noninvasive positive pressure ventilation (e.g., CPAP, BiPAP) remains controversial because of questionable compliance by agitated patients and risk of aspiration pneumonia due to lack of airway protection [Scala, 2011].

Hypoglycemia

Acute confusional state and seizures occur when blood glucose drops to around 30 mg/dL, and coma ensues at a level of 10 mg/dL. Irreparable brain injury occurs at this point unless glucose is provided. The structural integrity of neurons is gravely compromised and the cellular fuel, adenosine triphosphate (ATP), is exhausted following a progressive drop in blood glucose level.

Common causes of hypoglycemia include: accidental or deliberate overdose of glucose-lowering medications (e.g., insulin, oral diabetic agents), pancreatic insulin-secreting tumor, and diminished liver glycogen stores (e.g., liver failure, alcoholic binge, starvation) [Samuels, 2009]. Clinical manifestations are initially associated with adrenergic reactions, such as anxiety, palpitations, trembling and sweating. Confusion and combative behavior may then arise, followed by myoclonus, seizures, and, ultimately, coma. Prompt administration of glucose is the most vital intervention.

Hyperglycemia

Diabetic ketoacidosis and hyperglycemic hyperosmolar state are the two forms of severe hyperglycemia that may lead to encephalopathy. In the former, the combination of hyperosmolarity and acidosis were found to be the main predictor of altered consciousness [Nyenwe *et al.*, 2010]. Both cases may result in brain edema. The exact mechanism for brain injury, however, is unclear for both forms.

Diabetic ketoacidosis and hyperglycemic hyperosmolar state are typically triggered by infection, non-adherence to insulin regimen, and dehydration, and present with seizures and coma. In hyperglycemic hyperosmolar state, focal signs, such as hemiparesis, hemisensory defect, and homonymous visual field defect, are commonly observed. Treatment consists of aggressive fluid resuscitation and careful lowering of blood glucose using insulin.

Hypothyroidism

Drowsiness, inattentiveness, and apathy are early manifestations of severe hypothyroidism or myxedema. As the

condition progresses, hypothermia, hypoventilation, and coma (hence the term "myxedema coma") can occur. Infection and surgery often give rise to this condition. Thyroid hormone replacement is the cornerstone of treatment.

Hyperthyroidism

Thyrotoxic patients, including those suffering from acute extreme hyperthyroidism or "thyroid storm", experience various neurologic manifestations, such as confusion, psychosis, myoclonus, tremors, seizures, and coma. Apart from thyroid-suppressive treatment, benzodiazepines have been described in one study as being useful in controlling choreiform movements that accompany mental status change [Tavintharan and Rajasoorya, 1998].

Wernicke's encephalopathy

Wernicke's encephalopathy is caused by thiamine (vitamin B1) deficiency and presents with the classic triad of nystagmus and ophthalmoplegia, mental status changes, and unsteadiness of gait and stance. The full triad is observed in a mere 16% of cases [Harper *et al.*, 1986]. Mental status changes described in reports include mental sluggishness, apathy, inability to concentrate, hallucinations, and coma [Sechi and Serra, 2007].

Typically found in chronic alcoholics, this form of encephalopathy should likewise be considered in patients suffering from malnutrition, poor dietary intake, malabsorption, and other severe diseases that result in thiamine consumption and metabolism. Heye and coworkers reported this form of encephalopathy in patients with pancreatitis, CNS lymphoma, and vegetative alcoholic withdrawal state [Heye *et al.*, 1994]. Blood brain barrier dysfunction and cerebral hypoperfusion are the principal pathologic process leading to encephalopathy. Thiamine replacement is the main form of treatment.

Related to electrolyte disturbance

Hyponatremia

Diminished plasma sodium levels result from excessive free water intake or excessive urinary loss of sodium and potassium. Brain damage develops following untreated hyponatremia in the setting of post-operative state, polydipsia, congestive heart failure (CHF), and acquired immunodeficiency syndrome (AIDS) [Fraser and Arieff, 1997]. Early symptoms of hyponatremia include nausea and vomiting, weakness, muscle cramps and headache. As encephalopathy sets in due to increased intracranial pressure and brain herniation, the following manifestations may be noted: impaired response to different stimuli, bizarre behavior, decorticate or decerebrate posturing, altered temperature regulation, seizures, respiratory arrest, and coma.

The appropriate management of hyponatremia is guided by two factors: volume status and symptomatology. It is important to determine if the patient is hypovolemic, euvolemic or hypervolemic, as the management of each condition greatly varies (i.e., fluid administration for hypovolemic hyponatremia, fluid restriction for euvolemic, and diuresis for hypervolemic). Similarly, the presence of symptoms calls for active but careful intravenous administration of sodium chloride-based fluids to increase serum sodium, whereas an asymptomatic patient likely just requires discontinuation of offending drugs and water restriction. In addition, Fraser and Arief suggest that since the risk of further brain damage (i.e., central pontine myelinolysis) from improper sodium correction is rare, it is still more beneficial for the symptomatic patient to be treated incorrectly than not treated at all [Fraser and Arief, 1997].

Hypernatremia

Hypernatremia or serum sodium greater than 145 mmol per liter is caused by net water loss (e.g., unreplaced insensible loss, diabetes insipidus, diuretics, diarrhea, vomiting, enterocutaneous fistula, and burns) or hypertonic sodium gain (e.g., sea water or salt ingestion, hypertonic sodium infusions, primary hyperaldosteronism, and Cushing's syndrome) [Adriogué and Madias 2000]. Neurologic manifestations include confusion, seizures and coma. The underlying mechanism of brain injury is brain shrinkage caused by hyperosmolality within the brain's milieu. This mechanism brings about vascular rupture and intracerebral bleeding; thus, parenchymal and subdural hematomas are not uncommonly found in patients with severe hypernatremia. Important facets of treatment are reversal of the underlying cause and cautious correction. Rapid correction or overcorrection may lead to cerebral edema and further brain damage.

Hypocalcemia

The neurological features of hypocalcemia result from enhanced excitability of the nervous system and increased intracranial pressure in the latter stage, and include paresthesias, seizures, extrapyramidal signs (e.g., chorea, parkinsonism), depression, anxiety, confusion, and coma. Common causes of hypocalcemia are hypoparathyroidism,

Hypercalcemia

Hypercalcemia is caused by hyperparathyroidism (usually in young adults), osteolytic bone tumors (e.g., bone metastasis, myltiple myeloma), other malignancies, particularly of the breast and lung, granulomatous diseases, especially sarcoidosis, chronic renal failure, and vitamin D overdose. Signs and symptoms include: nausea and vomiting, constipation, fatigue, confusion, myoclonus, and drowsiness progressing to coma. Aggressive saline hydration is essential in managing hypercalcemia, followed by drugs that lower calcium level, namely bisphosphonates and calcitonin.

Hypomagnesemia

Magnesium deficiency is usually associated with abnormalities in potassium and calcium metabolism, but may also occur as a result of dietary deficiency, malabsorption, prolonged parenteral alimentation, alcoholism, diarrhea, and diuretics [Lockwood, 2004]. Weakness, lethargy, and tremors may also develop. Along with magnesium repletion, other essential electrolytes, chief of which is calcium, should be checked and replaced appropriately.

Related to organ failure or other systemic diseases

Hepatic

Hepatic encephalopathy is one of the more frequently encountered forms of encephalopathy, as well as one of the most thoroughly depicted in medical literature. This neuropsychiatric complication of both acute liver failure and chronic liver disease can present overtly or with minimal manifestations. In either form, established treatment regimens have been in place for many years and continue to evolve. In addition, the involvement of palliative care in the prevention, early identification, and prompt treatment of encephalopathy in patients with chronic liver disease has been well advocated [Coggins and Curtiss, 2012].

The manifestations of hepatic encephalopathy can vary from subtle cognitive changes to coma. Patients with minimal disease have impaired memory, attention span, and learning ability, and are unable to carry out daily tasks. As the disease progresses, mental status deteriorates to lethargy and apathy, confusion and somnolence, and, eventually, coma [Ferenci *et al.*, 2002]. Neurological signs that may be observed include: asterixis, dysarthria, myoclonus, and decerebrate posturing. The presence of liver dysfunction, as illustrated by deranged liver function tests, and the above manifestations clinch the diagnosis.

Episodes of hepatic encephalopathy have been reported to be precipitated by sedative medications, gastrointestinal hemorrhage, dehydration, excessive protein intake, electrolyte imbalance (e.g., hypokalemia), constipation, surgery, and infections [Lockwood, 2004]. The primary mechanism of brain injury is attributed to the accumulation of ammonia, which is normally converted to urea by the functional liver. The thrust of treatment measures is, therefore, to decrease circulating ammonia levels by reducing gut-derived nitrogenous products. This is primarily accomplished with lactulose, which is administered orally or through an enema. Other parts of established regimens include: treating the precipitating factors, reducing "ammoniagenic" bacteria with antibiotics like neomycin, metronidazole, and rifaximin, and carefully assessing and optimizing nutritional status.

Uremic

Encephalopathy can occur in either acute or chronic renal failure. Not only is brain injury ascribed to the accumulation of uremic toxins, but hypercalcemia due to secondary hyperparathyroidism, malnutrition caused by increased circulating inflammatory cytokines, hypertension, and increased CNS permeability have all been reported to play a role [Seifter and Samuels, 2011]. The combined effects of these processes lead to decreased metabolic activity and oxygen consumption [Brouns and De Deyn, 2004], as well as nervous system depression and neural excitation [Lockwood, 2004].

Uremic encephalopathy differs from other types in a way that impaired consciousness is almost always accompanied by motor disturbances, such as tremors, asterixis, myoclonus, and occasionally, generalized seizures. The foremost treatment is dialysis. Uremic seizures and psychosis may be challenging to manage as medications will need to be carefully dosed in the setting of renal failure.

Another type of encephalopathy related to renal failure is dialysis encephalopathy or "dialysis dementia". This is a subacute progressive disorder manifesting with myoclonus, abnormal speech, cognitive decline, behavioral changes, and seizures [Samuels, 2009]. This form of encephalopathy was previously linked to aluminum found in dialysate water and phosphate binders. Aluminum has now been purified off of dialysate preparations. Renal transplantation is the treatment for dialysis encephalopathy.

Autoimmune

Autoimmune encephalopathy is characterized by serologic evidence of autoimmunity, intrathecal inflammation in the cerebrospinal fluid (i.e., mild pleocytosis, mild to moderately elevated protein, and absence of infection), and neurologic findings that include headache, memory loss, hallucinations, language difficulties, myoclonus, and stroke-like episodes [Flanagan and Caselli, 2011]. This form of encephalopathy is common in middle-aged and older women. Treatment with high dose corticosteroids yields significant improvement and prognosis is usually good.

A variant of autoimmune encephalopathy that is worth highlighting is Hashimoto's encephalopathy. As with autoimmune encephalopathy, this type predominantly involves middle-aged women, and responds well to corticosteroid therapy. Majority of patients are euthyroid and test positive for anti-thyroperoxidase (anti-TPO) antibodies. Contrary to what the eponym implies, cases of Hashimoto's encephalopathy have been associated with both Hashimoto's thyroiditis and Grave's disease [de Holanda *et al.*, 2011].

Paraneoplastic

Paraneoplastic encephalopathy is part of a broader, immune-mediated class of encephalopathies which generally occur in a fluctuating and subacute manner. Neurologic signs and symptoms, such as cognitive and behavioral changes, tremors, myoclonus, ataxia, sleep disturbance, and seizures, evolve over several days or several months [Pruitt, 2011]. It is not unusual for these features to manifest before the underlying malignancy is discovered or early in the course of cancer treatment. Vigorous diagnostic testing, including tumor screening and antibody studies, should be initiated once symptoms are noted, especially in patients with cancer-associated risk factors. Treatment consists of supportive care, tumor removal, and appropriate oncologic therapy. The outcome of paraneoplastic encephalopathy is generally poor, and depends on whether the inciting tumor can be removed or not [Flanagan and Caselli, 2011].

Hypertensive

Hypertensive encephalopathy results from acute blood pressure elevation and presents with headache, nausea, vomiting, confusion, visual disturbance, and seizures. This typically occurs when patients with essential hypertension discontinue their antihypertensive drugs, or as a complication seen in patients with hypertension secondary to an endocrine or renal disease [Nakabou *et al.*, 2010]. Brain injury has been postulated to be due to blood brain barrier breakdown due to angioedema [Schwartz *et al.*, 1992], and cytotoxic edema leading to cerebral vasospasm, hypoperfusion, and, eventually, brain ischemia [Schaefer *et al.*, 1997]. Neurologic symptoms typically improve with antihypertensive medications, which should be administered cautiously to avoid brain ischemia provoked by drastic blood pressure drop.

Hypertensive encephalopathy has been recognized by other terms, such as reversible posterior leukoencephalopathy and PRES. It is important to note that PRES, although similar in clinical presentation to hypertensive encephalopathy, is further distinguished by neuroimaging findings mentioned above (see Neuroimaging and EEG) and its link to Guillain-Barre syndrome, eclampsia, autoimmune diseases, organ transplantation, hypoalbuminemia, and several chemotherapeutic agents [Shah *et al.*, 2012].

Pancreatic

Neurologic signs and symptoms, mainly mental status derangement, have been reported to occur in cases of severe acute pancreatitis. This has been described to take place in a fluctuating fashion within the initial two weeks of acute pancreatitis. Manifestations can either occur abruptly in the form of seizures, transient blindness, dysarthria, and focal limb weakness, or gradually with behavioral changes, and confusion progressing to coma [Ruggieri et al., 2002]. Proposed mechanisms include brain damage by pancreatic enzymes in the blood stream, excessive release of cytokines and oxygen free radicals, hypoxemia, bacterial infection, and concomitant thiamine deficiency [Zhang and Tian, 2007]. Other than the usual management of acute pancreatitis (i.e., conservative or surgical), adequate nutritional support and thiamine supplementation have been shown to prevent the onset of encephalopathy [Ding et al., 2004].

Infection-related

Sepsis-associated

Sepsis-associated or septic encephalopathy is a consequence of severe infection, which does not involve the CNS itself. Although much has been discussed in the preceding sections about the clinical features and pathophysiologic aspects of this type of encephalopathy, several critical points need to be mentioned. First of all, the mortality rate of septic patients with encephalopathy was found to be 49% compared with 26% in septic patients without neurologic deficits [Sprung et al., 1990]. As with all other types of encephalopathy, delirium is frequently the initial neurologic feature seen in sepsis-associated encephalopathy. In some patients, however, coma is the initial presentation. Another important point is that detecting encephalopathy can prove to be challenging in sedated patients. Iacobone and coauthors suggest daily neurologic examination for such patients and further investigation (i.e., neuroimaging, EEG, lumbar puncture, and biomarkers of brain cell damage) if the following are noted: sudden change in metal status unexplained by modification of sedative infusion rate, new focal neurologic sign, seizure, and neck stiffness [Iacobone et al., 2009]. The principles of treatment include: initiation of appropriate antibiotic therapy, management of organ failure, correction of metabolic disturbances, and avoidance of neurotoxic drugs.

Human immunodeficiency virus (HIV)

HIV-related encephalopathy, alternatively termed as AIDS dementia complex or HIV-1 associated dementia complex, is neither a result of direct HIV infection of brain cells nor an autoimmune reaction triggered by the virus [Antinori *et al.*, 2001]. Rather, brain injury is caused by neurotoxic substances (e.g., eicosanoids, free radicals, arachidonic acid) released by macrophages that have assimilated the retrovirus by phagocytosis. The neurotoxic factors induce brain cell injury and death resulting in cognitive and motor impairments that become apparent as the disease progresses [Zheng and Gendelman, 1997]. Typical manifestations of this form of encephalopathy include progressive memory loss, behavioral dysfunction, confusion, and agitation. Treatment with anti-retroviral drugs may result in reversal of neurologic deficits.

Other viruses and bacteria

Encephalopathy, as exemplified by a host of manifestations involving mental status change and motor disturbances, has been associated with various infectious diseases such as tuberculosis [Lammie *et al.*, 2007], Lyme disease [Kaplan and Jones-Woodward, 1997], pertussis [Halperin and Marrie, 1991], and influenza [Wang *et al.*, 2010].

Drug- and toxin-related

Chemotherapy

Neurotoxic effects occur frequently in patients receiving chemotherapy. This is usually the reason for either aborting an agent or revising a regimen. Specific agents that have been found to cause encephalopathy include: cisplatin, carboplatin, vincristine, paclitaxel, methotrexate, cytarabine, 5-fluorouracil, ifosfamide, cyclophosphamide, nitrosureas, procarbazine, etoposide, and capecitabine [Verstappen *et al.*, 2003].

Various mechanisms are involved in chemotherapyinduced encephalopathy. The electrolyte abnormalities caused by cisplatin, such as hypocalcemia, hypomagnesemia, and hyponatremia, and its direct toxic effect on the brain all contribute to inciting CNS injury. Ifosfamide encephalopathy occurs in 10% to 30% of patients even if conventional doses are used [Merimsky *et al.*, 1991]. Thialysine ketamine and chloroacetaldehyde, metabolites of ifosfamide, cross the blood brain barrier and inhibit mitochondrial respiration leading to neuronal damage [Hildebrand, 2006]. In encephalopathy caused by 5-fluorouracil, ammonia is the metabolite that accumulates and causes damage when the agent is given at high doses [Cheung *et al.*, 2008].

The onset of neurologic deficits may range from within days of receiving the first chemotherapy dose, to several months after stopping the drug, as in the case with methotrexate [Blay *et al.*, 1998] and 5-fluorouracil [Cheung *et al.*, 2008]. Manifestations typically consist of impaired consciousness, asterixis, cranial nerve palsies, extrapyramidal signs, psychotic behavior, and seizures. Encephalopathy typically improves following discontinuation of the drug, coupled with appropriate supportive care.

Other drugs

The antiepileptic drug sodium valproate is known to cause a modest rise in plasma ammonia level, which rarely results in encephalopathy [Lewis *et al.*, 2012]. The antibiotics metronidazole [Huang *et al.*, 2012] and cefepime have also been implicated. Methylene blue, a dye frequently used in staining parathyroid glands during surgery, has been reported to cause encephalopathy when used in conjunction with serotonergic antidepressants [Shopes *et al.*, 2013].

Metals

Lead and mercury are the two most recognized metallic causes of encephalopathy. Lead encephalopathy usually occurs in children, but may uncommonly be found in adults exposed through occupation (i.e., paint, batteries, pipes), recreation (i.e., guns, toys), and some traditional medicines [Dobbs, 2011]. Neurologic signs include apathy, stupor, coma, and non-specific neuroimaging findings, such as brain edema and calcifications. Patients exposed to toxic levels of mercury may experience paresthesias, incoordination, hearing loss, blindness, tremors, behavioral dysfunction, and coma [Dobbs, 2011]. Exposure is through industrial waste or consuming fish and seafood contaminated with mercury.

Some types of metallic toxin exposure have peculiar manifestations. Peripheral polyneuropathy is a common finding in arsenic toxicity along with psychosis, impaired concentration, and cognitive decline [Bolla-Wilson and Bleecker, 1987]. Thallium toxicity not only causes encephalopathy and peripheral neuropathy, but also hair loss, which may be a key clue, although this might not be seen until two weeks following exposure [Tromme *et al.*, 1998]. Manganese toxicity, on the other hand, is known to result in parkinsonian symptoms, which fail to improve after treatment with levodopa [Dobbs, 2011].

Treatment for encephalopathy caused by metallic toxins generally consists of eliminating the source of exposure, and chelation with ethylenediaminetetraacetic acid (EDTA), dimercaprol, or dimercaptosuccinic acid (DMSA).

Industrial agents

Organic agents that have the potential of causing brain injury, such as toluene, trichloroethylene, ethylene glycol, and carbon disulfide, are commonly encountered in the workplace. These chemicals can be found in cleaning solutions, degreasing agents, paints, gasoline, lacquers, and adhesives. Neurologic deficits can result from acute intoxication, as well as following chronic exposure. Supportive care and thorough removal of offending agent are the pillars of management. Antidotes, such as ethanol for ethylene glycol toxicity, may be helpful in some cases.

Pesticides

Exposure to high doses of organochlorines and carbamate insecticides, and low doses of organophosphate insecticides can cause delirium, seizures, coma, and even death. Organophosphates, in particular, are extremely toxic and cause injury by inhibiting acetylcholinesterase. Neurologic manifestations are, therefore, accompanied by cholinergic symptoms, such as nausea and vomiting, diarrhea, rhinorrhea, and increased respiratory secretions. Atropine is administered as an antidote, and benzodiazepines can be given to treat seizures.

Carbon monoxide

When carbon monoxide combines with hemoglobin, the resultant carboxyhemoglobin causes hypoxic brain injury as it prevents hemoglobin from releasing much needed oxygen to brain tissue. Headache, dizziness, fatigue, nausea

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and confusion may occur initially, followed by seizures, loss of consciousness, and death. Treatment is by providing 100% oxygen or hyperbaric oxygen therapy in severe cases. Delayed neurologic sequelae may develop 5 to 30 days after surviving an acute exposure, and is characterized by mood swings, depression, suicidal thoughts, and cognitive impairment [Dobbs, 2011].

Summary

Encephalopathy is a general brain malfunction brought about by a wide array of systemic diseases, drugs, toxins, and other precipitants. Prompt diagnosis may not be readily accomplished owing to the disease's diverse presentation and broad differential diagnosis. Altered mental status is a universal feature of encephalopathy, plus a combination of motor disturbances, behavioral dysfunction, seizures, and impaired consciousness. Most cases improve once the underlying illness is managed or the offending agent eliminated.

Palliative care bears an important role in managing encephalopathy, especially as the clinical course progresses to the point of non-reversibility. Specific tasks that the palliative care practitioner will need to fulfill include: establishing a trusting relationship with the patient and family, anticipating and effectively treating symptoms, initiating advance care planning, discussing goals of care, addressing end-of-life issues, providing prognostic information, refocusing hope, and advocating for deescalation of care when life expectancy becomes severely limited.

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Part III

Depression

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Do not be afraid to suffer, give the heaviness back to the weight of the earth; mountains are heavy, seas are heavy. Even those trees you planted as children became too heavy long ago—you couldn't carry them now. But you can carry the winds and the open spaces.

-Rilke

Introduction

Some degree of psychological distress can be expected from any person experiencing a progressive terminal illness. Much of the current literature explores this issue in terminally ill cancer patients, and less is known about those with other end-stage diseases such as pulmonary, cardiac, renal, and neurological conditions. Aside from those who succumb to an unexpected sudden death, most people experience some degree of loss at the end of life, which may include: progressive decline of physical health, psychological function, occupational role, self-image, self-esteem, sense of meaning, financial resources, sense of control, privacy, dignity, relationships, and independence [Lobb et al., 2006]. These losses are often cumulative, particularly for those who live for longer duration with a progressive terminal illness. Grief is a universal and uniquely personal response to these losses, and is considered a healthy and adaptive psychological reaction [Block, 2001]. Grief is a natural process that has physical, emotional, spiritual, philosophical, social, and cognitive dimensions. It allows people to adapt, accept and move forward in the context of loss. Psychiatric disorders, such as major depression, are more prevalent in individuals receiving palliative care services compared to the healthy population [Cassem, 1995]. Many palliative care patients have or develop major depression during the course of care; this should not be considered an adaptive or "normal" reaction for end-of-life patients [Hotopf et al., 2002]. Depression remains underdiagnosed and undertreated in this group [Rayner et al., 2009].

The clinician faces the complex challenge of differentiating between healthy, adaptive emotional distress and more severe, treatable psychiatric conditions. Expected emotional states such as sadness, loss, and anticipatory grief in a terminally ill patient can obfuscate assessment of treatable psychiatric disorders such as depression and anxiety. Common somatic symptoms of depression such as sleep disturbance, fatigue, and loss of appetite and weight can frequently be ascribed to palliative care patients' medical diseases or treatments. The issue is complicated further by the limited evidence and lack of certainty in clinically conceptualizing, assessing, and treating depressive symptoms and depressive disorders in palliative care patients [Wasteson et al., 2009]. Current expert consensus, however, recommends prevention, diagnosis, and a low threshold for treatment of major depression and other depressive disorders in the palliative care patient for several reasons. Firstly, psychological and psychiatric treatments for depression have relatively benign adverse effects compared to the potential benefits of reduced psychological distress and improved quality of life. Secondly, depression can interfere with the person's ability to experience pleasure, connect with others, engage in meaningful relationships, and results in poorer adherence to care and treatment [Block, 2000; Rayner et al., 2011]. Thirdly, depression is also associated with increased risk of suicide and requests to hasten death [Chochinov et al., 1995]. Finally, evidence suggests that depression is associated with increased pain, fatigue, and disability, as well as poorer prognosis and higher mortality rates from some physical disorders [Hotopf et al., 1998; Wells et al., 1989;

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Barkwell, 1991; Frasure-Smith et al., 1993; House et al., 2001; Lloyd-Williams et al., 2009].

Epidemiology

Depressive disorders are one of the most prevalent psychiatric conditions in the general population and are estimated to be twice as high in the palliative care patient [Ayuso-Mateos et al., 2001; Kessler et al., 2005a; Hotopf et al., 2002]. Depression is twice as common in women and is highly co-morbid with anxiety disorders and alcohol misuse [Kessler et al., 2005b]. Twin and adoption studies suggest that the genetic contribution to major depressive disorder is about 45%. Other general risk factors for depression include age (with highest rates observed in the 49-54-year-old age group), having or perceiving to have poor psychosocial supports, poor functional status, and lesser socioeconomic status [Belmaker and Agam, 2008]. The prevalence rates of depression reported in palliative care patient studies vary widely depending on study methodology; however, a recent systematic review reports that major depression affects about 15% of individuals at the end of life [Hotopf et al., 2002]. Additional risk factors for depression are co-morbid medical conditions which include chronic pain, thyroid disease, and sleep disorders, while high rates of depressive disorders are also observed in individuals with coronary artery disease, dementia, diabetes, and cerebrovascular accidents [Rodin et al., 2005]. In certain clinical samples, the association with depression is observed to be extraordinarily high. For example, up to half of individuals with specific cancers (particularly those with brain, head and neck, and retroperitoneal malignancies), multiple sclerosis, or Parkinson's disease suffer from co-morbid depression. A number of medications are also associated with depression, such as corticosteroids, methotrexate, and interferon [Shakum and Chochinov, 2005].

The neurobiology of depression

The classic monoamine hypothesis of depression has undergone refinement over the years from a simplistic monoamine [primarily serotonin (5-HT) and norepinephrine (NE)] deficit model to a more refined conceptualization of central nervous system monoamine circuit dysregulation and extra-monoamine neuropeptide and neuroendocrine system dysregulation [Flores *et al.*, 2004]. Novel extra-monoamine system therapeutic targets for the treatment of depression that are under exploration include: corticotropin-releasing factor (CRF) antagonists, glucocorticoid receptors antagonists, substance P receptor antagonists, *N*-methyl-D-aspartate (NMDA) system antagonists, omega-3 fatty acids, and melatonin receptor agonists [Rakofsky *et al.*, 2009].

There is evidence that the 5-HT, NE, and dopamine (DA) monoamine circuits play a role in depression and its treatment since most antidepressants act in some way to modulate one or more of these systems. Aside from the psychostimulants, all currently available antidepressants have a delayed therapeutic response, with symptomatic improvement typically starting after two to four weeks of treatment. Chronic treatment with antidepressant medication increases NE turnover and downregulates β -adrenergic receptors and α 2-autoreceptors. Depression is also associated with hypothalamic pituitary axis (HPA) dysfunction such as elevated cortisol and ACTH levels, increased secretion of CRF, and flattening of the circadian rhythm of cortisol [Flores et al., 2004]. Prolonged secretion of stress hormones such as CRF, ACTH, and cortisol damages hippocampal and prefrontal cortical dendritic branching, possibly by reducing brain derived neurotrophic factor (BDNF). Chronic antidepressant use reverses these effects. Sleep architecture is often significantly altered in depression by initial insomnia, early onset REM, more frequent awakenings, and longer and more frequent REM episodes earlier in the night [Flores et al., 2004]. Additionally, there is a reciprocal relationship between chronic pain and depression. Persistent pain has been shown to increase the risk of depression, and conversely depression increases the risk of developing chronic pain [Tsang et al., 2008; Tunks et al., 2008].

The diagnosis of depression

Common symptoms of an episode of depressive disorder include: persistently depressed mood, anhedonia, fatigue, somatic symptoms (e.g., sleep disturbance, diminished appetite, and weight loss), reduced attention and concentration, excessive feelings of guilt and worthlessness, bleak views of the future, and self-harm or suicidal thoughts or actions. Typically, significant symptoms are present every day or nearly every day for at least two weeks, and cause some degree of functional impairment. Depression may also be accompanied by significant anxiety, hypochondriacal preoccupations, irritability, and motor restlessness or retardation [WHO, 1992; American Psychiatric Association, 2013]. Many of the psychological and somatic

Table 1 Grief compared with depression in terminally III patients			
Characteristic	Healthy grief (adaptive response)	Depressive disorder (maladaptive response)	
Area of distress	Distress in response to a particular loss but is not	Distress is pervasive and affects all or many	
	generalized to all aspects of life	different aspects of life	
Symptom course	Comes in waves and often decreases with time	Constant and unremitting	
Mood	Sadness, dysphoria	Protracted, constant depression, constricted	
		range of affect	
Interests and capacity	Interests and capacity for pleasure intact but engagement	Markedly diminished interests and capacity	
for pleasure	in activities may be diminished due to functional decline	for pleasure (anhedonia)	
Норе	Episodic or focal loss of hope which may change over time,	Persistent and pervasive hopelessness,	
	some positive orientation towards future	negative feelings towards the future	
Self-worth	Maintained, but may have feelings of helplessness	Worthlessness, feeling that life has no value,	
		excessive feelings of helplessness	
Guilt	Regrets and guilt over specific events or behavior	Excessive or inappropriate feelings of guilt	
Suicidal ideation	Passive and fleeting desire for death to come quickly	Preoccupation with a desire to die	

[Block, 2000 (Adapted and reprinted with permission of author); Pessin H, 2005 (Adapted and reprinted with permission of Cambridge University Press); Widera and Block, 2012 (Reproduced with permission from Managing Grief and Depression at the End of Life, August 1, 2012, Vol 86, No 3, issue of American Family Physician Copyright © 2012 American Academy of Family Physicians. All Rights Reserved)].

symptoms of depression overlap with symptoms of terminal illness or treatments; therefore clinicians should be familiar with characteristics that will help distinguish healthy grief that is adaptive from a depressive disorder that warrants active intervention and treatment. These key differences are outlined in *Table 1*. In addition to the psychological symptoms and criteria listed in DSM-5 and ICD-10, other indicators of depression in terminally ill patients are: intractable pain or other symptoms, excessive somatic preoccupation, disproportionate disability, poor cooperation, refusal of treatment, and clinician hopelessness, aversion, or lack of interest [Block, 2000; Goldberg, 1983; Maltsberger and Buie, 1974].

Barriers to diagnosing depression

Depression and other types of psychological distress are well documented in palliative care patients, though depression remains underdiagnosed and undertreated for multiple reasons [Kaasa *et al.*, 1993; Steifel *et al.*, 1990]. Numerous factors interfere with the diagnosis of depression in the palliative care patient. These include: patient and clinician beliefs that depression is a natural consequence of the end of life process, and subsequent failure to differentiate healthy grief from clinical depression; patient and clinician minimization of or neglect to discuss

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psychological symptoms because of internalized or cultural stigmas; patient and clinician avoidance of exploration of psychological symptoms due to time constraints or fear of its causing increased patient distress; clinician lacking the skills to differentiate between adaptive emotional distress and clinical depression; clinician hesitancy to prescribe additional medication to avoid possible adverse effects; and the clinician feeling hopeless and experiencing therapeutic nihilism when caring for terminally ill patients [Block, 2000; Block and Billings, 1994; Jaeger *et al.*, 1985; Periyakoil and Hallenback, 2002] .

Screening tools for depression

Several simple screening tools for depression are available to the clinician [Lloyd-Williams *et al.*, 2003]. A single screening question such as: "Are you depressed?" has been found to be a sensitive and specific indicator of depression in terminally ill patients. Most patients who answer affirmatively are likely to receive the diagnosis of depression upon further comprehensive diagnostic interview [Chochinov *et al.*, 1997; Lloyd-Williams *et al.*, 2003]. Another two-item screening scale inquires about mood, hopelessness, and loss of interest or pleasure during the prior month [Akechi *et al.*, 2006; Payne *et al.*, 2007]. The hospital anxiety and depression scale (HADS) is a 14-

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item tool that screens for both depression and anxiety, and excludes somatic symptoms. A recent meta-analysis found the HADS useful as a screening instrument in palliative care settings, but its length may limit its use in the clinical setting [Zigmond and Snath, 1983; Lloyd-Williams *et al.*, 2001; Mitchell *et al.*, 2010]. The brief Edinburgh depression scale (BEDS) contains six items that inquire about guilt, insomnia, fear, sadness, inability to cope, and thoughts of self-harm. Studies suggest that it is a quick yet sensitive screening tool for depression in the palliative care setting [Lloyd-Williams *et al.*, 2007; Lloyd-Williams *et al.*, 2003].

Treatment of depression

Palliative care patients have complex medical and psychological needs and often receive care from a variety of clinicians and caretakers. Clinicians should communicate with palliative care patients in an open, non-judgmental, patientcentered manner and actively explore their concerns and feelings as part of routine assessment. The clinician will then be better prepared to provide information and support that are needed and in accordance with patients' wishes [Rayner et al., 2011]. It should not be assumed that another treatment provider is assessing or treating significant psychological distress. Coordination of care and regular communication between clinicians, caretakers, the patient, and other main family supports can help to optimize treatment and reduce the psychological distress of patients and families. When exploring psychological symptoms, the clinician needs to be sensitive to any specific cultural issues as well as anticipated or actual social stigma that may affect palliative care patients' willingness to discuss emotions and feelings.

Treatment of depressive disorders in individuals receiving palliative care may involve the use of one or more modalities including: psychotherapy, medications, psychosocial supports, and complementary and alternative medicine (CAM) approaches. When feasible, the avoidance or minimal use of certain medications that may worsen depression is advisable (e.g., corticosteroids, interferon). Effective management of severe pain and other somatic distress is vital to the successful treatment of depression. Vigilance towards the correction or mitigation of any underlying endocrine, nutritional, electrolyte, or other physical health abnormality where possible is also paramount. Although research in the optimal psychological and medical treatment of depression in palliative care patients remains limited, clinicians are encouraged to have a low threshold for treating depression because interventions are relatively benign, have been shown to relieve distress, improve quality of life, and sometimes even prolong life [Greer *et al.*, 1992; Speigal *et al.*, 1981; Speigal *et al.*, 1989; Fallowfield *et al.*, 1990; Fawzy FI, 1990a; 1990b].

There are several circumstances that should prompt referral for specialist psychiatric consultation—preferably a psychiatrist with expertise in the assessment and management of medically ill patients. These may include: a clinician uncertain about psychiatric diagnosis; a patient with pre-existing major psychiatric disorder; a patient who is suicidal, or requesting euthanasia or assisted suicide; a psychotic, confused patient unresponsive to first-line antidepressants; and a patient whose family is dysfunctional [Block, 2000]. Pervasive hopelessness, a persistent desire to die, psychotic symptoms, and organic mental disorders may put patients at higher risk for suicide [Block, 2000; Mackenzie and Popkin, 1987].

Psychotherapy

Individual and group psychological interventions have been shown to reduce psychological distress of patients and their families, improve quality of life, and even prolong life in some instances. A meta-analysis of psychological interventions that included six randomized controlled trials of supportive-expressive therapy, cognitive-behavioral therapy and problem-solving therapy for people with advanced cancer showed significant improvement in depressive symptoms despite not all subjects having clinically diagnosed depressive disorders [Akechi et al., 2008]. There have been few controlled trials of combined treatments (e.g., psychological and medication interventions). Cognitive behavioral therapy (CBT) is widely used and evaluated for major depression and several randomized control trials have displayed its effectiveness in the medically ill, but there are few studies in the palliative care population [Beltman et al., 2010; Moorey et al., 2009; Uitterhoeve et al., 2004]. Short term focused problemsolving therapy is being used in the palliative care setting to help patients resolve specific issues in their lives, tough there exists limited research evidence [Cuijpers et al., 2007]. Despite the dearth of studies, other therapies that may be of use in palliative care are group therapy, couple or family therapy, guided imagery, and mindfulness-based approaches.

Psychopharmacology

The mainstays of antidepressant treatment in the

Table 2 Antidepressant med	ications by type, common effects and general comments			
Antidepressant type and example agents	Common effects	Comments		
Psychostimulants				
Methylphenidate,	Well tolerated in elderly and debilitated, with cardiac disease	Decreases fatigue, improves cognition,		
dextroamphetamine,	can cause decompensation, occasionally confusion or	appetite, and energy in most patients. Rapid		
pemoline, modafinil	tolerance may develop, pemoline is potentially hepatotoxic	onset of action: 24-48 hours		
Selective serotonin reuptake inhibitors (SSRIs)				
Fluoxetine, paroxetine,	Insomnia, agitation, sexual dysfunction, gastrointestinal	First-line agents, fewer drug interactions, and		
sertraline, citalopram,	disturbances, serotonin syndrome, sedation, weight gain,	lower side effect burden. Onset of action 2-4		
escitalopram	fatigue, nausea, intense dreams	weeks		
Serotonin and norepinephrine reuptake inhibitors (SNRIs)				
Venlafaxine, duloxetine	Insomnia, agitation, sexual dysfunction, hypertension,	Increasingly used as first-line agents, but few		
	cardiotoxicity, liver toxicity	studies in palliative care patients. Onset of		
		action 2-4 weeks		
Tricyclic antidepressants (TC	As)			
Nortriptyline, amitriptyline,	Sedation, anticholinergic side effects, cardiovascular	A mainstay treatment, and if well-tolerated are		
imipramine, desipramine,	toxicity, hypotension, narrow therapeutic index, highly lethal	effective for chronic pain, insomnia, depression,		
clomipramine	in overdose, drug interactions	anxiety. Onset of action 2-4 weeks		
Monoamine oxidase inhibitors (MAOIs)				
Phenelzine, selegiline,	Insomnia, weight gain, hypertension,	Not first-line agents due to high side effect		
moclobemide,	drug interactions, tyramine effects	burden, drug interactions, diet restrictions.		
tranylcypromine,		Onset of action 2-4 weeks		
Isocarboxazid	and the fact of the second			
Selective norepinephrine reuptake inhibitors				
Reboxetine, atomoxetine	Insomnia, agitation, sexual dysfunction, sedation, nausea,	Limited data in palliative care patients.		
	weight loss	Unset of action 2-4 weeks		
Atypical antidepressants		The second se		
Buproprion	Agitation, insomnia, nausea, decreases seizure threshold	Few studies in pallative care, less sedating		
Mirtazepine	Sedation, weight gain, fatigue	Few studies but may be helpful with insomnia,		
T		appetite, anxiety. Onset of action 2-4 weeks		
	Highly sedating at antidepressant doses, priapism reported	Low doses often used for insomnia		
[Block 2000: Lliev] and Mü	ller-Oerlinghausen 2012: Farriols et al. 2012: Candy et al.	20081		

[Block, 2000; Ujeyl and Müller-Oerlinghausen, 2012; Farriols et al., 2012; Candy et al., 2008].

palliative care patient are the selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), and psychostimulants [Katon and Sullivan, 1990; Maguire *et al.*, 1985]. These medications may be of particular value when the severity of a patient's illness prevents him or her from engaging in psychotherapeutic interventions. The major types and common effects of currently available antidepressant medications are outlined in *Table 2*. A Cochrane review and meta-analysis by Rayner and colleagues concludes that there is evidence for the superiority of antidepressants over placebo at four to five weeks of treatment and beyond in palliative care patients [Rayner *et al.*, 2010]. A recent systematic review purported the safety and efficacy of antidepressants for the treatment of depression in palliative care patients with different medical conditions, including chronic obstructive pulmonary disease and heart failure, HIV/AIDS, cancer, multiple sclerosis, Alzheimer's dementia, and Parkinson's disease. A total of 36 randomized controlled trials met inclusion criteria, and four more studies were added when criteria were broadened to include patients who were not yet in advanced medical disease stages. Most studies

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examined the efficacy of SSRIs and TCAs. The authors propose that there is lack of conclusive evidence for the use of a particular class of antidepressant medications in certain terminal medical conditions due to the paucity of head to head trials; SSRIs, however, are generally shown to be well tolerated [Ujeyl and Müller-Oerlinghausen, 2012].

SSRIs are often used as first-line medications for depression. Sertraline citalopram, escitalopram, and paroxetine are commonly prescribed because they have fewer active metabolites and lower risk of toxicity. The TCAs are also used but are less well tolerated due to sedation and higher side effect burden, particularly anticholinergic side effects. Psychostimulants such as methylphenidate, dextroamphetamine, pemoline, and modafinil act rapidly (often within 24-48 hours), are generally well tolerated in elderly and debilitated patients especially, and can help improve fatigue, appetite, and cognition. Pemoline is generally not a first-line agent because it has been associated with hepatotoxicity and so hepatic function must be monitored regularly with its use. The research data supporting the use of these agents are limited, but there is evidence that they are safe and beneficial for some patients [Bruera et al., 1992; Candy et al., 2008; Woods et al., 1986; Masand and Tesar, 1996]. Although limited data exist, a recent review of prescribing practices shows that there is increased use of other selective dual-acting antidepressants such as duloxetine, venlafaxine, and mirtazepine in palliative care patients [Farriols et al., 2012].

Medications that modulate the glutamate system are currently being explored for their potential antidepressant effects [Lapidus *et al.*, 2013]. Ketamine, an NMDA receptor antagonist typically used as a short acting anesthetic agent, has been demonstrated to have rapid antidepressant effects in several small studies and in a recent randomized control trial with treatment-resistant major depression [Murrough *et al.*, 2013]. A small open-label 28-day trial of oral ketamine was shown to be effective in reducing depression and anxiety in patients with depression who were receiving hospice care [Irwin *et al.*, 2013]. More information on dose, response, and safety is needed before ketamine can be recommended for general clinical use.

Complementary and alternative medicine and other integrative treatments for depression

There is limited research supporting the use of CAM as effective therapies for depression and psychological distress in palliative care patients. These include yoga, meditation, acupuncture, and massage [Lin *et al.*, 2011; Lafferty *et al.*, 2006, Towler *et al.*, 2013]. Although further research is needed given the complexity of patients with different medical disorders, a recent integrative literature review has shown that acupuncture has been used successfully in palliative care for pain management, fatigue, xerostomia, hot flashes, dyspnea, nausea, vomiting, and anxiety. Although not a specific treatment target, acupuncture may be an effective intervention for depression in palliative care patients as suggested by the high association of depression with chronic pain and anxiety [Towler *et al.*, 2013].

A broad array of biological, nutritional, somatic, mindbody, and dietary approaches have limited or provisional evidence for treatment of depressed mood, but to date these have not been well studied in palliative care patients. However, these interventions may be useful as adjunctive approaches and should be highlighted for several reasons. Certain integrative and "natural" approaches may be more acceptable to some receiving palliative care, can potentially decrease feelings of helplessness and loss of control, have lower potential risk, and emphasize the need for future research.

Methodologies with limited research evidence in treatment of depression, primarily small studies and case reports, include: St. John's wort, S-adenosylmethionine (SAMe), vitamins B_6 , B_{12} , C, D, and E, Omega-3 fatty acids, exercise, morning bright light exposure therapy, mindfulness training, yoga, and massage. Other provisional treatments currently lack research evidence, but are generally lowerrisk interventions. These include: ayurvedic herbs, 5-hydroxytrytophan, L-tryptophan, acetyl-L-carnitine, inositol, dehydroepiandrosterone (DHEA), biofeedback, heart rhythm variability (HRV) biofeedback, homeopathy, and healing or therapeutic touch therapies [Lake, 2007].

Spiritual and social supports

Engaging the help of other health professionals, family, and members of a person's social community when appropriate can be of considerable help in the care of the depressed palliative care patient. For example, spiritual or chaplaincy services can assist the patient and family with any spiritual concerns. Social workers can assess and facilitate optimal engagement and, if needed, enrichment of the social network, coping strategies, and support system. Engaging the family and respected members of a patient's social community where culturally appropriate may help to decrease the psychological distress of the patient and family, facilitate human connection, contribute to meaning-making, and improve overall quality at the end of life [Block, 2000].

Summary

Palliative care by definition seeks to relieve the burden of pain and suffering of individuals with serious illness and optimize the quality of life for patients and their family. Losses at the end of life are often significant and cumulative, and grief is an expected, adaptive, yet highly personal reaction to such losses. Clinical depression is not adaptive and can significantly contribute to the pain and suffering of the individual. The literature suggests that depression continues to remain under recognized and undertreated in people during the end of life. Expert consensus generally recommends that physicians have a low threshold to treat depression in palliative care patients because psychological and medical interventions are effective and typically well tolerated. Some medications can have a rapid onset of action, and psychological interventions can help enhance connection, meaning, coping, and reconciliation in the dying process [Block, 2000]. Clinicians should be familiar with the differences between adaptive grief and clinical depression (recognizing their coexistence in some people), barriers to diagnosing depression, available treatment options, and when to refer to specialist psychiatric consultation. The prompt diagnosis and treatment of depression will significantly reduce the psychological distress of patients and their loved ones, and contribute to improved quality of life in palliative care patients.

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Part III

Death rattle

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Introduction

Death rattle heralds the last hours for some dying people. There are many references to it in the folklore of all cultures and countries, and carries with it apprehension and fears because of its association with imminent death. This makes it a particularly emotive phenomenon: one which carries different meanings and connotations for patients and their families, as well as for practitioners looking after them. The management of death rattle requires the sensitive integration of both art and science, perhaps even more than some other aspects of palliative medicine.

Death rattle is noisy breathing: the character of the sound ranges from gurgling and bubbling to rasping and rattling. The volume and pattern of breathing remain unchanged, unless Cheyne-Stokes breathing occurs simultaneously. Death rattle is reported to occur in 23-92% of dying people [Lichter and Hunt, 1990; Ellershaw et al., 1995; Bennett, 1996; Morita et al., 2000; Wildiers and Menten, 2002]. The wide range in reported incidence may relate to some differences in clinical practice (e.g., administration of artificial fluids) but are more likely to be due to methodological differences between these studies. Some are based on retrospective case note reviews, and rely on the documentation of anti-muscarinic prescription as proxy confirmation of death rattle. There is a suggestion that biochemical dehydration might be associated with a lower chance of developing death rattle in some patients but no clear link has been established [Ellershaw et al., 1995]. Similarly, others have identified a possible relationship between death rattle and cerebral malignancies, lung malignancies and hospice stay of greater than 9 days [Bennett, 1996, Morita et al., 2000] but these findings have not been replicated.

In traditional folklore, death rattle was simply recognised

as a sign of impending death. Where deaths at home are common, families learned to recognise the sound of death rattle and its implications. This learning was passed down from generation to generation. In cultures and countries where deaths occur at home much more rarely than in the past, it is easy for professional staff to forget that families may not recognise nor understand the implications of the death rattle. In those situations, they often fail to prepare families for the impending death.

Assumptions about death rattle

The management of death rattle is underpinned by three major assumptions. These assumptions must be made explicit so that established practice can be properly challenged. The first assumption is that death rattle is caused by retained secretions oscillating up and down the airways with respiration. This remains unproven. An alternative mechanism might be the vibration or intermittent collapse of upper airway muscles with respiration, akin to snoring. However, the assumption about retained airway secretions is so well established that pharmacological treatment (antimuscarinic drugs) is based entirely on that premise. The reference to death rattle as 'respiratory secretions', which abound in clinical and even research literature, is inaccurate because this implies a causation that remains unproven. A more accurate alternative term for death rattle would be 'noisy breathing', which simply describes the phenomenon.

The second major assumption is that patients' relatives and those around them are distressed by the sound of death rattle. The evidence underpinning this assumption, and the implications for practice, will be discussed later in this chapter. The third assumption is that death rattle does not cause any discomfort or distress to the patient. Clinical experience would support this assumption. It remains unproven at this stage but it is difficult to envisage how research can be carried out to test it.

Pharmacological management

The assumption that death rattle is caused by retained airway secretions means that anti-muscarinic agents remain the mainstay of pharmacological management. There are even suggestions that dying people should be given antimuscarinic agents before death rattle has developed, on the basis that anti-muscarinic agents can only inhibit further secretions, and do nothing for secretions that are already present in the airways. This would be a reasonable approach if the drugs had no adverse effects or if death rattle occurs universally in all dying patients. Neither is true. Antimuscarinic drugs cause dry mouth, urinary retention and other unpleasant side effects which the patient, at this stage, is unable to report. Administering anti-muscarinic drugs to all dving patients means exposing them all to potentially distressing side effects, whereas we know that not all dying people will experience death rattle. Therefore the practice of administering anti-muscarinic agents on a prophylactic basis is not recommended.

Once a decision has been taken to administer a pharmacological agent to a patient who is experiencing death rattle, the next step is to select which anti-muscarinic agent to use. The candidates are atropine, hyoscine or glycopyrronium. Comparative audits have shown that whichever drug is used, only up to 65% of patients with death rattle respond [Hughes et al., 2000; Back et al., 2001]. A Cochrane Review in 2008, updated in 2009 and republished in 2012 showed no conclusive evidence that one drug was superior to the other [Wee and Hillier, 2008]. A randomised, double-blinded, placebo-controlled, parallel group trial of 137 patients, published since then showed that sublingual atropine, given as a single dose, was no more efficacious than placebo in reducing the noise of death rattle [Heisler, 2012]. There are four main differences between these drugs, which have practical implications: some do not cross the blood brain barrier (e.g., hyoscine butylbromide or glycopyrronium) and therefore do not cause additional sedation; some have a quicker onset of action than others (e.g., hyoscine butylbromide versus glycopyrronium); some have a shorter duration of action than others following a single dose (e.g., hyoscine butylbromide versus glycopyrronium); some are more costly than others.

Research in this arena is beset by a number of problems.

relatives and loved ones is paramount, and key to providing good end of life care. It is clear from what has been written so far that our clinical options for diminishing the sound of death rattle are limited, especially when weighed against potential harm of the interventions to the patient. Despite that, professionals appear to feel the need to take some action, partly driven by their perception that the relatives' distress is caused by the sound of death rattle.

As always, effective communication with the patient's

First, many of the older evidence is based on audits, often retrospective, rather than controlled trials. Second, it is difficult to recruit large numbers of patients to properly powered randomised controlled trials, especially within single centres [Likar et al., 2008]. Third, not all studies were able to 'blind' the treatment to those who were administering it and/or those who were evaluating the effect [Wildiers et al., 2009]. In many cases, the same nurse who was looking after the patient both administered the treatment, and evaluated the effect. Fourth, the sound of death rattle is difficult to measure objectively although, in some cases, attempts were made using sound meters. Finally, it is not at all clear that the most meaningful parameter is being measured. A reduction in the sound of death rattle is usually what investigators try to measure, but arguably the nature of the sound or the emotion caused by the fact that the patient is imminently dving are the real factors causing distress. Choosing the right outcome measure is critically important.

Non-pharmacological management

Communication with relatives

The options for non-pharmacological management of death rattle are limited. For a long time now, repositioning the patient, usually on his or her side, is recommended, and has been shown to be clinically helpful. Gentle suctioning using a soft catheter may also be helpful. In a study of 200 consecutive patients, Lichter and Hunt [1990] found that 62 out of the 112 patients who developed death rattle responded to nursing interventions alone, with occasional suctioning, repositioning and reassurance. There is no other published evidence to back up or refute this finding. Importantly, practitioners should make the judgement based on the patient's best interests at all times, balancing the potential discomfort of repositioning or suctioning with an improvement in the noise of the death rattle.

Death rattle

Whilst it is true that some relatives and those by the patient's bedside are distressed by the sound of death rattle, not all are. A qualitative study involving in-depth interviews with bereaved relatives showed that less than half of the interviewees reported distress about the sound itself [Wee et al., 2006a]. Others expressed neutral feelings; some even regarded the onset of death rattle as a helpful indicator of impending death which began to prepare them, and other family members, for the patient's imminent death. A second study, which confirmed that not all relatives had been distressed by the sound of death rattle, explored how relatives made sense of the sound [Wee et al., 2006b]. The impact on relatives was influenced by the patient's appearance, and whether the relative felt that the patient looked disturbed. Their attitude to the sound ranged from matter of fact to overt distress, especially where they mistakenly thought that the sound was indicative of choking or drowning. This was particularly so where staff had not picked up on these misperceptions and had not explained what was going on, nor even made it explicit that the patient was dying. Relatives did not always ask for explanations, so professionals did not always realise that relatives were distressed, not by the sound itself, but by what else they thought was going on.

Decision making

There is an ethical conundrum in managing death rattle which is quite unlike that of other common palliative care issues (e.g., pain, breathlessness and anxiety). Patients are usually semi-conscious or unconscious by the time they develop death rattle. Most clinicians acknowledge that many patients appear to be undisturbed by the sound of the death rattle, and that instigating any pharmacological or non-pharmacological treatment is usually for the sake of the patient's relatives and those around them. So, patients are given treatments which may carry adverse effects or burdens without the opportunity to make an informed decision, for the benefit of others. This is one of those rare situations where the intervention is not in the patient's direct best interests, but in the assumed best interests of their loved ones. This is not necessarily wrong, but does need to be thought through. This is especially so since we now know that not all relatives are distressed by the sound of the death rattle, so the rationale for intervention is not watertight.

The emotive nature of death rattle can affect health professionals too. In a questionnaire survey, nurses reported feeling distressed when death rattle occurred [Watts and Jenkins, 1999]. In a later study, distress and helplessness were two key emotions identified by health professionals around the time of dying, both in relatives and in the professionals themselves [Wee, 2003].

Gaining insight into how professionals make decisions when faced with death rattle helps us to reflect on our own decisions and actions. Two focus group studies, one with separate groups for those from different professional backgrounds [Wee et al., 2008] and one with mixed professional groups [Hirsch et al., 2012], showed that decisions were influenced by the professional's own feelings about death rattle, concern for relatives and other patients, perceptions about what was expected of them, and feeling the need to use a therapeutic option because one was available. Opinions were divided about whether the patient would be expected to benefit from the treatment [Bradley et al., 2010; Hirsch et al., 2012]. The 'need to do something' was a particularly strong element that emerged from all these studies. As health professionals, it is crucial that our 'need to do something' does not drive us to actions which are not in the patient's best interests and, additionally, may cause discomfort and harm.

Summary

It is clear that many questions remain unanswered about the optimum management of death rattle. It may be that we shall never find a comprehensive answer to this question, perhaps because death rattle raises such complex issues for all those involved. Given the evidence we have to date, it is probably pointless to carry on with trials comparing different anti-muscarinic agents. Scientific inquiry into the actual mechanism of death rattle remains important: to develop more effective interventions, we need to understand the precise mechanism(s) of the sound of death rattle.

In the meantime, the art of palliative medicine is key to good management of death rattle. It is clear that relatives' response to the sound of death rattle is both complex and individual. For some, though not all, a timely warning that the patient's breathing may become noisy as they are close to death is useful. A helpful analogy to draw is that of snoring, i.e. that the person who is snoring is generally oblivious to the sound and undisturbed by it, whilst those around them may be badly affected by the sound. Another helpful analogy (admittedly based on the assumption of retained airway secretions) is that of the sound caused by blowing air through a tube in which there is some water. The key element of communication with relatives in this Part III

situation is to find out what they think is going on, and provide explanation and clarification. Some relatives may find reassurance when a professional goes with them to the patient's bedside and points out exactly why the professional does not deem the patient to be in distress. Because death rattle does not occur in all dying patients, for some relatives it may be prudent to wait to see if death rattle occurs before offering explanation. It is also important for professionals not to assume that relatives understand the implication of the onset of death rattle, i.e. that death is imminent—they may need to point this out to relatives.

Thoughtful and wise professional judgment is required when making decisions about how best to manage death rattle in a particular situation, whether and when to use any pharmacological or non-pharmacological intervention, and responding to relatives' questions with sensitivity, clarity and honesty. To develop such practical wisdom, professionals need to take time to reflect and engage in conversations with their peers about what they do and why they do it.

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Part III

Palliative emergencies

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Introduction

Palliative care emergencies are situations and/or conditions during which the life and/or the quality of life (QoL) of a patient with an incurable disease are acutely influenced in a negative way. Palliative care emergencies are causing major distress in patients and their surroundings and should be addressed beforehand in order to know and acknowledge the wishes of the patient in relation to their handling (end-of-life issues) and to inform them how to act when they occur. It is also imperative to try to prevent them and when they occur to act adequately in order to limit harm [Schrijvers, 2011].

Palliative care patients are suffering from a wide range of pathologies and were historically mostly cancer or neurological patients, or patients with acquired immune deficiency syndrome (AIDS) due to human immunodeficiency virus. In the last decade, the focus of palliative care has broadened to include other groups of patients with incurable diseases such as terminal cardiac, pulmonary and renal diseases. All of these different fields of medicine have determined and given guidelines for their disease-specific emergencies, and they are described elsewhere. This review focuses on specific physical emergencies that are prevalent in palliative care patients.

Pain

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage [Schrijvers, 2007]. Uncontrolled pain should be regarded as an emergency in palliative care since it has a profound impact on QoL. Pain is prevalent in palliative care patients with cancer (up to 95%), but pain has also been reported in patients with AIDS, heart disease, chronic obstructive pulmonary disease (COPD), or renal disease with

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prevalence rates between 34-96% [Solano et al., 2006].

Pain can be classified according to their duration (e.g., acute, chronic, breakthrough pain) or by their pathophysiologic mechanism (e.g., nociceptive or receptor-mediated versus neuropathic or neural damage-linked pain).

Many palliative care patients are suffering from chronic pain, which is defined as pain with a duration of 3-6 months. Breakthrough pain episodes, defined as transitory flare-ups of pain in the setting of controlled chronic pain by analgesics, occur in many patients and influence negatively QoL.

Both newly occurring acute and breakthrough pain should be managed adequately to prevent the worsening of QoL, while chronic pain should be controlled by using adequate pain control measures.

Pain management is inherent to palliative care and consists of different steps:

Evaluation of pain

Pain should be routinely evaluated by validated instruments [e.g., visual analogue scale (VAS), numerical scale], while specific scales can be used to differentiate between nociceptive and neuropathic pain (e.g., Leeds Assessment of Neuropathic pain, Pain ID, Neuropathic Pain Symptom Inventory, Neuropathic Trial Symptom Scale, Neuro-pathic Pain Scale). Pain scores should be recorded in the patient file to evaluate the evolution of the severity of pain and the impact of different interventions.

Medical management

Medical treatment is able to control pain in up to 80% of patients. It makes use of analgesics, which act on receptormediated pain and of adjuvant or co-analgesics, which have different mechanisms of action on processes involved in 492

the pain syndrome (e.g., neural damage, muscle spasm, inflammation) [Schrijvers, 2007].

Chronic nociceptive pain is treated with analgesics according to the guidelines (pain ladder) of the World Health Organisation (WHO). Patients with mild pain are treated with non-opioids (e.g., paracetamol, non-steroidal anti-inflammatory drugs); those with moderate to severe pain with fast-acting weak and strong opioids, respectively. Once treatment starts, it should be given in a continuous way (by the clock) to prevent and control pain; by the easiest administration form (oral, rectal); and adapted to the individual patient. Adjuvant or coanalgesics can be combined with analgesics for better pain control and their opioid-sparing effects.

Chronic neuropathic pain can be treated with analgesics, although suboptimal pain control is observed in many patients. Other drugs that can be used are anti-epileptics, anti-depressants and local anesthetics.

Breakthrough pain should be prevented or treated immediately with fast- and short-acting opioids. The most frequently studied agents are mucosal fentanyl or parenteral morphine [Zeppetella, 2011].

At the end of life, difficulties in swallowing or decreased systemic circulation with changed absorption are observed. Therefore, parenteral administration of opioids may be indicated to control chronic or breakthrough pain.

In the event of a severe increase in pain, an acute pain crisis may occur. This should be controlled by parenteral opioids. If the pain crisis is not controlled, midazolam in combination with opioids can be administered subcutaneously.

Dealing with acute side effects due to medical treatment

The use of analgesics and co-analgesics can lead to disturbing side effects and this should be discussed with patient and family.

In opioid-naïve patients, the use of opioids can lead to nausea and vomiting in around 26% of patients for which anti-dopaminergic drugs (e.g., haloperidol, metoclopramide) should be used while respiratory depression occurs in 1.5% [Cepeda *et al.*, 2003]. Other acute side effects that can occur both in opioid-naïve and opioid-treated patients are sedation, delirium, which should be treated with neuroleptic drugs and/or acute bladder retention leading to agitation [Benyamin *et al.*, 2008].

Acute dyspnea

Part IV

Dyspnea or breathlessness is defined as an uncomfortable

awareness of breathing and is a common symptom in palliative care patients [Schrijvers, 2011]. Breathlessness is a frequent symptom in palliative care patients with specific cancers (e.g., lung cancer), COPD and heart diseases with prevalence rates between 60-90% [Solano *et al.*, 2006]. Acute dyspnea is the most frequent reason for an emergency admission in palliative care and has a severe impact on the QoL.

The main causes of dyspnea are cardiovascular and pulmonary problems, acute anemia, or psychological distress. It is often associated with tachypnea, use of accessory respiratory muscles, pallor, cyanosis, tachycardia, or inspiratory stridor.

Management of acute dyspnea should be part of palliative care and consists of different steps:

Evaluation of dyspnea

The severity of the dyspnea should be scored by the patient using a VAS, the Borg or Modified Borg Dyspnea Scale or a numeric rating scale (NRS) and noted in the patient file to evaluate the evolution of the dyspnea and the effect of interventions.

Clinical examination can indicate pleural effusions, cardiac failure with increased central venous pressure or edema.

The arterial oxygen concentration does not correlate with the severity of dyspnea, but diagnoses hyperventilation or hypoxia. Other useful diagnostic tests are the hemoglobin level to exclude anemia, D-dimers to exclude lung embolism and a chest X-ray to exclude pleural or lung pathology.

Medical management of dyspnea

Patients with a specific diagnosis may benefit from a specific etiological treatment.

Symptomatic treatment can be with oxygen and medication [Ben-Aharon *et al.*, 2012].

Oxygen is only indicated in patients with hypoxia. In patients without hypoxia, no benefit is to be expected of oxygen therapy.

Systemic opioids are effective, while nebulized opioids are not indicated. Benzodiazepines can be used in patients with anxiety disorders or in palliative sedation.

Major bleeding

Major bleeding may be caused by blood vessel, platelet or

Dirk Schrijvers

Palliative emergencies

coagulation disorders. It occurs in up to 30% of patients with hematological malignancies, while in patients with solid tumors, it depends on the tumor location [Schrijvers, 2011]. Bleeding due to thrombocytopenia ($<10\times10^{\circ}/L$) is prevented by platelet transfusions.

Medical management

In patients with major bleeding, hemodynamic stabilization and transfusion of fresh frozen plasma or platelets should be given as indicated. Local pressure, endoscopic hemostatic therapy, or angiographic embolization can be used to control bleeding. In case of a known end-of-life directive against medical etiological intervention, palliative sedation should be initiated.

Acute function loss

Acute loss of a function constitutes an emergency in palliative care patients [Schrijvers, 2011]. Acute loss of a voluntary or involuntary function impairs QoL. Immediate diagnosis and treatment are necessary for recovery of functionality.

Acute motor function loss

Acute motor function loss impairs the movement of a palliative care patient and has an impact on QoL because the autonomy of the patient is influenced. The cause of the acute motor function loss can be local (e.g., pathological fracture) or most commonly due to a lesion of the nervous system (e.g., spinal cord compression, nerve compression, brain metastasis).

Pathological fracture of long bones

Patients with a pathological fracture present with moderate to severe pain that is worsened by movement. There may be tenderness, swelling and ecchymosis at the place of fracture while deformities can occur in case of dislocation. Diagnosis is made by radiography. Prevention of bone complications can by a preventive orthopedic intervention in case of an osteolytic lesion involving more than 50% of the cortex of a long bone [Schrijvers and van Fraeyenhove, 2010]. Treatment of a pathological fracture of a long bone is immobilization by a splint of fixation and pain treatment. Traction may be used to reduce patient discomfort. If signs of neurovascular compromise are present, the limb movement should be reduced by traction. Definite treatment is by an intramedullary nail followed by radiotherapy.

At the end-of-life, fixation and traction might be an option to alleviate pain, although this may lead to immobilization.

Spinal cord compression

Spinal cord compression may be due to a fracture of a spine or due to tumor invasion of bone metastases or meningeal metastatic disease. Neurological signs of spinal cord compression may be atypical. However, spinal cord compression should always be excluded in patients with cancer or osteoporosis. It can be prevented in patients with cancer by radiotherapy in case of involvement of the posterior wall of a vertebral body. Diagnosis is made by magnetic resonance imaging (MRI) of the spinal axis. Patients with a diagnosis of spinal cord compression should be nursed flat with neutral spine alignment until bony and neurological stability are ensured. A high loading dose of corticosteroids (e.g., 16 mg dexamethasone) is administered in order to decrease compression by edema. Corticosteroids should be continued until treatment with emergency surgery or radiotherapy.

Peripheral nerve compression

Peripheral nerve compression is a process that may takes some time and is seen in patients with lymph node or visceral pathologies in the vicinity of large nerves (e.g., sciatic nerve). Patients complain first of sensory deficits but eventually functional loss may occur. Diagnosis is made by electromyography and computed tomography (CT) or MRI. Acute peripheral nerve compression should be treated with anti-inflammatory drugs. In selected patients, surgery or radiotherapy to lesions causing compression can be indicated.

Brain tissue compression

Patients with brain tissue compression (brain metastases, bleeding) may complain of headache, vomiting, or visual disturbances. The functional loss is typically hemi-corporal and may be accompanied by epileptic insults. Diagnosis is made by CT-scan or MRI of the brain.

In patients with edema around a central lesion, corticosteroids may be used to diminish edema. If the symptoms of motor deficit improve and the lesion is due to tumor invasion, whole brain irradiation can stabilize the situation. If there is no improvement with corticosteroids, the effect of radiotherapy is usually limited.

Acute urinary retention

Acute urinary retention can be caused by outflow obstruction, neurological impairment, medication use, or psychological issues and is seen in around 20% of patients with acute neurological emergencies. There is an inability to pass urine, lower abdominal or supra-pubic discomfort, or confusion. Diagnosis is made by clinical examination or post-mictional echography. Acute urinary retention is treated with bladder decompression by urethral or suprapubic catheterization [Pannek *et al.*, 2012]. In patients with renal function disturbances, increased diuresis after decompression can worsen renal function.

Acute bowel obstruction

Acute bowel obstruction is due to interruption of the normal intestinal flow and is caused by intra- or extra-luminal processes or functional impairment of the gastrointestinal tract. Patients complain of abdominal distension, vomiting, abdominal cramps and pain, and the absence of flatus.

Diagnosis is made by clinical examination with highpitched or hypoactive bowel sounds, while plain abdominal radiography shows air- and fluid-filled loops. Etiological treatment comprises bypass with a stent, while patients can be symptomatically treated with nasogastric tubing, corticosteroids and somatostatin analogues.

Central nervous system disturbances

Delirium

Delirium is an acute confusional state and is present in up to 85% of palliative care patients at the end of life. It is characterized by a fluctuating mental state, disorganized thinking and an abnormal state of arousal. Significant causes are medication, withdrawal, infections, metabolic disturbances, or hypoxia.

General management

- In the first stages of delirium, the patient may be aware of the mental alterations and the patient should be reassured;
- The patient should be stimulated to perform easy tasks but excessive demands should not be made;
- The patient should be approached in an empathic and respectful way;
- The environment should be safe, comfortable and relaxing and should be familiar to the patient;

- The family should be explained that the patient is not 'losing his/her mind', that it may not necessarily be accompanied by pain or severe suffering and that it can fluctuate;
- If possible etiological factors should be treated.

Drug treatment

In case the patient becomes agitated or has perceptual disturbances (illusions, hallucinations, nightmares), symptomatic drug treatment is indicated.

Neuroleptics

Symptomatic control is brought about with the use of neuroleptics (e.g., haloperidol) [Candy *et al.*, 2012]. Haloperidol is effective for both hyperactive and hypoactive delirium and is the first treatment choice and can be administered orally, subcutaneously, intravenously, or intramuscularly. It generally has a favorable side effect profile but can lead to adverse events such as extrapyramidal symptoms with muscle stiffness, dyskinesia, and trembling.

Benzodiazepines

Benzodiazepines are effective in delirium associated with convulsions or in those induced by alcohol or sedative withdrawal. Also if a delirium does not respond to haloperidol or in case of severe agitation, a trial with benzodiazepines may be recommended. However, when used as single agent, benzodiazepines might not control delirium and worsen confusion and cognitive disturbance. When sedation is indicated, midazolam can be used.

Epileptic seizures

Epileptic seizures result from electrical hypersynchronization of neuronal networks in the cerebral cortex and are seen in patients with brain metastases, primary brain tumors, cerebrovascular incidents, metabolic disorders, medication, or substance withdrawal.

Diagnosis is made by anamnesis, the clinical picture and electro-encephalography.

Acute treatment is with benzodiazepines. In the event of an epileptic state, phenytoin or phenobarbitone is indicated.

Refractory symptoms and palliative sedation

Refractory symptoms cannot be adequately controlled within an acceptable time period and without compromising consciousness in spite of every possible intervention.

Palliative emergencies

Dyspnea and delirium are among the most common refractory symptoms in palliative care.

Treatment of refractory symptoms consists of palliative sedation, which is the intentional administration of sedative drugs to reduce the consciousness of a patient. Sedation is brought about by continuous administration of benzodiazepines or by anesthetics. Pain medication is continued and a bladder catheter is placed. Prevention of complications is intensified and support for the family is expanded [Cherny *et al.*, 2009].

Summary

Palliative care emergencies impact negatively the QoL of palliative care patients and should be dealt with to limit harm to this patient group. Certain emergencies can be anticipated and they should be discussed with the patient and family, possible scenarios should be given, and advanced directives should cleared out in order to act according to the wishes of the palliative care patient.

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Malignant wound management

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Introduction

Malignant wounds, often referred to as malignant cutaneous wounds or malignant cutaneous lesions, result from the proliferative, invasive, and destructive effects of neoplastic cells within the skin and supporting tissues [Maida, 2011]. Malignant wounds are rather varied in origin and may represent primary cutaneous neoplasm, local recurrence, or metastatic disease. Examples of primary cutaneous neoplasms include melanoma, basal cell carcinoma, squamous cell carcinoma, Kaposi's sarcoma, angiosarcoma, and cutaneous T-cell lymphoma (mycosis fungoides) [McDonald and Lesage, 2006; Gerlach, 2005; Grocott et al., 2005; Naylor, 2005; Haisfield-Wolfe and Rund, 1997]. Local and regional recurring malignancies, most commonly arising from primary skin cancers, head and neck and breast cancers, are thought to be due to residual microscopic disease or intraoperative wound contamination [Schulz, 2003]. Generally speaking, primary cutaneous neoplasms and local and regional recurrences propagate through contiguous spread. Truly metastatic cutaneous lesions arise via hematogenous and/or lymphatogenous spread from remote primary cancers [McDonald and Lesage, 2006; Gerlach, 2005; Grocott et al., 2005; Naylor, 2005; Haisfield-Wolfe and Rund, 1997].

Malignant wounds represent profoundly visible and often palpable stigmata of advanced cancer. They are

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capable of generating untold quantum multidimensional suffering for the patient and their caregivers. Thus, dealing with malignant wounds is highly complex and challenging. Optimal outcomes may be achieved through the adoption of a whole patient approach (Wound Management) as opposed to an approach that only focuses on the wound itself (Wound Care) [Maida, 2013]. Moreover, foundational to successful Malignant Wound Management is the adoption of interprofessional collaboration, an integrative approach within healthcare systems (vertically and horizontally), together with adherence to the principles of patientcentered care [Maida, 2013].

Epidemiology

A retrospective study that reviewed the records of an American cancer institution over a 10-year period reported that 5% of cancer patients of all stages had metastatic cutaneous involvement [Lookingbill *et al.*, 1990]. Subsequent analysis on the same cohort reported that 10.4% of patients with metastatic cancer experienced metastatic cutaneous involvement [Lookingbill *et al.*, 1993]. A prospective study of advanced cancer patients referred for palliative medical management found malignant wounds occurring in 14.5% of patients together with an incidence rate of 3.9 new malignant wounds per month per 100 patients [Maida *et al.*, 1993].



Figure 1 Advanced squamous cell cancer with destruction of bridge and left nasal ala.



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Figure 2 Metastatic cancer of the parotid. Complex combination of fungating, ulcerative, nodular, and indurative feature.

et al., 1999]. A recent prospective study of patients, initially diagnosed with venous and/or arterial ulcers, yielded malignant histopathology in 10.4% of chronic ulcers after being subjected to punch biopsy [Senet et al., 2012].

Wound assessment

Morphologically, malignant wounds seldom manifest singular morphologic features [Maida, 2011]. They are usually complex and are composed of multiple morphologic elements in variable proportions [Maida, 2011] as demonstrated in Figures 1-5. For this reason, it is daunting to develop a universally-accepted classification system. In one study of advanced cancer patients, 60% of the malignant wounds had a predominance of fungating (exophytic) morphology [Maida et al., 2008]. Other morphologic features manifested by malignant wounds include ulceration, induration, nodularity, and erythema. A lexicon of terms with their corresponding morphologic features is summarized in Table 1. Given the challenges in being able to describe and manually document the various morphologic details and their associated proportions and locations, it is recommended that digital wound photography be employed in the assessment of malignant wounds. The potential of digital wound photography to improve wound assessment and quality of care and outcomes is enhanced when it is part of a Wound Electronic Medical Record

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Figure 3 Advanced breast cancer showing zosteriform distribution of malignant.



Figure 5 Exophytic rectal cancer.

(WEMR) [Rennert *et al.*, 2009]. Digital photography of wounds promotes increased accuracy in the documentation of wound morphology, geometry and dimensions [Rennert *et al.*, 2009]. Examples of two-dimensional digital protocols include VERG and VISITRAK [Ahn and Salcido, 2008]. These digital methods demonstrate increased accuracy over manual two-dimensional documentation of wounds. The use of stereophotographic technology and protocols have



Figure 4 Exophytic rectal tumour arising from site of perineal resection. Ulcerative component shows active bleeding.

the potential to document wounds in three dimensions, hence are able to estimate wound volumes. Examples of three-dimensional digital protocols include ATOS II and MAVIS [Ahn and Salcido, 2008].

Prevention

Given the profound effects that malignant wounds have on patients it behooves healthcare professionals to embrace all available evidence-based methods for their primary and secondary prevention. Adjuvant radiotherapy and chemotherapy in the setting of women with breast cancer, following a modified radical mastectomy, have been associated with improved survival together with reduced rates of cutaneous recurrences in both premenopausal and postmenopausal women that presented with nodal disease [Rutqvist and Johansson, 2006]. Early excision of primary cutaneous malignancies may decrease the risk of recurrence [Sladden et al., 2009]. In the case of primary cutaneous melanomas, a recent systematic review and meta-analysis has demonstrated more evidence to support a 2 cm margin than a 1 cm margin as the minimum margin for surgical excision; this was associated with the best overall disease-free survival and lowest rate of loco-regional recurrence [Haigh et al., 2003]. Surgical techniques targeting intraoperative wound contamination and residual microscopic tumor at surgical sites are being studied. A xenograft model using human hypopharyngeal squamous cell carcinoma, demonstrated lower rates of loco-regional recurrence in both treatment groups that were irrigated with saline or gemcitabine

Iable I Morphologic element	nts of Malignant Wounds (adapted from www.vincentmaida.com)
Common nomenclature	Morphologic features
Fungating	Exophytic
Ulcerative	Cavitating
Subcutaneous nodules	Hard nodules beneath intact skin
Carcinoma erysipeloid	Indurated skin that is flat but erythematous having the appearance of cellulitis but does not respond to antibiotics
Carcinoma en cuirasse	Indurated skin that is flat
Elephantiasic	Indurated skin that is raised, thick and lymphedematous. Hyperkeratosis and papillomatosis is often present
Schirrous (Morphea)	Scleroderma-like tightness due to dermal reaction. May be localized or multifocal
Carcinoma telangiectoides	Red patches with telangiactasia
Zosteriform	Pustular appearance similar to herpes zoster. Often in a peripheral nerve or dematomal distribution due to perineural propogation

[Allegretto et al., 2001].

Prognosis

Within Wound Management prognosis may be stratified into "quoad sanantionem", the likelihood of wound healing, and "quoad vitam", the association between the wound and the patient's survival [Maida, 2013]. Intuitively, when malignant wounds are small, singular, and occur in the setting of younger patients, intact performance status, early stage disease, and relative lack of medical co-morbidity, there may some marginal potential for complete resolution through definitive surgical resection together with adjuvant disease modulating therapies such as chemotherapy and radiation therapy. However, when malignant wounds occur in the setting of advanced metastatic cancer, with limited life expectancy, resolution is not a realistic outcome. In fact, there are only incompletely substantiated anecdotal case reports, involving small numbers of patients, where complete resolution of malignant wounds occurred [Lo et al., 2007; Haisfield-Wolfe and Rund, 1997]. Although complete wound healing is unlikely, malignant wound maintenance (stabilization) may be achieved through the use of 6% Miltefosine, a topical cancer cytostatic agent. A randomized, double-blind, placebo-controlled, multicenter trial demonstrated that 6% Miltefosine was superior to placebo in extending the time to treatment failure of malignant wounds in a cohort of breast cancer patients [Leonard et al., 2001]. A novel therapy that also holds potential to achieve malignant wound maintenance (stabilization), as well as wound palliation (wound-related pain and symptom management) is

electrochemotherapy [Grocott *et al.*, 2013; Mali *et al.*, 2012]. Electrochemotherapy consists of administering, either locally or systemically, low-permeant drugs (e.g., cisplatin) or non-permeant cytotoxic drugs (e.g., bleomycin), followed by the application of electric pulses to the area to be treated at a point when the concentration of the drug in the tumor is at its peak. This process leads to the formation of nanoscale defects on the cancer cell's membrane. As a result, molecules of the cytotoxic agents can freely diffuse into the cytoplasm and exert their cytotoxic effect. A recent systematic review and meta-analysis of electrochemotherapy, derived from 44 studies and involving 1,894 malignant wounds, demonstrated complete response rates and objective response rates of 59.4% and 84.1% respectively [Mali *et al.*, 2012].

Survival of patients with malignant wounds has been increasing over the past four decades. Data published in 1966 demonstrated that patients survived an average of only three months after the development of cutaneous metastases [Reingold, 1966]. Data published in 1993 demonstrated that patients survived an average of 11.27 months after the development of cutaneous metastases, with patients diagnosed with cancers of the lung, ovary, and foregut faring the worst [Lookingbill et al., 1993]. Retrospective studies from Canada [Viagno et al., 2000] and Hong Kong [Lam et al., 2007] demonstrated that malignant wounds were not associated with decreased survival in advanced cancer patients. A recent prospective study of patients advanced cancer referred for supportive and palliative care has revealed that malignant wounds are not associated with decreased survival (HR of 1.17; 95% CI, 0.88-1.56; P=0.285) [Maida et al., 2009b]. This study used multivariable

analysis and controlled for the co-occurence of all other wounds, age, gender, Charlson comorbidity index (CCI), and Palliative Performance Scale (PPSv2) [Maida *et al.*, 2009b]. The improved survival of cancer patients with malignant wounds together with data that shows that malignant wounds are not independent factors for reduced survival are likely the result of advancements in oncologic disease modulating therapeutics over the past few decades, especially in the setting of breast cancer.

Wound palliation

Given that malignant wounds are predominantly nonhealable in the setting of advanced cancer one of the prime goals of wound management relates to optimizing wound palliation (wound-related pain and symptom management). Malignant wounds generate the greatest levels of physical symptoms among all wound classes [Maida et al., 2009c]. Pain is the commonest symptom caused by malignant wounds and is reported by almost one third of patients [Maida et al., 2009c]. Other common symptoms include exudation, odor, pruritus, and bleeding [Maida et al., 2009c; Schulz et al., 2002]. Patients with malignant wounds also report being distressed from the mass effect of fungating wounds, as well as being concerned about their cosmetic/ esthetic implications [Maida et al., 2009c]. One of the keys to ensuring optimal wound palliation is the ability to measure and quantify patient-reported accounts of their pain and other wound-related symptoms. This may be facilitated through the use of the Toronto Symptom Assessment System for Wounds (TSAS-W) [Maida et al., 2009c]. Designed as a concise and easily administered assessment instrument, TSAS-W may be applicable to all wound classes. Modelled after the globally adopted Edmonton Symptom Assessment System, TSAS-W utilizes 10 numeric rating scales, each ranging between 0 and 10, that allow for the scoring of the commonest wound-related symptoms (Figure 6). The summation of all ten scales equates to the Global Wound Distress Score (GWDS) [Maida et al., 2009c]. In addition to being able to assess clinical outcomes in clinical wound palliation, TSAS-W may also be useful in evaluating wound palliation through clinical audits and research.

Pain

Pain associated with malignant wounds may be within the wound itself, peri-wound skin, regional, or referred. A

prospective study of malignant wounds in patients referred for palliative care demonstrated that of all morphologic types, malignant ulcers have the greatest propensity to be painful [Maida et al., 2009a]. In addition, the anatomic sites associated with the highest pain prevalence are the perineum and genitalia [Maida et al., 2009a]. Pain related to malignant wounds may be temporally categorized as baseline pain and breakthrough pain [Gallagher, 2013; Woo et al., 2013; Maida et al., 2009c]. Baseline pain, also referred to as background or persistent, occurs without movement or other provocative factors [Payne, 2007; Portenoy and Hagen, 1990]. Breakthrough pain represents a transitory and episodic escalation of pain experienced when a patient has a reasonably stable and adequately controlled level of baseline pain [Gallagher, 2013; Payne, 2007; Portenoy and Hagen, 1990]. Breakthrough pain may be stratified into pain that occurs spontaneously, without any provocation, or that which occurs as a result of a particular inciting factor. The latter has been dubbed "Incident Pain" [Payne, 2007; Portenoy and Hagen, 1990]. There are two subtypes of Incident Pain, volitional (voluntary) and non-volitional (involuntary) [Payne, 2007; Portenoy and Hagen, 1990]. Volitional incident pain is the commonest sub-type associated with malignant wounds and occurs during dressing removal, wound cleansing, new dressing application, and debridement. The latter may also be referred to as "wound-related procedural pain" (WRPP) [Gallagher, 2013]. Another example of volitional incident pain occurs during the passage of urine and/or stool in the setting of perineal or genital malignant wounds. An example of non-volitional incident pain occurs when a patient with a cranio-facial malignant who suddenly coughs or sneezes.

Pathologic mechanisms through which malignant wounds generate pain include nerve damage, tissue ischemia, inflammation, and infection [Gallagher, 2013; Woo et al., 2013]. Thus, wound-related pain is generated through a combination of nociceptive (inflammatory) and neuropathic mechanisms. When wound pain becomes chronic, secondary mechanisms mediated through NMDA activation, neural sensitization (peripheral and central), and neuroplasticity may serve to perpetuate and amplify a patient's pain experience [Jarvis and Boyce-Rustay, 2009]. However, it must be acknowledged that wound-related pain is a multi-dimensional construct that includes not only the physical, but also psychological (cognitive and emotional), social (personal and contextual), spiritual, and existential dimensions [Woo et al., 2013]. Thus, it is consistent with the concept, initially forwarded by Dame Cicely Saunders,

Patient's Nar	ne:								-	Da	te:	dd	Time:
Study ID:	w	lour	nd I	D:					_		١	Vour	nd assessment number:
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*Please circl	e the number t	hat l	bes	t d	eso	crib	es	yo	ur 1	wo	un	d-re	lated symptoms over the past 24 hou
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No Pain betw and/or debride	een dressings ement	0	1	2	3	4	5	6	7	8	9	10	Most severe Pain between dressing and/or debridement
No Drainage (or Exudation	0	1	2	3	4	5	6	7	8	9	10	Most severe and/or continuous Drainage or Exudation
No Odor		0	1	2	3	4	5	6	7	8	9	10	Most severe Odor
No Itching		0	1	2	3	4	5	6	7	8	9	10	Most severe Itching
No Bleeding		Ō	1	2	3	4	5	6	7	8	9	10	Most severe and/or continuous Bleeding
No Cosmetic concern and/c	or Aesthetic or distress	0	1	2	3	4	5	6	7	8	9	10	Most severe Cosmetic or Aesthetic concern and/or distress
No Swelling o around woun	r Edema d	0	1	2	3	4	5	6	7	8	9	10	Most severe Swelling or Edema around wound
No Bulk or Ma from wound	ass effect	0	1	2	3	4	5	6	7	8	9	10	Most severe Bulk or Mass effect from wound
No Bulk or Ma from dressin g	ass effect js	0	1	2	3	4	5	6	7	8	9	10	Most severe Bulk or Mass effect from dressings

Figure 6 TSAS-W tool that assesses wound palliation (wound-related pain and symptom management).

of "Total Pain" [Saunders, 1963].

Management of baseline pain

Successful management of wound-related pain may be achieved through a multifaceted and patient-oriented approach [Woo *et al.*, 2013]. This is comprised of pharmacologic agents, systemic and topical, together with appropriate local wound measures, physical therapies, cognitive therapies, patient education, patient empowerment, and anxiety reduction [Woo *et al.*, 2013]. Given that all of the aforementioned therapies cannot be delivered by a single healthcare professional, it is clear that interprofessional collaboration is an imperative. As no one analgesic is a panacea, combination therapy is indicated as described by the WHO pain ladder and Twycross' method of "broad-spectrum" analgesia [Twycross, 1999]. Generally speaking, combinations of opioids and adjuvants such as the gabapentinoids, tricyclic antidepressants, SNRI's, SSRI's, and cannabinoids, as outlined in the Canadian Pain Society's guidelines for chronic neuropathic pain, are effective in the majority of cases [Moulin *et al.*, 2007]. Topical analgesia may be achieved through the use of, opioids, such as morphine sulfate [Zeppetella *et al.*, 2003; Twillman *et al.*, 1999], or methadone [Gallagher *et al.*, 2005], compounded with hydrogels. Although the topical local anaesthetic Lidocaine-prilocaine, also known as EMLA (eutectic

Table 2 Commonly used	local wound management products		
Main objective	Wound management product category	Sample product	Additional benefits
Absorbent	Foam	Biatain IBU™	Topical analgesic
	Hydrofiber	Aquacel [®] Ag	Topical anti-microbial
	Alginate	Katostat™	Topical hemostatic
	Alginate with ethylene methylacrylate contact layer	Silvercel™ non-adherent	Topical antimicrobial Non-adherent
	Cellulose pulp with polypropylene contact layer	Mesorb®	Non-adherent + protects clothing
	Textile with silver complex	InterDry™Ag	Skin fold management to treat & prevent moisture lesions
Hydrating agent	Hydrocolloid	NU-DERM [™] Hydrocolloid	Autolytic debridement
	Hydrogel	Purilon™ Gel	Autolytic debridement
Topical antimicrobial	Nanocrystalline silver	Acticoat™	Absorbent
	lonic silver + hydrogel	Silvasorb [®] Gel	Hydrating agent + topical antimicrobial
	Cadexomer iodine	lodosorb™	Absorbent
	10% povidone iodine	Inadine™	Non-adherent
Anti-odor	Metronidazole	Metrogel™	Topical antimicrobial
	Charcoal	CarboFlex™	Absorbent
Non-adherent wound contact layer	Cotton + polyethylene contact layer	Telfa™	Allows moisture vapour exchange
	Polyamide net covered with Silicone	Mepetel®	Flexible & conforms to contours
Protect peri-wound skin	Barrier cream	Cavilon™	Hypo-allergenic

mixture of local anesthetics [Vanscheidt *et al.*, 2001], and the use of foam dressings containing slow-release Ibuprofen have demonstrated pain relief in painful chronic leg ulcers, no studies exist in the setting of malignant wounds [Briggs and Nelson, 2010]. Although mild levels of pain may be satisfactorily managed with topical analgesics alone, moderate to severe levels of pain will invariably require a combination of systemic and topical analgesics.

Management of WRPP

The degree of WRPP may be reduced with optimal management of baseline pain. Since WRPP may be exacerbated by removal of dressing materials that have become adherent to dry wound beds, all efforts must be made to ensure atraumatic dressing changes. Dry wound beds may be hydrated using topical agents such as Nu-Derm gel or other hydrogels (*Table 2*). However, care must be taken to avoid overhydration as the resultant maceration of the wound and its perimeter may predispose

to infection and increased necrosis. Prevention of WRPP may also be achieved by selecting wound contact layers that are non-adherent (*Table 2*) [Woo and Sibbald, 2010]. A recent study concluded that patients experienced significantly more pain with gauze than with other types of occlusive dressings [Ubbink *et al.*, 2008]. Examples of nonadherent contact layer materials used in available wound dressings include polyethylene (TelfaTM), polypropylene (MesorbTM), polyamide/silicone (MepetelTM), and ethylene methyl acrylate (SilvercelTM non-adherent). However, a recent Cochane systematic review that looked at dressings for fungating wounds did not reveal superiority of any particular dressing product [Adderley and Smith, 2007].

Given that WRPP is a type of breakthrough pain that is quite brief in duration, effective analgesics are those that match the temporal profile of the pain episode [Gallagher, 2013]. The analgesics that best fit this need are members of the Fentanyl series of opioids. These agents possess kinetic profiles that make them possess rapid onset and short

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duration [Gallagher, 2013; Casuccio *et al.*, 2009]. They may be used parenterally, or transmucousally (oro-buccal or nasal), in pre-emptive fashion, 5-10 minutes prior to the procedure [Gallagher, 2013; Casuccio *et al.*, 2009]. An alternative to the fentanyl series of opioids, in anticipated cases of severe WRPP, Nitrous oxide gas (Entonox) may also be effective [Parlow *et al.*, 2005].

Odor

Odor has been reported as the most distressing symptom reported by patients living with a malignant wound [Naylor, 2002]. One study of advanced cancer patients reported that 11.9% of patients with malignant wounds experienced wound-related odor [Maida et al., 2009a]. Wound odor may be embarrassing and lead to depression, self-imposed isolation, decreased appetite and reduced quality of life [McDonald and Lesage, 2006; Naylor, 2002; Elsenberger and Zeleznik, 2003; Gorecki et al., 2009]. Often times, the odors from fungating wounds are obvious to anyone in close proximity to the patient [Van Toller, 1994]. The pathophysiology of malignant wounds is that poor vascularization leads to devitalized, necrotic tissue which is vulnerable to bacterial colonization and infection [Rodeheaver, 1997]. Aerobic and anaerobic bacteria thrive on devitalized tissue and produce volatile amines and diamines such as cadaverine and putrescine which are thought to cause the malodor. The most common odor causing organisms are anaerobic and enteral bacteria (e.g., Enterococcus and Escherichia Coli). Recent studies found that dimethyl trisulfide (DMTS) caused malodor in malignant wounds [Shirasu et al., 2009; Woo et al., 2008].

It is important to have a holistic assessment and discussion about goals for wound care and treatment prior to initiating therapy. The American National Pressure Ulcer Advisory Panel-European Pressure Ulcer Advisory Panel (NPUAP-EPUAP) Guidelines recommend a variety of approaches for controlling odor including wound cleansing, particular dressings, proper disposal of dressings, antibiotic therapy, and, if extended life-expectancy, debridement of necrotic tissue after appropriate premedication with pain medication. The most common antibiotic approach to the treatment of malodorous wounds is topical metronidazole gel (0.75-0.80%) applied directly on the wound once per day for 5 to 7 days or more often as needed [Kalinski et al., 2005; Newman et al., 1989]. Metronidazole tablets may also be broken and the powder contents sprinkled into the wound. Systemic metronidazole might be considered if there is evidence of deep tissue infection causing malodor, however this treatment can be limited by side effects of nausea, neuropathy and alcohol intolerance [McDonald and Lesage, 2006]. One systemic review of topical treatments to control the odor of malignant wounds found that topical metronidazole and Mesalt® dressing (absorbent nontissue material made up of viscose or polyester impregnated with sodium chloride and whose action stems from the hypertonic effect produced on the lesion) yielded 2b level of evidence. Those that had 2c level of evidence were activated carbon dressings and curcumin ointment (main biologically active phytochemical compound of tumeric, Curcuma longa. Curcumin ointment is a compound that has anti-inflammatory properties by the mechanism of inhibiting cyclooxygenase and other enzymes that regulate the inflammatory cascade [Mamédio de Costa Santos et al., 2010].

More frequent dressing changes may be helpful, along with frequent wound irrigation, with normal saline, to remove exudate and odor [Naylor, 2002; NPUAP, 2009; Hampton, 2006]. Cadexomer Iodine is an antiseptic that allows for low-concentration release of iodine over time and promotes an acid pH that enhances the antimicrobial action of the iodine [Falanga, 1997]. Gauze may be saturated with Dakin solution 0.25% (sodium hypochlorite) and packed into the wound [Ferris and von Guten, 2005]. Wound odor may also be addressed by the use of dressings impregnated with activated charcoal, silver sulfadiazine or honey [McDonald and Lesage, 2006; Grocott et al., 2013; Molan, 2002]. Activated charcoal dressings have been found to minimize wound odor by attracting and binding to wound odor molecules. [McDonald and Lesage, 2006; Navlor, 2002; Goldberg and Tomaselli, 2002; Williams, 2001]. Debridement, the removal of nonviable tissue, may be beneficial to reduce odor and/or infection and to reduce pain in the ulcer. Debridement can be surgical, using a scalpel or scissors, mechanical, using irrigation or wet to dry gauze, autolytic, including occlusive moisture retentive dressings, hydrocolloids or hydrogels, enzymatic, most agents using papain or collagenase, and biologic, such as the use of larval therapy. Consider patient comfort when selecting the debridement method. Pre-medicate with pain medication before sharp or surgical debridement, and plan ahead for ways to control bleeding, which is the major limiting factor for using debridement for fungating ulcers [Eisenberger and Zeleznik, 2003].

External odor absorbers such as a tray of kitty litter or activated charcoal under the bed may be helpful.

Introducing other strong odors such as vinegar, vanilla or coffee should be avoided as the addition of these strong fragrances to the wound malodor may be nauseating for patients and caregivers.

Electrochemotherapy may reduce tumor volume and improve symptoms such as odor, exudate and bleeding. It is generally well tolerated with minimal side effects, and given over a single outpatient session over a couple hours. It may be effective for malignant wounds which are refractory to other treatments [Grocott *et al.*, 2013].

Exudate

Almost one fifth of patients with malignant wounds referred for palliative care require measures to control woundrelated exudation [Maida et al., 2009a]. Wound tissue edema and vasodilation creates an inflammatory process and fluid production in the extracellular space. This exudate from chronic wounds can injure surrounding tissue and aggravate the inflammatory process. The denuded tissue is painful and increases the size of the ulcer [Alvarez et al., 2002]. Exudate can contain proteins, and when exudate volume is high or chronic, serious hypoproteinemia can occur, possibly exacerbating an already low albumin level due to other comorbidities in the patient [Alexander et al., 1995]. Excess exudate may cause periwound maceration [Hampton, 2006; White and Cutting, 2006]. Protecting periwound tissue is important and may be a challenge. Copious exudates can be absorbed with alginates, absorbents and foam dressings. It is important to change dressings when strikethrough is present. If the wound has a small opening with high output, exudates may be contained by placing drainage stoma appliance (such as a urostomy bad) over the wound. When exudate is high, care should be given to the periwound area to include the use of a skin protectant or barrier cream [McDonald and Lesage, 2006; NPUAP, 2009].

Bleeding

Bleeding occurs in about 5% of patients with malignant wounds [Maida *et al.*, 2009a]. Dressings must be removed carefully to avoid excess wound bleeding. Warmed saline may be used to moisten the dressing and prevent adherence to the wound. Hemostatic dressings include calcium alginates, such as Kaltostat[®], (with caution in fragile tumors), collagen, non-adherent gauze, gel foams and sucralfate paste. Silver nitrate sticks or sucralfate paste may be applied directly to the wound when there is a small amount of bleeding. If active bleeding persists, hemostasis is usually achieved by applying gentle pressure for around ten minutes [Goldberg and Tomaselli, 2002]. If the wound continues to bleed, apply gauze saturated with an epinephrine 1:100 solution (may cause local necrosis), topical low dose (100 µ/mL) thromboplastin, or 0.5-1% silver nitrate [Naylor, 2002]. Hemostatic surgical sponges may be used but are also costly. Oral antifibrinolytics, radiotherapy and embolization are sometimes used to control spontaneous bleeding from fungating wounds eroding into surrounding blood vessels. If the patient is close to the end of life and is having a large amount of uncontrolled bleeding, use of dark bed sheets and towels for cleanup will lessen the shock of bright red blood on white linens for the staff and family. When this occurs, time permitting, sedation with benzodiazepines and pain control with opioids is suggested [McDonald and Lesage, 2006].

Pruritus

Pruritus occurs in about 5% of patients with malignant wounds [Maida *et al.*, 2009a]. Malignant wounds may be very pruritic and are often unresponsive to systematic antihistamines. A randomized controlled trial of chronic, closed burn wounds found that topical doxepin 5% cream, a tricyclic antidepressant with antihistamine properties, was successful for pruritis, but not assessed for malignant wounds [Demling and Desanti, 2003]. One study showed gabapentin to be effective for pruritic healing burn wounds in children [Mendham, 2004]. Other treatments have been tried, such as cooling a hydrogel dressing, or topical menthol compounded in a cream on closed wound surfaces [Naylor, 2002]. A trial of transcutaneous electrical nerve stimulation (TENS) may also be attempted [Grocott, 2000].

Psychosocial implications of malignant wounds

There has been minimal investigation of psychosocial and spiritual issues associated with malignant wounds. Issues that have been identified include: effects of malodour; social isolation [Alexander, 2010; Chrisman, 2010; Watret, 2011]; reduced self worth [Alexander, 2010]; altered body image [Lazelle-Ali, 2007]; stigma; altered relationships [Lawton, 2000]; affective disorders [Alexander, 2010]; existential issues associated with approaching death and the search for meaning—in life, in suffering and in death [Piggin and Jones, 2007]. Unless they are in denial, it is difficult for patients to ignore existential issues when the rapid and ongoing destruction of a part of the body serves as a constant reminder of the progression of the cancer and impending death [Watret, 2011]. Any distress associated with a malignant wound is likely to be heightened still further if the wound occurs in highly visible (head and neck) or intimate (breast or perineum) areas [Watret, 2011; Lawton, 2000]. When faced with such issues, it is perhaps easy to understand why people with malignant wounds describe their lives as altered existences dominated by the demands of a wet and smelly wound [Alexander, 2010].

One phenomenon recognised in the literature is the delay in seeking medical assistance because of embarrassment and shame related to the malodorous and exuding wound. Unfortunately, by the time some patients seek assistance, wounds are well advanced and treatment options are limited [Dolbeault and Baffie, 2010; Lund-Nielsen et al., 2011; Nashan et al., 2009]. This phenomenon is a good example of psychosocial issues influencing physical treatment. It also highlights the need for greater understanding of psychosocial issues so holistic treatment can be designed to maximise patient outcomes. However, the lack of investigation into the psychosocial and spiritual needs of patients with malignant wounds has resulted in a concomitant lack of evidence on which to base their management. The need for evidence-based guidelines will become even more crucial in the future as increasing longevity and cancer survival rates increase the incidence of malignant wounds [Nashan et al., 2009]. In the meantime, although not totally satisfactory, broader principles of palliative care and chronic wound care may be drawn upon for guidance. However, particularly in a disorder as distressing as malignant wounds, clinicians must bear in mind the probability that general guidelines will require contextualisation if they are to be effective.

Psychosocial management

The first step of any management plan must be a comprehensive and individualised assessment to identify issues and guide interventions. Assessment must also be ongoing to identify changes and determine the success of interventions [Chrisman, 2010]. In the context of malignant wounds, it will also be necessary for clinicians to remember that they may have limited time in which to implement treatment plans.

Borrowing some of the strategies from the increasingly popular narrative therapy, storytelling is a simple and cost-effective intervention that recognises patients as the experts on how the wound has affected their lives [Emmons and Lachman, 2010; Lindahl *et al.*, 2010; Lund-Nielsen *et al.*, 2005]. There are other benefits for both patients and clinicians. Patients can benefit therapeutically and cathartically when they know their stories have been heard and their difficulties acknowledged [Richardson, 2002]. Clinicians may benefit by learning more about the presenting condition and its impact on patients [Taylor, 2011]. Time permitting, legacy therapy can also be invoked to assist patients to turn their stories into a lasting memorial or legacy for their family. Also known as dignity therapy, legacy therapy has been shown to reduce suffering in palliative care by helping people focus on the positive aspects of their lives [Chochinov and Cann, 2005].

The benefits of a social support network have also been reported extensively in the literature [Detillion *et al.*, 2004; Karnell *et al.*, 2007]. Interactions with friends and family can assist in reducing stress and positively influencing wellbeing and coping processes. Unfortunately, it is often the case in palliative care that friends and family decrease the duration and frequency of their visits because they are unsure of what to say or how to handle such a sensitive situation. Similarly, just sitting with somebody and 'being present' while they endure distressing events has also been shown to be effective [Lindahl *et al.*, 2010; Fenton, 2011; Nolan, 2011].

There is good evidence of the effectiveness of cognitive behaviour therapy (CBT) and counselling in the management complex chronic conditions. Even when time is limited, CBT can be helpful through the development of enhanced coping skills [Mishra *et al.*, 2010]; relaxation; and distraction [Tremblay and Breitbart, 2001]. A study on the use of CBT in a disfigurement support unit reported positive results. Participants reported improvements in anxiety, depression, appearance-related distress and life satisfaction [Kleve *et al.*, 2002]. The combination of CBT and narrative therapy may assist patients to gain new insights into life events.

Hope is an important part of human life. It helps people cope in times of distress and trauma. In cancer patients, hope has been shown to positively influence quality of life by mediating the relationship between psychological distress and life satisfaction [Rustoen *et al.*, 2010]. Even in circumstances as distressing as malignant wounds, there is still room for hope [Alexander, 2010]. Although hope for cure is probably unrealistic, there can be alternatives: hope to leave a legacy; hope for a peaceful and pain free death.

Relationships and effective communication are also an important part of managing psychosocial and spiritual

issues for patients with malignant wounds. Because of the many needs, it is likely that care will be provided through a multidisciplinary team (MDT) approach [Emmons and Lachman, 2010]. To ensure optimum patient-centred care, effective communication with all members of the team—including the patient and family—is paramount [Lindahl *et al.*, 2010; Richardson, 2002]. Although wound care will be a major component of the management plan, it should not be allowed to eclipse the other needs of the patient [Lindahl *et al.*, 2010]. Empathy, comforting words and validation are personal skills that can be as effective as pharmaceutical interventions but with the advantage of having less side effects and being more cost effective [Chrisman, 2010; Mishra *et al.*, 2010].

Depending on the status of the patient, there may be a role for anti-depressants or other pharmacological interventions. Depression is common in palliative settings [Rhondali et al., 2012], but often overlooked [Irwin et al., 2008] or perceived as an expected outcome of terminal illness [Noorani and Montagnini, 2007]. As in other settings, however, untreated depression and other psychological morbidity can impact significantly on quality of life [Hotopf et al., 2002]. It can also increase suffering, the sensation of physical pain and is associated with increased risk of suicide and desire for hastened death [Rhondali et al., 2012; Irwin et al., 2008; Noorani and Montagnini, 2007; Rayner et al., 2011]. A systematic review concluded that antidepressants are effective in treating depression in palliative care, but the authors emphasised the need for early detection and intervention [Rayner et al., 2011]. Use in combination with CBT should also be considered [Tremblay and Breitbart, 2001]. Aware that time to therapeutic effectiveness is not always an option in palliative care, Irwin and Iglewicz reported good response rates following the use of alternatives such as ketamine and methylphenidate, but cautioned that further research is required [Irwin and Iglewicz, 2010].

Finally, consideration must also be given to the clinicians and lay caregivers providing care for the patient with the malignant wound. The small number of studies that have been conducted typically describes the experience as 'unforgettable' and generating vivid and sometimes intrusive memories over long periods of time [Alexander, 2010; Probst *et al.*, 2012; Wilkes *et al.*, 2003]. Such intense reactions place caregivers at risk of developing psychological morbidity unless appropriate support mechanisms are implemented. Although further research is required into support for care providers, formal counselling, peer debriefing and education have been shown to be helpful [Alexander, 2010].

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Cancer care for infants, children and adolescents

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Introduction

The World Health Organization (WHO) defines pediatric palliative care as "the active total care of the child's body, mind, and spirit and also involves giving support to the family. It begins when illness is diagnosed, and continues regardless of whether or not a child receives treatment directed at the disease" [WHO, 2013]. For more than ten years the American Academy of Pediatrics (AAP) has endorsed the integration of palliative care services for children with life-threatening and complex medical conditions, emphasizing a combination of disease modifying therapy with symptom relief to improve quality and quantity of life [AAP, 2000]. Pediatric Palliative Care espouses the same philosophy of palliative care interventions as seen in adult patients. However, there are some unique aspects of caring for children and their families that create a different set of challenges for care providers. In this chapter we will review some of the specific characteristics of caring for children and their families that must be considered to deliver optimal and effective pediatric palliative care.

Epidemiology

National data indicate that approximately 54,000 children die annually in US [Arias *et al.*, 2003; Hoyert *et al.*, 2006]. Seventy percent of childhood deaths are related to congenital anomalies, prematurity, cancers, progressive neurologic disorders and metabolic derangements. The causes of childhood deaths are vastly different from those seen in the adult population, thus palliative care guidelines that might suit the adult population are not necessarily appropriate for children.

More than 50% of all childhood deaths occur within the first year of life. Despite advances in prenatal care and neonatal medicine, a number of premature and sick infants do not survive to discharge [Vohr and Allen, 2005]. Early involvement with pediatric palliative care teams can offer help in complex decision making, address symptoms and quality of life issues, and support legacy building for struggling families attending a critically ill neonate. A significant number of premature infants do survive however, and live with significant disabilities. Pediatric palliative care teams can offer additional support to these families and their care providers as they navigate the complex medical landscape. Many of these children will traverse the hospital setting over and over as they grow. Early introduction to the pediatric palliative care team can be a consistent partner to help support the family emotionally, guide goals of care, and facilitate hospital re-entry as needed. The continuity of care offered by the pediatric palliative care team is especially helpful in large hospital systems where children are managed by a myriad of hospital based medical teams.

Beyond the first year of life, cancer is the leading cause of childhood mortality in the United States. With the significant improvements in curative oncology outcomes, most children diagnosed with cancer are not introduced to a palliative care. Symptom management and goals of care are managed by the primary oncology team [Dalberg *et al.*, 2013]. Even in situations of relapse disease and diagnoses with poor prognosis, only a small number of children are offered palliative care intervention [Himmelstein, 2006]. Distressed patients and parents want to "keep fighting" the disease and see palliative care involvement as "giving up". Invasive and life sustaining measures continue to be an integral part of the care for many children with life threatening illness, even at the end of life [Carter *et al.*, 2004a].

Children with congenital anomalies, cardiac malformations, neurodegenerative conditions, and genetic/

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metabolic disorders have significant morbidity, but are rarely considered to be terminally ill [Williams *et al.*, 2003]. However, many of these children will struggle with failure of medical therapy or develop debilitating symptoms later in their medical journey. Children with more chronic conditions including respiratory illness such as cystic fibrosis, blood disorders, cancers, and chronic neurologic disorders can endure years of medical therapy, only to succumb to complications or progressive disease. Each of these disease groups are targets for concurrent palliative care.

Barriers to providing expert pediatric palliative care still exist. Medical providers are skeptical of the value of palliative care intervention. They fear loss of autonomy in medical decision making and that integration of the palliative care team will create confusion and anxiety for the family [Dalberg et al., 2013]. Providers are confused about the global definition of pediatric palliative care and therefore are reluctant to engage due to their misconceptions. For instance, many medical providers consider palliative care as a field of medicine that only deals with end-of-life care. They have not recognized that the current philosophy of pediatric palliative care is more encompassing and does not preclude curative therapy. The major focus is on life-prolonging medical care that respects the patient's autonomy and quality of life [AAP, 2013]. As the national campaign for concurrent palliative care intervention builds, it is encouraged that palliative care should be offered to families early in the diagnosis of any life-altering condition.

Elements of pediatric palliative care

There are four main elements of palliative care.

(I) Medical care includes pain and symptom management, understanding illness trajectory and medical therapy options, and coordination of the medical care for optimal delivery;

(II) Communication with the child, family, and the medical providers ensures adequate understanding of disease process and prognosis, options for treatment, including alternative therapies;

(III) Goals of care planning may include advanced directives, illness prognostication, and end of life planning for patients with advanced illness. For patients with chronic complex medical disease, the role may include targeting compliance with the medical regime or support for the patient with chronicity and frustration with an uncertain medical outcome; (IV) Psychosocial and spiritual aspects of palliative care include understanding the individual and family infrastructure, defining their coping skills and understanding of disease process, assessing family resources and financial concerns, and spiritual assessment of child's hopes and dreams, spiritual life, and their beliefs about death. The delivery of these many aspects of pediatric palliative care takes a team of professionals with overlapping, yet unique roles.

The pediatric palliative care team

The delivery of palliative care services to neonates, children, adolescents and their families is a complicated task and requires a team with broad experience and expertise. The multidisciplinary team consists of physicians, nurses, social workers, chaplains, child life specialists, music therapists, teachers, and other service providers to enhance the child's experience, while supporting the medical interventions and communication with the medical team. The palliative care team providers should have experience managing children with complex chronic disease and life-limiting illness. Ideally, the team members will have achieved certifications within their own scope of practice.

Unique to Pediatric Palliative Care Team is the role of the child life specialist who addresses the child's concerns taking into account the developmental and cognitive level. These professionals play a pivotal role in dealing with the affected child and their siblings, helping them understand the complexities of the illness and medical care. They delve into the emotional reactions to the medical situation and gather information about the child's fears and worries about what is happening to them. They often engage the child in playful activities that are informative and non-threatening. This type of information is shared with the care team and ensures that the family and team can work together to address not only the concerns about the medical care and illness progression, but also the child's hopes and fears. Child life professionals also help families participate in legacy building and bereavement planning. More and more they are called upon by adult medical teams to attend the children of sick adults to help them understand and cope with end of life situations [Sutter and Reid, 2012].

Another unique feature of pediatric palliative care includes engaging the broader community for the affected child; involving teachers, spiritual community, extended family and classmates. Education about the medical illness, disease trajectory, and declines in health helps to inform and set expectations for when the affected child returns to school and their community. It helps to create an atmosphere of open communication and dispels the mystery and confusion that often accompanies a child's return. Furthermore, as the medical journey unfolds, open communication with community participants will allow them time to prepare for changes in the child's health. In situations of expectant loss, a social worker, chaplain, and child life specialist on the palliative care team can direct anticipatory grief, bereavement support and legacy building that can be instrumental in helping the family and their larger community engage in mutual support, grief, life celebration and healing.

Music therapy and art therapy are often utilized by pediatric palliative care teams to engage the child in selfexpression and play [Fagan 1982; Stevens 1993]. Frequently this nonverbal, indirect expression can allow the child to reveal their emotions about their unique situation and opens the door for discussion about their feelings and needs. Hopes, fears, anger and frustration can safely be put on paper or in a drawing and can be the trigger a therapist needs to begin to explore those feelings. Art therapy can be a very effective tool for siblings as well, depending on their age and involvement.

There are a host of other supporting team members that may include a pharmacist to help with medication recommendations; home care agencies to deliver home based medical equipment and medical supplies, public health nurses, tutors, and medical transportation companies. Massage therapy, physical, occupational, and speech therapies, as well as acupuncture can be used in specific situations to provide optimal symptom relief and improve quality of life.

Unique aspects of caring for children and adolescents

In pediatric medicine, it is critical to understand the family structure. Unlike adult medicine where the patient has the autonomy to make all the decisions, it is the parents of the affected child who determine the medical decisions with the physicians. Depending on the family structure, cultural perspective, and even spiritual community, the medical team might find a group of people participating in the medical care of the child. Understanding the hierarchy and role that each person plays is pivotal in creating a working relationship with the group to maximize the benefit to the child. More challenging, is the setting of separated/divorced parents where agreement about medical decision making may be conflicted. The palliative care team often assists in helping to assign roles and can also function as mediator for family meetings, particularly when aligning the goals of care and communication with care providers become problematic. It is especially important to come to consensus about how to present information about diagnosis and prognosis to the affected child and siblings. Often parents are uncomfortable with telling their children all of the details of the medical care, particularly if the diagnosis is serious or life threatening. Utilizing the child life specialist in conjunction with the medical team can alleviate parental anxieties and create a safe space for open dialogue about the diagnosis and what it means.

Developmental age

It is particularly important to consider the age and developmental stage of the affected child (and siblings) when considering discussions about diagnosis, prognosis, medical intervention, and future plans. Finding a way to relate to the child at a developmentally appropriate level will help alleviate fears on the part of the parents about their child's understanding. To do that, one must first understand how children conceptualize illness and death [Thompson and Gustafson, 1996; Kenyon, 2001; Gibbons, 1993]. A child under the age of two years will not have any concept of illness or death. They will mainly react to the stimuli around them and need parents to console them. Preschool aged children will not perceive that death and living are mutually exclusive. They often have magical thinking at this age and may believe that death is like sleeping or someone who has gone away. They rarely are intuitive about their own mortality. They also see illness and the medical interventions and painful procedures as punishment for something they did wrong. They need repeated assurance that nothing they did caused the illness.

The school age child is more likely to have a concrete view of death. They have more intuitive understanding of their own health and often are aware of their prognosis without being told. They also are more likely to pretend that they feel better than they do in an effort to protect their parents. Open ended communication about their hopes and fears should be encouraged. This allows the patient to express fears, but also creates the stage for them to complete undone tasks, like organizing gifts to their siblings of special mementos, collections, etc.

The younger adolescent (11-13 years) is typically still immature and is fairly concrete in their thinking. They are emotionally vulnerable and still view consequences in distant terms. The older adolescent is capable of more realistic understanding and often can speculate of the consequences of death. As a teen gets older they establish a sense of who they are as people, who they relate to, and can appreciate the loss of what life was going to be for them. They also take on more independence and want and deserve more autonomy about decision making. For some older teens with chronic debilitating disabilities, they may be cognitively limited, but still yearn for the independence of their peers. Even teens who are cognitively intact struggle with personal freedoms due to the demands of medical care and/or physical limitations of their disease. Palliative care teams need to be sensitive to the need for adolescent autonomy and respect their need to be offered and make choices independently.

It is important for the pediatric team to recognize that the psychological suffering related to pediatric chronic and life-threatening illness is not limited to the affected child and will extend to immediate and extended family and their community. The pediatric palliative care team often will work with the family to identify important people to include in the circle of support.

Legal and ethical issues

Legal and ethical issues surface in palliative care specific to decision making for minors, advanced care planning, and withholding or withdrawing life sustaining treatment. In the aftermath of the "Baby Doe" regulations in the mid-1980s in which withholding medical care for an infant with life-threatening condition was deemed medical neglect, neonatologists have adopted various strategies in managing extremely premature and critically ill newborns. The current approach is variable with a spectrum of approaches including supportive care only for infants with highly unfavorable prognosis (i.e., trisomy 18) to aggressive therapy for all infants and then re-evaluation to see if the baby survives. In some cases, the infant is unable to make the anticipated progress and discussion ensues about withdrawing life sustaining support.

Pediatric palliative care teams use a set of widely accepted bioethics principles for guiding medical decisions: (I) treatment is ethically obligatory because it clearly benefits the child; (II) treatment is futile and should not be provided; and (III) treatment outcomes are ambiguous and uncertain and medical providers, parents, and children, if they are capable, must make decisions together about whether or not life-sustaining treatment should be offered [Lantos, 2011]. In settings where a child is dying, the issues are typically straightforward and palliative care teams can work collaboratively with primary medical services to provide symptoms relief and anticipatory guidance as the case moves towards its natural end. Ethical issues arise when there is conflict either between the family members themselves, the patient and medical providers, or between the medical professionals. In that case, involving the hospital Ethics Team can be extremely helpful in clarifying the concerns and arriving at a conclusion.

Decision making

Respect for autonomy is a fundamental ethical principle within medicine. In the care of minors (children less than 18 years), parents have been assigned the role of surrogate decision maker in the medical setting. While we want to inform the child about the medical problem and the treatment plan, it is generally felt that parents are the persons best able to act in the child's best interest. However, in the case of the middle to older adolescent child, there is research suggesting that they are competent to make decisions for themselves, including the ability to make decisions about end-of-life care and should be given the opportunity to participate in these discussions [Freyer, 2004; Hinds et al., 2005]. Children and younger teens may have capacity to understand the gravity of the medical situation and should be given decisional opportunities with their parent's knowledge and support. While autonomy of action may not be appropriate for young children and adolescents, their thoughts and feelings about their diagnosis, prognosis, and treatment must be respected.

Communication to all of the caregivers will help to foster collaborative working relationships working towards the same goals of care. Open communication will help to resolve conflicts and misunderstandings about disease process and prognosis between the medical providers, patient, and family. Many parents want to shelter their child from information about the prognosis; however, it is very important that medical providers remain steadfast in their responsibility to provide accurate and truthful information to the patient directly, to avoid giving misinformation or false hope.

End-of-life

Discussions surrounding end-of-life care should be orchestrated so that the meeting includes the most important family members, members of the care team, and the patient if appropriate. Planning ahead allows for

unhurried and thoughtful conversation about current health of the patient, personal beliefs to be shared about what they hope for, and wishes expressed for future interventions. Involving the child in these discussions will depend on their age and developmental level. Decisions to consider advanced directive choices allows a patient and family to choose the elements of care that are right for them, including CPR, IV hydration, and even life-prolonging therapy. So often the discussion about advanced directives creates anxiety and a sense of dread, when in fact, it can be empowering by allowing the patient and family's choices for medical intervention to be clearly stated and honored. Planning this discussion in anticipation of future concerns leads to better quality decisions and improved outcome [Ashwal et al., 1992; AAP, 2003]. It is also important to state that a decision to forgo life-sustaining medical treatment does not imply an intent or choice to hasten the death of a child. The goal of palliative care is to relieve the patient of pain and suffering, improve communication and understanding, and optimize the quality of the child's experience, rather than hasten the dying process.

In some circumstances, the process of supporting a terminal patient might require rapid escalation of pain medication and anxiolytics. Many parents and providers struggle with the resultant sedation, and fear that the medications are hastening the decline they see. It is very important to stress that the disease process is contributing to the decline and that the goal of therapy at this point in their journey is to allow the patient to expire gently with dignity and without suffering. It is not unusual for distraught families to ask providers to give stronger doses of medicine to relieve the suffering of their dying child with the intent to "get it over with". Requests for euthanasia and assisted suicide cannot be granted and should be addressed compassionately. In that setting, it is critical to understand the causes of family distress that led to their request and address the issue appropriately [Dussel et al., 2010]. The Groningen Protocol was developed for specific indications when euthanasia is permissible in the Netherlands [Verhagen and Sauer, 2005]. It remains a controversial and hotly debated topic [Postovsky et al., 2007].

Cultural/spiritual issues

Dealing with the potential loss of a child is a catastrophic experience for any family. However, unique cultural differences may further influence the introduction and acceptance of palliative care. Forty percent of pediatric

providers identified cultural barriers as a deterrent to palliative care intervention [Davies et al., 2008]. Many parents will continue to seek life-prolonging medical care for poor prognosis conditions driven by cultural beliefs. For instance, Latino families often believe that every effort should be made to save the child regardless of medical prognosis [Thibodeaux and Deatrick, 2007]. African American parents with Christian values may believe in divine rescue and are hesitant to withdraw life-sustaining treatments [O'Neill et al., 2003]. Those parents might view palliative care as "less than optimal care". Discordance in treatment goals, poor understanding about palliative care services, and the need "not to give up hope" often leave medical providers and families at odds leading to a delay in palliative intervention [Davies et al., 2008; Mack and Wolfe, 2006; Koenig and Davies, 2002]. These varied examples underscore the need for providers to be mindful and sensitive to cultural preferences.

In some cultures medical decision making about goals of care will be a family decision that might include religious leaders or elders within the family. In other cultures, the mother assumes that role, based on her primary role in caretaking for the child. In some cultures, a child is not to be told that they are dying. Whereas other cultures feel that the child should be allowed to participate to the best of their developmental stage. Many Asian cultures do not want the child to know of their life threatening diagnosis or prognosis [Elwyn *et al.*, 1998; Brolley *et al.*, 2007; Song and Ahn, 2007]. Medical staff will need to ask families about their cultural preferences for caregiving and work within that context to provide the optimal care [Wiener *et al.*, 2012].

Spirituality

Spirituality is not tied to any one religious practice, but is a deeply personal sense of what is meaningful to that individual. Children are spiritual beings. Allowing the pastoral staff to participate in the care of the patient will enable each child and family to define what is most important to them. Most families have some customs surrounding end-of-life care that they would like to adopt. Asking family members about their preferences and rituals will allow providers to best provide the needed elements and avoid assumptions or stereotyping [Wiener *et al.*, 2012]. Whenever possible, offering to involve community spiritual advisors will also comfort and help support the family and child, especially at end of life, and allow continuity in bereavement and beyond.

Symptom management

Symptom management is at the heart of what medical providers try to achieve. Medications for infants and children are always determined by a weight based calculation, using milligram per kilogram. Medications for children can be delivered orally, subcutaneously, rectally, intravenously, intranasally, sublingually, and transdermally. Finding the most advantageous route will depend on several factors, including availability of IV access, alertness and neurologic function of child, organ function, and pharmaceutical availability. It is useful to know what routine medications your pharmacy stocks in order to tailor your prescription planning. In addition, it is useful to know if the pharmacy has compounding capability as most young children will not swallow pills and will need a liquid preparation and/or a pill crushed and mixed in pudding, applesauce, or yogurt.

Pain

Of all the distressing symptoms patients experience, pain is particularly troublesome, and sadly, undertreated in children for several reasons. One study estimated that only 27% of children dying from cancer had adequate pain relief [Wolfe et al., 2000]. Wolfe found that many prescribers are reluctant to prescribe regular doses of opiates due to lack of experience, fear of respiratory depression, medication interactions, and contributing to hastening death. Many patients are afraid of the taste, the side effects of the medication, and/or the stigma of taking "drugs". In many cases for children, the primary caregiver is a parent or guardian who fears addiction or tolerance to the narcotic, often leading to under dosing of the medications. The pediatric palliative care team should ensure adequate education of the family and reassure them of the safety of the medications and the schedule. Close monitoring, frequent assessment, and appropriate dose adjustments may be necessary and require vigilance and regular communication with the family and patient.

Pain assessment

The assessment of pain in a child differs from that of an adult in that one must consider the developmental age of the child. As in adults, the gold standard assessment relies on self-reporting and the oldest school aged children are able to participate in their own assessment. Caregivers and medical staff also participate in the overall pain assessment of a child.

For infants and very young children the CRIES scale is

used, which is an acronym that cues five pain indicators; crying, requirement of oxygen, increased blood pressure/ heart rate, expression, and sleeplessness [Krechel and Bildner, 1995]. Each factor is given a numerical score of 0-2 and the scores are added up. Scores that are equal or greater than 6 indicate a level of pain that necessitates analgesia. The Premature Infant Pain Profile (PIPP) was developed specifically for premature infants and measures gestational age, behavioral state, heart rate, oxygen saturation, and facial expression [Ballantyne et al., 1999]. In a similar fashion to the CRIES scale, each factor is given a scale and then tallied. High scores indicate distress and warrant medication support. Two other tools: the Neonatal Infant Pain Scale, and the Neonatal Pain, Agitation, and Sedation Scale have also been used to assess pain in infants and young children [Lawrence et al., 1993; Hummel et al., 2008]. The goal is to understand the nonverbal cues of each child, determine distress level, and intervene as needed.

As a child gets more verbal in toddlerhood it is easier to assess their play activity level and ask questions about where they hurt. Parents are able to report what they observe. It is common that young patients in pain will withdraw from normal activity, including feeding, and may require caregivers to draw conclusions from their observations. The FLACC scale was developed for children from infancy to seven years and does not require verbal interaction. It assesses five categories, face, legs, activity, cry, and consolability, hence the acronym, and scores each 0-2 points. The higher the score indicates more severe pain [Merkel *et al.*, 1997].

Another frequently used pain scale, the Wong-Baker faces rating, is used in many hospitals and clinical settings to let the parent or child identify the face that they relate to that is then correlated to pain or discomfort level. This scale uses six faces from happy smiling face to sad crying face and asks the individual to indicate what they feel today. The faces are paired with numerical even numbers to allow for a number correlate [Bieri *et al.*, 1990]. Ongoing assessment for each patient will help the clinician trend the responses to intervention and guide further management.

Pain management

Pain management principles are very like those in adult settings [Friedrichsdorf and Kang, 2007]. The WHO Pain Ladder [WHO, 1998] is a simple tool that correlates patient pain scores with graduated pain medication recommendations. The chart starts with simple non-narcotic analgesics for mild pain (scores 1-4). It recommends a week opioid for moderate pain with scores of 5-7 and use a strong opioid for severe pain with scores of 8-10. Most practitioners agree that round the clock dosing for moderate to severe pain is warranted, along with additional breakthrough pain medication as needed [Carter and Levetown, 2004b]. In general the oral route of administration is preferred; however transdermal, intravenous, rectal, subcutaneous and sublingual are accepted options, based on the patient symptoms and wishes. It is important to reiterate that dosing in children is calculated based on weight in mg/kg. See Table 1 for drug dosing recommendations. Very young infants may need substantially less medication compared to an older child due to liver metabolism. As a general rule start with 25-30% of the mg/kg estimate with neonates and infants and titrate accordingly [Moody et al., 2011]. Respiratory depression is often a reason for caregivers to withhold or under dose children with adequate narcotics, yet this complication is rarely reported in children [Gill et al., 1996].

The use of non-narcotic pain medications should be considered in each child, when appropriate. Adjuvant medications such as anticonvulsants or antidepressants can offer benefit for neuropathic pain and nonsteroidal anti-inflammatory drugs are particularly useful for musculoskeletal pain [Carter and Levetown, 2004b]. However, non-steroidal drugs such as ibuprofen should not be used in infants under six months of age [Ullrich and Wolfe, 2009]. Topical medications such as Lidoderm patches using transdermal approaches are also useful for local bone and muscular pain. Bisphosphonates and IV steroids have also been shown to be helpful with bone pain from refractory cancer in both children and adults.

Pruritis and constipation are the two most common side effects of narcotics and need to be proactively addressed with each patient. Depending on age of the child and dosing of narcotic, the side effects might be minor; however, without the proper attention to bowel habits and encouraging a scheduled laxative regimen, constipation may result. Pruritis often responds to antihistamines.

Nausea

Nausea is an unpleasant symptom that children find hard to articulate. Medications, bowel obstruction, central nervous system disease, radiation, renal failure, reflux, middle ear dysfunction, ocular problems, are just a few examples of possible causes of nausea. The prevalence of nausea and vomiting in terminally ill children was reported as high as 50% [Santucci and Mack, 2007]. Anticipating nausea and vomiting will help avoid delays in recognizing and treating the symptoms. A thorough physical exam will be needed to assess central nervous system and abdominal pathology. Re-assessment and close observation will help direct the frequency of therapy. Multiple medications are available for use in children with many options for oral, transdermal, rectal and injectable formulations.

Constipation

Constipation, defined as the difficult passage of stool, can be an uncomfortable and painful symptom. In young children it often is overlooked and can lead to irritability, abdominal distention, vomiting, and obstruction. Careful history and physical exam, and possible rectal exam, may be needed. Abdominal X-ray can be informative, especially if bowel obstruction is suspected. For typical constipation, oral agents that increase motility are recommended. Polyethylene glycol, senna, psyllium, and/or lactulose can be used to prevent constipation. Rectal suppositories, infant enemas, and child enemas are used in limited fashion. New agents, such as amitiza and methylnatrexone, are used in older patients and when traditional agents have failed.

Dyspnea

Dyspnea, the feeling of breathlessness, can be frightening for the patient and the caregivers. Dyspnea reportedly occurs in 30-80% of dying children [Wolfe *et al.*, 2008; Stenekes *et al.*, 2009]. Patients with cystic fibrosis, cancer, heart failure, renal failure, pneumonia, and neuromuscular and neurodegenerative disorders have been described with dyspnea. Depending on the underlying cause, medical interventions can be used to relieve symptoms. The medical management of dyspnea in children is similar to that seen in adults primarily with the use of opiates. Fluid overload can be treated with diuretics. Oxygen may be offered. Benzodiazepines are recommended for anxiety. Cool air with a fan is often enjoyed and gives the patient a feeling of relief.

Anorexia/cachexia/feeding

Anorexia is a common symptom that causes distress for patients and parents during a chronic medical trajectory. Focus on nutrition and feeding is a natural reaction to weight loss and cachexia. Multiple small meals and calorie supplement drinks might be successful for some patients. Appetite stimulants such as megestrol acetate, periactin,

Drug Route Dose/interval Max dose Comments Used for mild per- section mild per- sec
Used for mild pair and fever V 10-15 mg/kg q 4-6 hours 2 grams Acetaminophen PO 10 mg/kg IV q 6 hours total/day Ibuprofen PO 5-10 mg/kg q 6-8 hours 40 mg/kg/d Not for use in children <6 months
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IV/SC 1-2 µg/kg IV q 1-2 hours
IV infusion 0.05 μg/kg/hour infusion titrated
Methadone PO 0.2 mg/kg q 8-12 hours Long half-life; delayed sedation. Dose reduced
IV/SC/IM 0.1 mg/kg IV 1 8-12 hours once pain relief to avoid accumulation. At point of sedation. Stop medication
KetaminePO0.5-2 mg/kg orally q 8 hoursNot standard. Used for breakthrough pain not
IV/SC 0.1-0.5 mg/kg IV titrated responding to traditional drugs. Hallucinations/
Infusion 0.1-0.2 mg/kg/hour infusion euphoria and twitching are dose limiting side
titrated effects
Neuropathic pain
Amitriptylline PO 0.5-1 mg/kg/day Titrate to Side effects constipation and prolonged QT
150 mg/d syndrome
Gabapentin PO 5-10 mg/kg/day div tid 2,400 mg/day Titrate up to 30 mg/kg/day
Pregabalin PO 25 mg BID and titrate up Increase dose every 3-5 days up to 150 mg BID

and dronabinol can be effective. As the disease progression continues, however, honest and caring discussion with families is warranted to address the role that feeding and nutrition will play as the patient is nearing end of life. The burden of forced feeds may outweigh the long term benefit. Families need reassurance that the body metabolism will slow down as end of life nears and that persistent force feeding will not reverse the disease progression or trajectory. Moreover, they need reassurance that they have not starved their loved one and that the decline in food interest is neither painful nor stressful to the patient.

Symptoms management at end of life

As a child progresses toward the last stages of his/her life, families will need guidance about what will happen as their child dies. "What symptoms should we watch out for? How much time do we have left with our child?" are questions frequently asked by families. The ability to predict the timing of death with any reasonable certainty is poor [Himmelstein, 2006]. Families will need ongoing support from the medical staff to help the family understand what physical signs are present indicating each step of medical decline. Parents consistently report that honest and complete information is critical to help them participate in further decision making. Further, the medical staff needs to reassess the child's medical needs, eliminate anything unnecessary, and focus the medical interventions on comfort care and symptom relief. Discussion should take place about where to be for this last stage, how best to deliver the care needed, and how to support the family, whether at home or the hospital. Developmentally appropriate care should be extended to the siblings to help them understand what to expect.

In the final hours of life, physical changes appear that help guide the anticipatory counseling for the caregivers and family members. Coolness of the skin, particularly the extremities, decreased spontaneous movements, decreased consciousness, changes in breathing pattern, diminished urine output are typically seen in the final hours. Helping families understand what these physical changes mean will alleviate parental anxiety and help them prepare for the final moments. Medical staff will need to frequently assess the patient and manage terminal symptoms. In addition, staff will need to address the concerns of parents, answer questions as best they can, and be present. Medical providers underestimate how much their presence helps to support the family at this critical time [Knapp and Contro, 2009; Kars *et al.*, 2010]. Families report that demonstration of caring attitude by medical staff is greatly valued and long remembered. Furthermore, family perceptions of caring hospital staff is associated with healthy long term bereavement outcomes [Meyer *et al.*, 2006].

At the moment of death, the expression of grief will take on many forms. Allowing the family time to mourn and get over their shock is essential in the first hour after death. Some families will have specific rituals that are important to them. Identifying what these traditions are ahead of time will help ensure that they can be performed according to the family wishes. Allowing for friends and close family members to be present immediately after the loss can be a big support for the primary family. Often, in the hospital setting this requires organizing a conference space or large waiting space for family and friends to congregate in between their visiting the bedside. Child Life specialists and social workers help to coordinate the gathering and can also help with grief counseling and support, especially for siblings and young members present.

Bereavement assessments can begin before death as a family prepares for the end of life stage. Understanding the family composition, their experience with previous death and dying, their attitudes about the child's illness and medical course, cultural preferences, and spiritual supports will all be important factors in helping assist the family at the death. Activities like memory boxes, cutting a lock of hair, hand prints, and bathing can be soothing and gentle way of letting expressing their love for their child. Allowing family time at the bedside after death allows them time to process the death, express their grief, and gain strength from their family and friends. Support from medical staff may be welcome and needs to be respectful of what each individual family requires.

Ongoing follow-up with bereaved families is encouraged and often welcome [Contro *et al.*, 2002]. However, some bereaved families may not be able to accept support from the hospital staff if they perceive their experience in a negative way. It is not unrealistic to expect that families will grieve for months. Ideally, palliative care teams continue contact with families during their acute bereavement and can offer community bereavement resources to families that are local and easy to access.

Summary

The care of children with life-limiting and complex chronic disease is a challenge that many pediatric providers will face, perhaps only a few times in their career. Creating resources

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for community pediatric providers to have easy access to palliative care teams will hopefully enable providers to seek advice and collaboration for their patients. Ongoing efforts to raise awareness and educate more professionals about palliative care will hopefully dissolve some of the current barriers that hinder access to pediatric palliative care programs. With strong endorsement from the Academy of Pediatrics [AAP, 2013], it is hoped that all children with serious medical conditions can be offered concurrent palliative care support, focused on quality and quantity of life.

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Evaluation and management of aerodigestive conditions

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Introduction

According to the American Cancer Society, there will be an estimated 17,460 new cases of esophageal cancer and 226,160 new cases of lung cancer in the United States in 2013 [Siegel *et al.*, 2012]. Many of these patients will present at an advanced stage not amenable to cure, but will require palliation of their dyspnea and dysphagia [Mergener and Kozarek, 2002].

The goals for palliation of these patients include limiting dysphagia and dyspnea, and prevention and management of bleeding. Management of these patients requires a multimodality approach utilizing traditional chemotherapy and radiation as well as multiple different endoluminal therapies from photodynamic therapy (PDT) to stenting. This chapter focuses on the locoregional therapies used in the palliation of unresectable esophageal and central airway malignancy with a particular emphasis on endoluminal stents.

Esophageal cancer

Diagnosis

The classic presentation of esophageal cancer can be divided into three main categories. The first two consist of a middle-aged white male with a sudden onset of dysphagia, with or without a history of gastroesophageal reflux or a hiatal hernia. The clinical diagnosis of these patients is of adenocarcinoma of the distal esophagus or gastroesophageal junction respectively. These patients typically present without weight loss or other constitutional symptoms. The third presentation is of dysphagia and weight loss in a heavy drinker and smoker. These patients are typically middle-aged non-white males in endemic areas, with lower socioeconomic status, and have a clinical diagnosis of squamous cell carcinoma.

Staging of esophageal cancer follows a TNM classification, with depth of invasion identifying T stage, and number of lymph nodes and distant metastases defining N and M stages. Classically, barium esophagram was the diagnostic modality of choice, revealing an asymmetric, abrupt narrowing of the esophagus with nodular or ulcerated surfaces. Barium esophagram is 98% sensitive in detecting a lesion and 96% specific for esophageal cancer, with a positive predictive value of 42% [Levine et al., 1997]. Once identified, flexible video esophagoscopy allows for pathologic diagnosis and staging using cytologic brushings and tissue biopsies. Endoscopic ultrasound (EUS) with fineneedle aspiration provides information not accessible via esophagoscopy including evaluation of depth of invasion and paraesophageal lymph nodes. Distant disease is usually evaluated by positron emission tomography/computed tomography (PET CT) [Li and Rice, 2012].

Nutrition

Nutritional support must be individualized for each patient based on life expectancy, degree of dysphagia, prior surgeries, the potential for maintaining oral nutrition, and the patient's wishes. While parenteral nutrition may be used as a temporary measure, the goal for most patients should be maintenance of enteral nutrition, as parenteral nutrition has been associated with an increased risk of infectious complications, potential electrolyte and liver abnormalities, and has a high cost [Rivadeneira et al., 1998]. We prefer to attempt to maintain esophageal patency and minimize dysphagia to allow for oral nutrition for the psychological impact it has for the patient as well as limiting potential complications associated with placement of feeding tubes. If maintenance of adequate oral nutrition is not possible then gastric or jejunal feeding tubes should be placed. Percutaneous endoscopic gastrostomy (PEG) is often the first therapy of choice but if there is a possibility of future esophagectomy then surgical placement of a feeding jejunostomy should be considered to preserve the blood supply of the stomach.

Palliation of dysphagia

The palliation of dysphagia has become the primary goal of treatment in the majority of patients who present with advanced esophageal cancer. Locoregional treatment modalities including palliative surgery, repeated dilation, laser therapy, PDT, ablation therapies, and chemoradiation therapy have been used to ameliorate dysphagia; however most of these techniques usually do not offer immediate relief and can require several treatment sessions [Vakil et al., 2001; Mergener and Kozarek, 2002]. As a result, esophageal stents have become a popular method to palliate dysphagia in patients with esophageal cancer because of the immediate improvement, low complication rate, and potential for long term relief, as well as the ability to combine stenting and other therapies. This section provides an evidence based review of locoregional treatment modalities for the palliation of dysphagia and bleeding with a focus on esophageal stenting.

Surgery

Surgical palliation of esophageal cancer, including esophagectomy and esophageal bypass, is in limited use today. Patients with locally advanced or metastatic disease have excessive morbidity and mortality from surgical procedures, especially given the lack of curative intent and the fact that dysphagia and hemorrhage can usually be controlled by other techniques [Freeman *et al.*, 2012].

Esophageal dilation

Unlike most of the palliative methods in this section,

esophageal dilation with a bougie or pneumatic balloon can provide immediate relief from dysphagia [Boyce, 1999]. However, as the amount of tumor is not affected, the recurrence of dysphagia usually occurs quickly and multiple repeated attempts at dilation are often necessary, each with a small risk of perforation, which increases if dilation is performed without wire or fluoroscopic guidance [Hernandez *et al.*, 2000].

External-beam radiation therapy (ERT) and chemoradiation

While ERT has shown minimal long-term survival benefit it can provide significant palliation of dysphagia. However, it can take 1-2 months for effective dysphagia relief to occur, and duration of palliation is variable and may be too short for patients with life expectancy greater than 3-6 months [Freeman *et al.*, 2012]. Caspers *et al.* [Caspers *et al.*, 1988] reported a series of 127 patients with esophageal cancer in which improvement in dysphagia occurred in 71%. However, only 54% of patients had adequate palliation. In a series of 103 patients undergoing ERT Wara *et al.* [Wara *et al.*, 1976] reported improved dysphagia in 89% of the patients, however improvement of symptoms lasted an average of 3 months, with only 14% sustaining dysphagia relief past 12 months.

Chemoradiation (RTCT) is often the preferred initial palliative therapy for unresectable esophageal cancer in patients who do not have severe dysphagia, or in combination with mechanical interventions including dilation or stenting. In a series of 120 patients undergoing combination chemotherapy and RT, Coia *et al.* reported an 88% improvement in dysphagia within 2 weeks with maximal benefit seen at 4 weeks. Two-thirds of patients were free of significant dysphagia recurrence at last follow-up or death [Coia *et al.*, 1993].

Possible complications of RT and RTCT include tracheoesophageal fistula and post-radiation stricture which may lead to recurrent stricture requiring further intervention. Both modalities also require a significant time commitment from these patients with limited life expectancy. These considerations, in addition to the complications associated with systemic chemotherapy, must be considered when determining treatments used for palliation only.

Brachytherapy

Endoluminal brachytherapy involves repeated endoscopic placements of radioactive material at the tumor site.

Evaluation and management of aerodigestive conditions

Improvement in dysphagia with endoluminal brachytherapy has been reported in up to 70% of patients, however treatment consists of 6-8 weeks of therapy with dysphagiafree intervals of only 2-3 months [Rovirosa *et al.*, 1995]. Complications, including fibrotic stricture and fistula formation, have been reported in up to 25% of patients [Freeman *et al.*, 2012]. Thus, the significant lag time to and short duration of dysphagia relief, significant complication rate, and need for repeated endoscopies, limits the use of brachytherapy for palliation of dysphagia.

PDT

PDT uses a photosensitizer, intravenously administered prior to treatment, which is selectively taken up by the tumor tissue due to differences in tumor vascular supply and lymphatic clearance. A light matching the activation wavelength of the photosensitizer is fired onto the tumor and a chemical reaction occurs with the release of oxygen free radicals, resulting in tumor necrosis. Follow-up endoscopic assessment is often performed 2-3 days later and PDT can be repeated as necessary.

In a series of 215 patients with esophageal cancer Litle *et al.* [Litle *et al.*, 2003] reported improvement in dysphagia scores in 85% of patients 4 weeks after treatment. Mean dysphagia-free interval was 66 days. Thirty-eight percent required multiple treatments and 16% required stenting for recurrent dysphagia at a mean interval of 59 days. Of 31 patients with hemorrhage, 29 had successful resolution of bleeding.

PDT is effective at palliating malignant dysphagia and bleeding due to internal obstruction and external compression. It is relatively simple to perform and is useful in cervical pathology which has fewer therapeutic options.

Complications include chest pain, fever, leukocytosis, odynophagia, recurrent dysphagia secondary to stricture, pleural or pericardial effusion, and transient worsening of dysphagia. The photosensitizer has a relatively long half-life and can result in skin photosensitivity in up to 10% of patients, so sun exposure must be avoided for 6 weeks following treatment. PDT is expensive compared to other endoluminal techniques.

Laser therapy

Laser therapy involves the administration of light from a neodymium:yttrium-aluminum-garnet (Nd:YAG) laser to fulgurate the malignant tissue. Improvement in dysphagia can occur in 70-80% of patients but successful palliation often requires 3-4 sessions. Perforation occurs in less than

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5% of patients [Dallal *et al.*, 2001]. Limitations include high cost, difficulty in treating long-segment lesions, and need for repeated treatments.

When compared to PDT, Marcon [Marcon, 1994] found PDT to have superior palliation and fewer complications than Nd:YAG laser therapy, especially in proximal cancers and strictures greater than 8 centimeters in length. In a series of 236 patients reported by Lightdale *et al.* [Lightdale *et al.*, 1995], PDT and laser therapies provided similar rates of relief of dysphagia, but there was a trend towards a more complete response with PDT for proximal and longsegment tumors. Treatment was aborted due to adverse events in 3% of PDT patients and 19% of laser patients. PDT was limited by photosensitivity in 19% of patients.

Conflicting data exists for the comparison of laser therapy to stenting for palliation of esophageal malignancy. In a randomized controlled trial Adam *et al.* [Adam *et al.*, 1997] found a significantly greater improvement of dysphagia with self-expanding metal stents (SEMS) than with laser therapy. Dallal *et al.* [Dallal *et al.*, 2001], who randomized patients to stenting or thermal ablation, mostly by Nd:YAG laser, found that patients undergoing thermal ablation to have a longer median survival but had a longer hospital length of stay and higher healthcare costs.

Cryoablation

Cryotherapy uses endoscopic catheter directed application of a super coolant to cause cryonecrosis of the tumor. Greenwald *et al.* [Greenwald *et al.*, 2010] found a complete intraluminal response in 63% (31/49) of patients, however 20% (10/49) developed benign stricture following therapy. No serious complications were reported. Cryotherapy can also be used to manage intraluminal bleeding.

Argon plasma coagulation (APC)

APC uses charged argon gas to carry an electrical current and cause tissue fulguration. Eikhoff *et al.* [Eickhoff *et al.*, 2007] reported improvements in dysphagia scores in 94% of patients with esophageal and gastroesophageal junction tumors with an overall response of 85%. Bleeding was the most common complication.

Endoscopic sclerotherapy

Injection of alcohol or chemotherapeutic agents has been performed but there is limited data on these methods. Alcohol injection is inexpensive and does not require any special equipment, however potential complications include chest pain, mediastinitis, tracheoesophageal fistula,



Figure 1 Select esophageal stent models. (Arrows indicate strings for stent removal/repositioning. Arrowheads indicate anti-reflux valves). 1. *Gianturco* stent with Dua anti-reflux valve; 2a. Uncovered Ultraflex stent; 2b. Covered Ultraflex stent; 3. Flamingo Wallstent; 4. Wallstent Esophageal II (Covered Wallstent); 5a. Removable Fer-X Ella anti-reflux stent (initial version); 5b. Revised Fer-X Ella anti-reflux stent (Boubella); 6. Polyflex removable plastic stent; 7a. Removable Choo stent; 7b. Removable Do anti-reflux stent with internal valve (revised version); 8a. Removable Niti-S single stent; 8b. NIti-S double stent with outer uncovered segment. Reprinted from ROST—Registry of Oesophageal Stenting; The British Society of Interventional Radiology; First Report 2004 with permission from Dendrite Clinical Systems Ltd.

and perforation. Duration of palliation is often short and therapy requires multiple injections [Freeman *et al.*, 2012].

Injection of cisplatinin-epinephrine gel has been preliminarily reported with an improvement of dysphagia in some patients and requires further investigation [Harbord *et al.*, 2002].

Esophageal stents

Part IV

Modern esophageal stents are comprised of self-expanding metal or silicone frames that are introduced over a guidewire under fluoroscopic or endoscopic guidance and can be used to regain luminal patency or cover a perforation or fistula. They may be covered or uncovered and may contain anti-reflux valves to combat gastroesophageal reflux when placed near or at the gastroesophageal junction. Unlike many of the above therapies, stents offer immediate palliation of symptoms and many can be removed if not tolerated or complications occur. Stents can also be used in combination with other therapies as a temporary bridge to longer-term palliation. As such, stents have become the first line treatment for many patients. Early complications (occurring within 4 weeks) include chest pain, fever, stent migration, perforation, bleeding, globus sensation, and acid reflux. Delayed complications can present months later and include restenosis from tumor ingrowth or benign tissue hyperplasia, recurrent strictures, fistulization, and stent migration. Migration is the most common early and late complication occurring in up to 75% or patients [Hindy *et al.*, 2012]. Here we provide a brief overview of the use of esophageal stents for the palliation of esophageal malignancy. *Figure 1* shows a selection of different types of esophageal stents.

Esophageal stents

The use of stents to palliate esophageal cancer is not new. The first attempts using decalcified ivory tubes made by Leroy d'Etiolles in the mid 1800s were unsuccessful [Beynon *et al.*, 1991]. The first successful intubation of the esophagus occurred in 1885, and is credited to Sir Charter Symonds, who used a stent constructed from boxwood with a long silk stitch placed around the patient's ear to prevent migration [Symonds, 1885]. The technique was popularized in 1924 by Sir Henry Souttar using coiled metallic tubes inserted under



Figure 2 Conventional plastic stents: Atkinson (top), Wilson-Cook (middle), and Celestin (bottom). Reprinted from Gastrointestinal Endoscopy, 43(3), Kozarek RA, Expandable versus conventional esophageal prostheses: easier insertion may not preclude subsequent stent-related problem, 2., 1996, with permission from Elsevier.

direct vision [Souttar, 1924]. In 1959, Celestin developed the first plastic stent which he inserted via laparotomy [Celestin, 1959]. With the advent of fiberoptic endoscopy in the 1970s, Atkinson and Ferguson were the first to insert a plastic endoprosthesis in the esophagus endoscopically [Atkinson and Ferguson, 1977]. These conventional plastic stents (CPS) were initially the most widely used stents to be endoscopically inserted in the esophagus (*Figure 2*).

These semi-rigid plastic stents required significant dilation (up to 18 mm in some cases) prior to insertion, and were frequently (as high as 30%) associated with acute complications including a perforation rate as high as 15%, mortality rate as high as 17%, and a migration rate over 15% [Knyrim *et al.*, 1993; De Palma *et al.*, 1996; Roseveare *et al.*, 1998; Siersema *et al.*, 1998]. As a result, new self-expandable metal stents (SEMS) with a smaller and more flexible delivery system were designed.

In 1983, Frimberger inserted the first SEMS endoscopically, but it was not until 1990 that Domschke first inserted a SEMS to palliate a patient with a malignant esophageal stricture [Frimberger, 1983; Domschke *et al.*, 1990]. SEMS were easier to deploy than CPS, and because of the smaller delivery system, usually did not require significant dilation prior to insertion. With data to suggest decreased complication rates, shorter length of stay, improved dysphagia, and some evidence for decreased mortality, SEMS have replaced CPS as the most popular stent for the palliation of esophageal malignancy [Knyrim *et al.*, 1993; De Palma *et al.*, 1996; Roseveare *et al.*, 1998;

Siersema et al., 1998].

SEMS

Although SEMS offer immediate relief for dysphagia, recurrent dysphagia secondary to tumor ingrowth through the metal struts of the stents continues to be an issue. To help combat this problem, membrane covered SEMS were created. Vakil et al. [Vakil et al., 2001] performed a prospective randomized trial in which 62 patients were randomly assigned to either an uncovered (n=32) or covered SEMS (n=30). At one week a significant but similar improvement in dysphagia was seen in both, however, tumor ingrowth causing obstruction occurred significantly more often in the uncovered SEMS group (9/32) when compared to the covered group (1/32) (P=0.005), with reinterventions for tumor ingrowth significantly higher in the uncovered SEMS group (27% vs. 0%, P=0.002). As a result of this trial, covered SEMS were shown to offer effective palliation, with acceptable rates of migration and the benefit of preventing tumor ingrowth.

Much of the progression of stent technology has been the result of an attempt to limit associated complications. The partial covering of SEMS led to a decrease in tumor ingrowth but an increase in stent migration rate. The uncovered ends also embed into the walls of the esophagus, preventing removal, and resulting in late-term restenosis secondary to tissue hyperplasia. Fully covered SEMS had the benefit of being more easily removable but with an even further increase in migration rates [Talreja *et al.*, 2012],



Figure 3 *Bonastent*, a removable, fully-covered self-expandable metal stent with symmetrical flares. *Reprinted with permission from Endochoice*.

leading to investigation into ways to limit stent migration.

The fight to minimize stent migration is not new. The method of using a silk thread tied to the patient's mustache or ear used by Symonds in 1885 to prevent distal migration [Symonds, 1885] is occasionally used today [Shim et al., 2001]. Other methods include metal barbs on the outside of the stent [Ji et al., 2011], antimigration rings [Uitdehaag et al., 2010], or double layered stents designed to incorporate in the esophageal wall [Verschuur et al., 2006]. A recently developed fully covered SEMS (Bonastent; EndoChoice; Atlanta, GA) was designed with symmetrical flaring of the proximal and distal ends (Figure 3) in an attempt to limit migration while maintaining the retrievable and anti-tumor ingrowth/benign tissue hyperplasia properties of fully covered SEMS. In our experience, in which 58 stents were placed in 47 consecutive patients, all stents were placed successfully (Figure 4) and there were no instances of stentrelated hospital morbidity or mortality. Mean dysphagia scores were reduced from 3.0 to 1.2 (P<0.001) and the migration rate was 6.9% (4/58), which compares favorably to the 12-36% migration rate of FCSEMS reported in the literature [Sreedharan et al., 2009; Uitdehaag et al., 2009].

Self-expanding plastic stents (SEPS)

In an attempt to combine the benefits of SEMS with the low cost of CPS, a self-expanding silicone covered polyester stent was developed (*Polyflex*; Boston Scientific Corp. Watertown, Mass.) (*Figure 1*). Combining the benefits of



Figure 4 Malignant esophageal stricture before (A) and after (B) Bonastent insertion.

SEMS and CPS, the *Polyflex* stent has the advantage of being fully covered and easily removable. These SEPS can be inserted under sedation, but due to the diameter of the delivery system, dilation prior to insertion is usually required. While initial case series were promising with SEPS demonstrating similar palliation of dysphagia to SEMS at a lower cost [Bethge and Vakil, 2001; Decker *et al.*, 2001; Costamagna *et al.*, 2003; Dormann *et al.*, 2003], two randomized controlled trials were performed comparing SEPS to SEMS [Conio *et al.*, 2007; Verschuur *et al.*, 2008] both of which demonstrated a significantly higher migration rate with SEPS, with one of the trials also showing an increased frequency of major complications with SEPS.

While the lower cost and initial success of SEPS led to an initial increase in their use as an alternative to SEMS, more recent evidence suggests that increased migration rates and a larger diameter introducing system requiring more aggressive dilatation and the addition of greater radial force minimizes the benefits as compared to SEMS [Dua, 2007].

SEMS with anti-reflux valves

With the increasing incidence of adenocarcinoma secondary to gastroesophageal reflux, a significant number of patients presenting with malignant dysphagia have tumors located in the distal esophagus and/or the gastric cardia [Siegel *et al.*, 2012]. Although SEMS can be effectively utilized in this location, they often cause severe gastroesophageal reflux, placing patients at high risk of aspiration. In an attempt to ameliorate this issue, certain SEMS have been modified to include some form of anti-reflux valve incorporated into the distal end of the stent (*Figure 2*). Of the three randomized studies comparing SEMS with anti-reflux valves to SEMS without, one study reported decreased reflux [Laasch *et al.*, 2002] while the other two reported similar or increased rates of reflux with SEMS with anti-reflux valves [Homs *et al.*, 2004a; Shim *et al.* 2005]. The disparity in results may be attributed to the different stent designs available. Further evaluation is necessary in comparing these stents to each other, as well as to medical anti-reflux therapies.

SEMS and radiation therapy

Concern is often raised when SEMS are inserted in patients who have been previously treated with radiation therapy (RT) and/or chemotherapy (RTCT) as conflicting data appears in the literature, even when evaluated by the same investigator [Siersema et al., 1998; Siersema et al., 2001]. Homs et al. [Homs et al., 2004b] prospectively evaluated the outcomes of SEMS in the palliation of malignant dysphagia in 49 patients who had previously received RTCT compared to 151 patients who had not. They found no significant difference between the groups when comparing major complications (perforation, bleeding, severe pain, fever, and fistula formation), recurrent dysphagia due to stent migration, tumor overgrowth, or food impaction, or median survival. Only mild retrosternal pain occurred more frequently in the group of patients that had received prior RTCT and the authors concluded that insertion of covered SEMS is safe and effective in palliating malignant dysphagia in patients who have received prior RTCT.

Another issue is whether patients treated with SEMS can benefit from and/or tolerate the addition of RT. In a retrospective review by Song et al. [Song et al., 2002] comparing SEMS alone to SEMS before and after RT the group found a median survival benefit in the post-stent RT group (23±7 weeks) compared to the pre-stent RT group (10 ± 1 weeks) and the stent-only group (13 ± 2 weeks). Fourteen percent of the stents were removed at a mean follow-up of 4 weeks for complications including migration and sever pain. The same group then performed a prospectively randomized study using SEMS in 47 patients one week prior to RT with half the patients undergoing planned removal of the stent at 4 weeks (or sooner for complications) and the other group only having their stents removed if complications occurred. They found a decreased incidence of stent related complications as well as improved overall survival and dysphagia-free median survival in the group undergoing planned removal of the stent. The authors concluded that RT should be preceded by temporary placement of SEMS.

SEMS versus brachytherapy

Two prospective studies have been published comparing

brachytherapy to SEMS [Homs *et al.*, 2004c; Bergquist *et al.*, 2005]. In the first study by Holms *et al.* 209 patients with malignant dysphagia were randomly assigned to receive either single-dose brachytherapy (12 Gy) (n=101) or SEMS (*Ultraflex*; n=108). There was a more rapid improvement in dysphagia in the SEMS group but long term relief was better in the brachytherapy group. The SEMS group developed more complications when compared to the brachytherapy group (33% *vs.* 21%; P=0.02). There was no difference in median survival (145 *vs.* 155 days; P=0.23) or in the incidence of persistent or recurrent dysphagia (40% *vs.* 43%; P=0.81). Overall costs were similar, while quality-of-life (QOL) scores favored the brachytherapy group.

Bergquist *et al.* [Bergquist *et al.*, 2005] reported significantly better health-related quality of life (HRQL) scores for dysphagia at 1 month in the SEMS group, but most other scores subsequently deteriorated. In the brachytherapy group, significant improvement in dysphagia scores became evident at 3 months. Median survival and complication rates were similar but median total costs were higher in the brachytherapy group.

The available data seems to suggest that SEMS provide better short term palliation of dysphagia while brachytherapy provides improved long-term palliation. Further investigation of brachytherapy combined with temporary SEMS placement compared to brachytherapy alone is needed.

Stent failure

For most of the common early complications of stent placement, including pain, globus sensation, bleeding, and migration, the stent can be removed and either replaced with a smaller stent to limit pain or a longer or uncovered stent to reduce migration. Late stent failure, which often involves either migration or restenosis due to either tumor ingrowth through an uncovered stent or benign hyperplasia at the ends of a covered stent, can often be managed by replacement of an uncovered stent with a covered stent, or placement of a longer covered stent, possibly in combination with an adjuvant therapy.

Esophageal cancer summary

There are numerous effective methods of palliation of esophageal malignancy and the choice should be individualized for each patient as each have specific benefits and complications. Esophageal stents provide immediate relief from dysphagia and may provide a bridge to other longer-term palliative methods. Stents are also useful in the management of perforation and fistulae. As technology continues to evolve we can expect to see a further improvement in outcomes and a decrease in complications.

Airway cancer

Endobronchial airway tumors occur with numerous malignancies and frequently result in obstruction. The most common malignancy to do so is lung cancer. Approximately 20 to 30 percent of lung cancer patients will have an endobronchial component [Stohr and Bolliger, 1999]. Metastases from other malignancies are not uncommon and include renal cell carcinoma, breast cancer, and melanoma to name a few.

Symptoms can range from mild dyspnea to overt respiratory failure, pneumonia, hemoptysis, and loss of airway. Palliation in these circumstances can be of significant benefit to patients. Not only can symptoms be improved or eliminated but it can improve the patients' functional status to the point where additional treatments directed at their tumor are now possible. Palliation not only improves short term QOL but can and frequently does increase long term survival even when cure is not possible.

Airway compromise results from luminal compromise and restriction of movement of air or secretions in a normal fashion. This compromise is secondary to either intrinsic obstruction or extrinsic compression from the tumor. A variety of palliative treatments are available for both scenarios. Treatments include external beam radiation (ERT), rigid bronchoscopy, laser therapy, APC, cryotherapy, PDT, and airway stenting. Frequently more than one treatment modality is used to manage symptoms. Familiarity with multiple treatment options is critical in order to successfully palliate these complex patients.

Pathophysiology of airway obstruction

Symptoms secondary to airway obstruction result from abnormal movement of air from the lung, abnormal clearance of secretion, or atelectasis and subsequent effusion development. The onset of these symptoms can be gradual or sudden and are seen when the airway lumen decreases at least 60-70%. The most common symptoms are acute or chronic dyspnea and hemoptysis. The decrease in luminal diameter can be caused by either extrinsic or intrinsic pathology, each resulting in airway compromise. The majority of cases are in unresectable primary lung cancer which is the most common cause of central airway obstruction (CAO) [Ernst *et al.*, 2004]. Wood *et al.* reported that 42% of patients in their series of patients with CAO had extrinsic compression and 27% had an endobronchial tumor. Of the patients who had extrinsic compression the most common cause was lung cancer, followed by mediastinal, thyroid, and esophageal cancers, mesothelioma, or metastatic lesions from the kidney, thyroid, sarcoma, or breast [Wood *et al.*, 2003]. Less common indications for airway palliation include either primary or metastatic laryngeal cancer, lymphoma, myeloma or lymphadenopathy of any etiology [Wood *et al.*, 2003; Ernst *et al.*, 2004; Madden *et al.*, 2004].

Airway palliation

ERT

Two forms of radiation treatment can be used to palliate airway compromise:

ERT and brachytherapy. ERT is without question the most commonly used modality for the palliation of obstructing airway tumor. In all likelihood this will continue owing to its wide availability. Improvement in symptoms is commonly reported to range between 20-50% depending on tumor location and severity of symptoms. In some cases true and immediate palliation is accomplished with endobronchial techniques which subsequently allow patients to initiate ERT with a focus of maintaining or further improving symptoms.

Brachytherapy

Brachytherapy is an appropriate enodbronchial therapy for patients where ERT doses have been maximized. Brachytherapy is typically performed through a trans-nasal approach and the most common method is by an after-loading technique using Iridium 192 by which a thin polyethylene catheter is first positioned at the tumor site then the radiation source is loaded [Ernst *et al.*, 2004]. One of the largest series was by Macha *et al.* in 1995 in which 365 patients were administered a high dose of radiation (500 cGY at 10 mm for 3 or 4 fractions) with a 66% palliation rate [Macha *et al.*, 1995]. More recently Celebioglu *et al.* reported 95 patients receiving a higher dose rate (750-1,000 cGY at 10 mm for 2 or 3 weekly fractions) with significant improvement of symptoms [Celebioglu *et al.*, 2002].

Endobronchial therapies overview

Endobronchial therapies may be used in a complementary

role to other therapies including ERT or airway stents. In the case of ERT some patients are not well enough to tolerate treatment and require some endobronchial intervention to control symptoms. In the case of stents it is often necessary to perform some kind of airway debridement prior to stenting. As detailed by Santos *et al.*, [Santos *et al.*, 2004] laser therapy, PDT, cryotherapy, cautery and brachytherapy, in combination with stenting, often produce a more favorable outcome then stenting alone.

Rigid bronchoscopy

Rigid bronchoscopy can be used to core out the tumor, dilate an airway stricture, and provide superior airway control. It is a tool that most thoracic surgeons are familiar with, and it can provide the means by which the flexible bronchoscope is passed for more distal visualization, adjustments of stent position, or for balloon dilation of the airway. Essentially any therapy can be applied via rigid bronchoscopy including laser, electrocautery, APC, PDT, cryotherapy, or the use of a microdebrider [Lunn *et al.*, 2005]. It is most popular with surgical groups in North America for the endoscopic relief of airway obstruction [Mathisen and Grillo, 1989], it appears to be the preferred technique for airway management and stent deployment [Wood *et al.*, 2003], and has the distinct advantage over other techniques in a providing a controlled airway.

Electrocautery and argon plasma cautery

The use of cautery in the airway was first described by Gilfoy in 1932 [Gilfoy, 1932]. More recently, forceps have been modified to be passed through the large channel flexible bronchoscopes, providing both grasping capability and the ability to cauterize the tissue resulting in simultaneous tumor necrosis and hemostasis. Snares places through the bronchoscope can be used with great success for tumors that are polpyoid in nature. This technique allows extraction of large pieces of tumor much like during colonoscopy. Argon plasma coagulators are a non-contact form of electrocoagulation and have also been used for obtaining cauterization within the airway. Frequently endobronchial debridement and coagulation techniques, like APC, are used in conjunction with other therapies. When used alone, in appropriate circumstances they can be highly effective.

Laser therapy

The use of laser in the airway is well documented. It can be delivered through the flexible or rigid bronchoscope. The

most commonly used laser is the Nd:YAG laser can achieve tissue penetration up to 10 mm. The largest series to date using endoluminal laser therapy for central airway lesions are by Cavaliere [Cavaliere *et al.*, 1988; Cavaliere and Toninelli, 1994], Venuta [Venuta *et al.*, 2002], and Dumon [Dumon *et al.*, 1982]. All of these studies demonstrate the palliation of symptoms with a high degree of success (90-100%). Success is more common in central tumors and in tumors that are not completely obstructing. In lobar tumors causing obstruction successful palliation is accomplished in approximately 60% of patients, many of the failures occurring in completely obstructing tumors.

Laser therapy appears ideally suited for tumors causing complete or near complete obstruction and in non-polypoid like tumor growths. Complications are uncommon but when they occur they are typically a result of bleeding which can range from mild to life threatening. Complications for laser therapy vary widely based on a combination of clinician experience, tumor location, tumor size, as well as the clinicians/patients risk benefit aversion level.

PDT

As described above, PDT is a treatment modality that uses a photosensitizer, intravenously administered prior to treatment, which is taken up by the tumor tissue [Cavaliere et al., 1994; Moghissi et al., 1997; Moghissi et al., 1999; Moghissi and Dixon, 2003; Moghissi, 2004; Chen et al., 2006; Loewen et al., 2006; Vergnon et al., 2006; Moghissi et al., 2007; Moghissi and Dixon, 2008; Allison et al., 2011]. A light matching the activation wavelength of the photosensitizer (Photofrin Axcam pharmaceutical) is fired onto the tumor and a chemical reaction occurs with the release of oxygen free radicals, resulting in tumor necrosis. This technique can be used for superficial lesions as well as bulky tumors. Repeat bronchoscopy is usually necessary to "clean up" the airway following PDT. This treatment modality has been well documented by Moghissi et al. [Moghissi, Dixon et al., 1997; Moghissi, Dixon et al., 1999; Moghissi, 2004]. In each of these reviews it is clear that this therapy can not only palliate patients with advanced stage disease but can also potentially treat early lesions. In the most recent analysis by Moghissi, a review of 24 articles (1,153 patients) in the world literature was performed, and he concluded that bronchoscopic PDT is a safe and effective therapeutic method for the palliation of advanced lung cancer [Moghissi, 2004]. Others have also reported their experience with favorable outcomes for the use of PDT. A review from Roswell Park Cancer Institute concluded that

PDT is an effective tool for the palliation of endobronchial cancers obstructing the central airways [Loewen *et al.*, 2006], and Chan *et al.* from the University of Pittsburgh concluded that PDT is effective in the palliation of lung cancer [Chan *et al.*, 2003].

Despite the success of PDT in the palliation of aerodigestive disorders, QOL as it relates to photosensitivity for patients treated with this modality remains a major issue and needs to be discussed with patients particularly when alternatives exist that can accomplish the same goal. Photosensitivity can be severe and as a result PDT appears to be falling out of favor.

Cryotherapy

This is a technique that uses repeated freeze thaw cycles to achieve tumor necrosis [Maiwand and Homasson, 1995; Noppen *et al.*, 2001; Chan *et al.*, 2003]. The method utilizes temperatures in the –80 to –160 °C range and causes cell death by intra- and extracellular crystallization and microthrombosis [Chan *et al.*, 2003]. Cryotherapy can be delivered via flexible or rigid bronchoscopy and can be used to successfully palliate endobronchial cancers. This is a safe technique but has the major disadvantage of having delayed effects [Chan *et al.*, 2003]. The largest series to date was by Maiwand in 1995 which reported 622 cases with reasonable improvement in dyspnea and hemoptysis [Maiwand and Homasson, 1995]. More recently Noppen *et al.* achieved 80% airway patency rates in their series [Noppen *et al.*, 2001].

Airway stents

Airway stenting can be a successful treatment for acute and chronic airway obstruction. Stenting of the airway likely plays a much smaller role than stenting of the esophagus. This is a result of excellent results using alternative treatments as discussed above and because of inherent problems with stents. These problems include migration, failure to clear secretions, and obstruction of healthy airways. There are no randomized clinical trials examining the utility of stenting for the palliation of airway malignancy, but rather limited series from multiple institutions support the use of stenting techniques in these patients. The palliation of symptoms by stenting in appropriately selected patients is almost immediate and offers short term improvement in QOL, with little or no effect on long term and overall prognosis [Lemaire et al., 2005]. The common goal in all cases is palliation of hemoptysis or respiratory failure. Various stents are available for use in the airway, some of which are shown in *Figure 5*. Data does not support the use of one specific type of stent over another. These choices seem to be oriented toward surgeon experience and institutional preferences.

Airway stents

There are no randomized clinical trials comparing metal to silicone stents for the palliation of lung cancer, or comparisons of stents to other therapies, possibly due to the ethical dilemma that is created by such life threatening conditions [Macha *et al.*, 1994; Santos *et al.*, 2004]. What does exist are series from various institutions in the US and worldwide that provide their experience and their preferences. The common goal in all cases is palliation of hemoptysis or respiratory failure.

There are several large series looking at stenting for malignant CAO. All of these studies share one thing in common, which is that stenting can improve upon and thus palliate the symptoms caused by airway compromise. Survival is limited for this group and can be measured in terms of months, 3-4 months on average.

One of the largest series to date is from Dumon *et al.* in 1999 which reported their results with 1,574 stents in 1,054 patients. This was a multicenter European study which also included stenting for benign strictures as well as for malignant CAO and reported good resolution of airway patency with minimal complications. The three most common complications in this series were migration (9.5%), granuloma formation (7.9%), and mucus impaction (3.6%). The average duration of stent placement was 4 months [Dumon *et al.*, 1999].

Saad et al. [Saad et al., 2003] analyzed their 6-year experience with 112 SEMS (*Wallstent* and *Ultraflex*; Boston Scientific; Natick, MA) (*Figure 6*) in 82 patients. The majority of patients had dyspnea (80%) and 16 patients were on ventilators. Of the 16 patients on ventilators 14 were able to be extubated and there were no deaths. The most common complications included infections (15.9%), obstructive granulomas (14.6%), and migration (4.7%). The median follow-up time was 42 days (range of 1-672 days).

Wood *et al.* [Wood *et al.*, 2003] placed 309 stents in 143 patients, 67% of which were for malignant airway obstruction. Eighty-seven percent of the stents were molded silicone rubber (Hood Laboratories; Penbroke, MA) and 13% were metal stents. Of the 96 patients with malignant CAO, 88 (92%) had received previous radiation, chemotherapy, or both, and 14% had previous surgery for



Figure 5 A selection of airway stents. 1. Montgomery T-tubes; 2. Orlowski tracheal stent; 3. Dumon tracheal stent; 4. Dumon bronchial stent; 5. Polyflex tracheal stent; 6. Polyflex bronchial stent; 7. Polyflex stump stent; 8. Noppen tracheal stent; 9. Hood bronchial stent; 10. Gianturco stent; 11. Palmaz stent; 12. Tantalum Strecker stent; 13. Uncovered Ultraflex stent; 14. Covered Ultraflex stent; 15. Uncovered Wallstent; 16. Covered Wallstent; 17-24. Various metal and compound stent prototypes; 25. Westaby T-Y stent; 26. Bifurcated Orlowski stent; 27. Hood Y-stent; 28. Bifurcated Dumon stent; 29. Dynamic stent. Reprinted from Tracheobronchial Stents, In: Interventional Bronchoscopy, Prog Respir Res., Freitag L, Bolliger CT, Mathur PN (eds). 2000;30:171-86 with permission from Basel, Karger.

lung, esophageal, or thyroid cancer. In addition, 68% of the patients had additional palliative procedures (laser therapy, core-out, dilation, brachytherapy, or PDT) to prepare for or as an adjunct to stenting. Ninety-five percent of the patients noted significant improvement of their symptoms. In this study, 45 of the 53 patients with malignant disease (85%) maintained airway palliation for follow-up periods of 1 to 13 months (mean =4 months), with 28% requiring further bronchoscopic interventions.

Shin et al. [Shin et al., 2003] evaluated the safety and

effectiveness of covered retrievable expandable nitinol stents (*Figure* 7) in 35 patients with malignant tracheobronchial strictures with the intent of palliation. In this study dyspnea was assessed according to the Hugh-Jones classification. Average survival was 9.6 weeks (range, 2 days-26 weeks). The authors concluded that stent placement is safe and effective, with improvement noted in terms of dyspnea and improved QOL.

Lemaire *et al.* [Lemaire *et al.*, 2005] presented their outcomes with tracheobronchial stents in 172 patients. In

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Figure 6 Polyflex airway stent.

Figure 7 Uncovered (A) and covered (B) versions of the Ultraflex airway stent.

this group 225 stents were placed overall, with 172 stents placed in 142 patients for malignant disease. The study sought to assess the short term (<30 days) and intermediate term (>30 days) risks and benefits of tracheobronchial stenting. The complications related to stent placement included tumor ingrowth (n=9), excessive granulation tissue (n=7), stent migration (n=5), and restenosis related to extrinsic compression (n=2). Five of the complications occurred in the first 30 days, while the rest occurred after 30 days. The latter complications were mostly related to excessive granulation tissue and tumor ingrowth. Median survival after stenting was 3.4 months with a 1-year survival rate of 15%. The authors concluded that the stents offer minimally invasive palliation of symptoms in patients with unresectable malignant CAO with an acceptable risk of complications at short and intermediate time points.

Airway cancer summary

Part IV

Palliation of bleeding and respiratory compromise secondary malignant CAO involves the use of multimodality treatment including radiation therapy ERT and brachytherapy, and endoluminal therapies including laser therapy, PDT, electrocoagulation and APC, cryotherapy, and stenting. Stenting, while an accepted method of palliation of symptoms in patients that are dying from lung cancer, is used less often than in esophageal palliation given the excellent results using the alternative treatments above and because of inherent problems with stents, including migration, failure to clear secretions, and obstruction of healthy airways.

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Management of malignant bowel obstruction

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Introduction

Malignant bowel obstruction (MBO) is a frequent and troubling complication in patients with cancer, especially those of digestive or gynecological origin, whether as a primary presenting symptom or associated with advanced or metastatic disease. MBO can be divided into mechanical or functional etiologies, both of which result in the inability for flatus and contents to flow through the gastrointestinal tract. The obstruction may be at one or many sites along the bowel from the esophagus to the ano-rectum, and may partially or fully obstruct the bowel lumen. Even though the patient population that develops MBO generally has advanced cancer, the obstruction *per se* may be benign or malignant [Krouse *et al.*, 2002].

Prevalence

Bowel obstruction involves the small intestine roughly twice as frequently as it does the colon [Ripamonti *et al.*, 2001]. The frequency of MBO has been found to be approximately 5-51% in patients with gynecological malignancies, and between 10% and 28% in primary intestinal cancers [Walsh *et al.*, 2009]. It is also reported in patients with lymphoma, melanoma, lung, and pancreatico-biliary neoplasms. MBO is the root cause of death in patients with ovarian cancer, most of those patients dying within a year of developing the obstruction [Baines, 1997]. Patients with MBO due to metastatic disease face a poor prognosis due to risks of aspiration, pneumonia, and malnutrition, leading to an estimated life expectancy after MBO of 1-9 months [Sabharwal *et al.*, 2007; Mirensky *et al.*, 2012]. Because its occurrence is of such prognostic significance, discussions regarding the realistic goals and the plan of care, individualizing for each patient and their unique circumstances, need to be had [Soriano and Davis, 2011].

Pathophysiology

Gastric emptying and flow through the bowel is impeded either mechanically or functionally in a MBO. Several mechanisms have been described, though the end result is the same. Patients with previous abdominal or pelvic surgeries for malignancy are predisposed to mechanical obstructions due to the development of adhesions, both "benign" (i.e., fibrotic) and of malignant origin. Tumors themselves can cause intraluminal or intramural occlusion and directly block bowel transit. Primary tumors or recurrence of omental and mesenteric masses can extrinsically cause occlusion by kinking the bowel. Radiation fibrosis and intraperitoneal chemotherapy can also cause extrinsic occlusion [Mercadante, 2009].

Functional obstruction should be thought of as a disorder of motility. Infiltration of the myoenteric or celiac plexuses can disrupt nervous system signaling resulting in decreased or disordered peristalsis and obstruction. Tumors may also infiltrate the intestinal muscularis, rendering it unable to contract and relax properly. A subset of patients with Autoimmune Paraneoplastic Autonomic Neuropathy, which is a paraneoplastic syndrome, may develop autonomic disturbances which can cause pseudo-obstruction [Chinn and Schuffler, 1988].

Once the bowel transit is disrupted, regardless of the

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mechanism, there is an accumulation of luminal contents and an accumulation of secretions which are not absorbed. This leads to an increased secretion of water and sodium into the lumen and a decrease of water and sodium reabsorption from the bowel. The secretions collect in the lumen, increasing bowel and abdominal distension, damaging the intestinal epithelium, releasing cytokines and other noxious compounds, and resulting in a widespread inflammatory response. The intraluminal pressure rises and may obstruct venous drainage in the area affected, which may eventually lead to intestinal mucosal slough or even perforation, though more extensive, frank gangrene is uncommon in the absence of a "closed loop" obstruction [Krouse *et al.*, 2002].

Clinical presentation

The patient's history and the clinical presentation of MBO can often lead the clinician to the location of the bowel obstruction. Though colorectal cancer patients usually present, at least initially, with single-site large bowel obstructions, gynecologic cancer patients or others with peritoneal carcinomatosis often suffer from multiple jejunal and ileal occlusions, and thus with different symptomatology [Feller and Schiffman, 1987].

The obstruction that results as a consequence from narrowing of the bowel lumen is often chronic, developing over weeks and months, and incomplete, which may lead to vague symptoms until the lumen becomes nearor completely obstructed [Hirst and Regnard, 2003]. Common symptoms of MBO include nausea, vomiting, colicky abdominal pain vs. continuous pain, xerostomia, constipation, and overflow diarrhea [Ripamonti and Bruera, 2002]. Functionally, the bowel attempts to overcome the evolving obstruction by increasing frequency and intensity of contractions, which results in colicky abdominal pain. As described previously, due to the obstruction the bowel becomes edematous and luminal contents increase due to excess secretions, leading to nausea and vomiting. With the inflammatory response then comes abdominal distension. Overflow diarrhea may result as the resistance to flow of fecal material increases, gut flora acts to liquefy contents, and these are finally forcefully expelled [Ripamonti and Bruera, 2002].

Obstruction in the proximal gastrointestinal tract usually results in emesis of recently ingested material. The presence or absence of bile in the emesis indicates a level of obstruction above or below the pylorus and proximal small bowel. In small bowel obstructions, vomiting is usually watery or bilious and occurs within 45 minutes to one hour of ingestion, whereas it takes several hours or a time later in the day for a patient with distal small intestinal or large bowel obstruction to report worsening nausea and vomiting [Roeland and Gunten, 2009; Correa *et al.*, 2011]. If patients report intense crampy pain in brief intervals, it is often as indication of a jejunoileal obstruction or "high" SBO [Roeland and Gunten, 2009]. Pain, cramps or emesis occurring later in the day, often described with fecaloid content, indicates a more distal location of the obstruction.

The pain related to a small bowel obstruction is generally periumbilical and colickly, as compared to the more steady, localized pain in a large bowel obstruction which may or may not be episodic or colicky. This acute phase pain often presents as an exacerbation of more chronic pain from extensive intra-abdominal disease; each requires directed therapy, which will be described. When the abdomen becomes distended, which occurs more frequently in distal small or large bowel obstructions, continuous pain with variable intensity is often reported [Correa *et al.*, 2011]. Constipation or obstipation may also occur intermittently with a partial obstruction, whereas the patient may report scant flatus or bowel movements initially with a complete obstruction, followed by complete obstipation [Fainsinger *et al.*, 1994].

Diagnosis

"Listen to the patient, doctor: He is trying to help you." William Osler, Aphorisms

The key to patient care is in obtaining a thorough history and physical. Though the diagnosis of an MBO is often made clinically, it is usually confirmed through the use of radiographic modalities. Furthermore, given the emphasis on cost effective medicine, it seems prudent to discuss which test(s) should be ordered within the first 24 hours of presentation to investigate a MBO. In addition to radiographic evaluation, blood work should also be obtained, as these patients frequently have both acute and chronic metabolic abnormalities.

A plain radiographic abdominal series (upright, flat, decubitus views) of the abdomen is the easiest and least expensive way to define the extent and estimated location of the obstruction. However, plan X-rays have their limitations; an ileus often looks similar to an obstruction, and multiple sites may be involved, which is difficult to

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discern on a plain film, and the physician may be limited by the lack of sensitivity when trying to diagnosis a MBO, as studies have shown that as many as 75% of plain X-rays may be non-diagnostic [Maglinte *et al.*, 2005]. Regardless of its limitations, the first step in diagnosing a bowel obstruction radiographically should be an abdominal X-ray in which the presence of dilated bowel loops and air-fluid levels may suggest an MBO.

Contrast radiography may distinguish between mechanical and functional causes as well as localize the site and extent of the obstruction [Silva *et al.*, 2009]. The use of this study can be limited if the patient is suffering from intractable nausea, is unable to swallow the contrast, or contrast can not be placed via an enteric tube. Water-soluble contrast, such as gastrografin, is preferable to barium as barium may be retained or cause subsequent impaction or aspiration [Ripamonti and Bruera, 2002].

Computed tomography (CT) scans have become the imaging tool used most frequently when a patient has a suspected MBO, as it has a specificity of 100% and a sensitivity of 94% [Maglinte et al., 2005]. Abdominal/pelvic CT scans with both oral and intravenous contrast agents can localize an obstruction, reveal lymphadenopathy and bowel wall irregularities, as well as delineate the extent of tumor burden in the abdomen and pelvis [Bordeianou and Yeh, 2013]. Because of their specificity and sensitivity, other forms of radiography are generally not used as CT scans with contrast are the most valuable [Stevenson, 2008]. Though MRI may provide more detailed information regarding the extent of disease (e.g., peritoneal implants), it is more cumbersome, restrictive, and expensive, hence less frequently employed in clinical practice in favor of the CT scan.

Operative surgical management

"First, he would have to know when or not to operate, then how to operate, then when to stop operating."

Dr. Charles Mayo, on the qualities in the surgeon chosen to operate on him

Consideration of operative intervention for MBO requires deliberation and judgment, with individualization of its application to the case at hand. The penalties to be paid for imprudent intervention, with the attendant rates of complication, death, and failure to provide meaningful symptom palliation, let alone life prolongation, are too significant to be minimized. Discussion and concurrence regarding the goals of care, realistic expectations for outcomes both operative and beyond, framed substantively and compassionately beyond the common rosary of "potential risks and benefits" need be had with the patient, if possible, and with surrogate decision-makers.

For the patient with unproven intra-abdominal malignancy and fair-good performance and nutritional status, it is generally agreed that laparotomy is indicated to establish a definitive diagnosis, stage the disease intraabdominally, and relieve the obstruction by venting, lysis, resection, bypass, or debulking.

Operative surgical intervention in other circumstances needs be nuanced by known outcomes in patient populations balanced against what constitutes "benefits" for the individual patient consistent with their overall goals for care. Reasonable candidates for exploration are those with an estimated life expectancy of two or more months, an ECOG performance status of two or better, a Palliative Performance Scale (PPS) rating of 40 or more, and slowly growing tumors. Ominous prognostic factors for surgical intervention include those patients with palpable abdominal masses, extensive ascites, multiple levels of obstruction, distant metastases, a history of abdominal radiation, hepatic or renal insufficiency, malnutrition/ hypoproteinemia <2.5 gm albumin, or previous laparotomy for obstruction. Multiple series of patients with these co-morbidities reveal morbidity/complication rates 7-90%, subsequent re-obstruction in 10-50%, and mortality rates 15-30% with a disconcerting number occurring in less than 30 days [Feuer, 2000a; DeBernardo, 2009].

For certain lesions, endoscopic stenting may offer an alternative to formal surgical intervention, offering either temporizing palliation of obstruction or a "bridge" to subsequent formal laparotomy. This approach may be considered for patients with lesions of the esophagus, gastric outlet and duodenum, or distal colon/proximal rectum who have a single point of obstruction or extensive regional disease, or who are otherwise too high a risk for more extensive surgery. For proximal lesions, stenting offers relief of nausea and vomiting and shorter hospitalizations and fewer complications than "open" surgical approaches, as well as avoidance of intestinal stomas. In experienced hands, even some distal duodenal and proximal colonic lesions are amenable to stenting. Initial success rates, both technical and clinical, are reported >85%, with immediate (perforation, bleeding) complication rates <10%, and subsequent stent migration or occlusion 10-15% [Turner et al., 2008].

Non-operative management

General considerations

For many patients with MBO, placement of a nasogastric tube is a prudent initial or temporizing intervention allowing for decompression of the often painful, distended proximal gastrointestinal track as fluid and electrolyte abnormalities are corrected and subsequent care deliberations made. However, long term use of NG tubes is uncomfortable and not without its own complications such as sinusitis, aspiration, xerostomia, and even social isolation. Fortunately, clinical experience has demonstrated that the majority of patients with MBO can be satisfactorily managed as described below without prolonged nasogastric intubation. For those patients not considered operative surgical candidates or those whose symptoms do not respond to medical therapy, a venting gastrostomy should be considered as its may provide significant relief of nausea, vomiting and distension.

Similarly, intravenous hydration is usually an appropriate initial step in restoring depleted intravascular volume, correcting electrolyte abnormalities, and clearing accumulated metabolites. However, prolonged use of crystalloid fluids, particularly in malnourished or hypoproteinemic patients, leads to increased extravascular fluid, uncomfortable edema, increased lung water with pulmonary complications, and does not prevent the sensation of thirst. Much of the perception of thirst derives from dry oral mucosa, and all patients with restricted PO intake should have meticulous attention to mouth care and oral hygiene, including scheduled routine moisture every two hours and artificial saliva applied to tongue, lips, and palate every 4-6 hours.

Like surgical intervention, the use of total parenteral nutrition (TPN) needs be a studied decision. The majority of patients with MBO or extensive cancers, particularly those with cancer cachexia, do not benefit from TPN, as manifested by lack of significant improvement in qualityof-life measures, performance status, or overall survival [Soriano and Davis, 2011]. Moreover, as a technical intervention requiring close monitoring and frequent manipulations, it can be a distraction or impediment to social interactions. In addition, it is not without its own risks and complications such as local infection, line sepsis, vascular thrombosis, and hyperglycemia. While it may benefit in select patients who are likely to die of starvation rather than the malignancy, or in time-limited goal-specific circumstances such as family milestones, its utilization should be accompanied by clearly articulated goals and

agreed upon parameters for assessing its benefits and continuation [Ripamonti *et al.*, 2001].

Medical management

Medical management seeks minimization of pain, nausea and vomiting. As orally administered drugs are inconsistently absorbed in the presence of nausea, distension, and stasis, and certainly with emesis, medications should be provided initially by parenteral routes, either intravenous, subcutaneous, or (rarely) intramuscular. Once nausea and emesis are controlled and gastrointestinal motility restored-a not uncommon outcome often lasting many weeks-consideration can then be given to sublingual, oral or transdermal administration of some of the pharmacologics. However, it is almost always necessary to use a combination of analgesics, antiemetics, anticholinergics, corticosteroids, and octreotide to achieve symptom resolution. Once achieved, many of the drugs used—such as morphine, metoclopramide, haloperidol, and glycopyrrolate-are compatible in solution and can be combined for a consolidated infusion.

Pain

Two types of pain are typical in patients with MBO. The first is the "background" pain of extensive malignancy, usually constant or continuous. This is dealt with by titration to effect of potent opioids such as morphine, hydromorphone, fentanyl, or methadone. Co-analgesics such as ketorolac may have an opioid-sparing result, particularly if used short-term as other components of the regimen take effect.

Colicky pain results from the increased or discoordinated effort of peristalsis, particularly as distension progresses. Paroxysms occur at more frequent intervals with jejunal obstructions than with more distal or ileal obstructions. These are treated with anticholinergics, which inhibit motility while also decreasing intestinal secretions and emesis. Glycopyrrolate in doses of 0.1-0.2 mg SQ/IV/1-2 mg PO every 6-8 hours may be the drug of choice given its pharmaceutical versatility. Moreover, it has fewer cardiac side effects and a lower likelihood of triggering delirium than atropine (0.4 mg IV/SQ every 6-8 hours; transdermal 1.5 mg. every three days [Ripamonti *et al.*, 2001].

Nausea/vomiting

A variety of drugs are useful for treating nausea and

vomiting. Haloperidol, a selective D2 antagonist, can be used SQ/IV or subsequently PO in doses from 0.5-2 mg every 4-6 hours, with the added advantage of treating the delirium which often accompanies advanced illness. Phenothiazines such as prochlorperazine and chlorpromazine are also effective, though they cannot be administered subcutaneously. Metoclopramide is versatile, both a D2 antagonist and a 5HT4 agonist, thus combining the central chemoreceptor trigger inhibition of the phenothiazines with a pro-motility action [Ripamonti *et al.*, 2008]. Effective in doses of 5-10 mg SQ/IV every six hours, it is helpful in incomplete obstructions and as other components of therapy take effect. It should be dose adjusted or discontinued if colic worsens, and is contraindicated in fixed, complete obstructions.

Olanzapine inhibits multiple neurotransmitters involved in initiating emesis, and is seeing increasing use in problematic cases of intractable nausea. An atypical antipsychotic, it is used in doses of 2.5-10 mg/day for bowel obstruction, is available as a sublingually dissolving tablet and, in restricted use, as an intramuscular injection [Glare *et al.*, 2004].

Corticosteroids

The presumed mechanism by which corticosteroids help ameliorate MBO is by inhibiting the inflammatory response and reducing peri-tumoral edema and associated pain. They likely also act centrally to reduce nausea. Their net effect is improvement of bowel function, often relieving incomplete obstruction temporarily and helping restore bowel function. Dexamethasone in doses 8-16 mg/day IV/SQ is most frequently chosen, usually for a trial period of 5-7 days to assess for efficacy and continued indefinitely if effective [Feuer and Broadley, 2000b].

Antisecretories

An additive to the effect of anticholinergics in reducing intestinal motility, octreotide inhibits release of many intestinal secretions, including gastrin, vasoactive intestinal polypeptide, pancreatic enzymes, and bile. It also reduces splanchnic blood flow, thereby reducing the vascular congestion of the bowel wall which accompanies MBO. Dosed as 100-200 micrograms SQ or IV q6-8h, it is considered an essential component in non-operative management of nausea, vomiting and colic [Mercadante *et al.*, 2007].

Summary

"Same disease, different patient."

Old surgical adage

The management of MBO challenges clinicians, patients and their families. Operative surgical interventions must be judiciously employed given significant associated morbidity and mortality, and less invasive procedures such as stenting or venting may provide substantive benefit. Non-operative medical management is often successful in relieving its distressing symptoms, often for many weeks or several months, but because MBO, particularly if inoperable, is a harbinger of limited life expectancy, its occurrence calls for comprehensive, compassionate discussions with patients and families, and coordinated care tailored to each patient and their caregivers, to identify and achieve mutually agreed upon, realistic goals of care.

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Evaluation and management of pleural conditions

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Introduction

Physicians often identify, evaluate, and then manage patients with pleural effusions. Primary care physicians, pulmonologists and thoracic surgeons are often faced to manage patients with pleural conditions that require palliation. Among these conditions are malignant pleural effusion (MPE), chronic benign pleural effusion, pneumothoraces secondary to severe underlying pulmonary disease, and pleural air space diseases that are typically postinfectious or post-operative in nature. While many benign pleural effusions are transient and self limiting, others are related to non-malignant fluid imbalances frequently caused by heart failure and hemodialysis, and those tend to be more persistent and potentially challenging to manage. However, nearly 45% of all effusions are secondary to malignancy, including lung cancer (35%), breast cancer (23%), lymphoma (19%), or even an unknown primary 12% [Hausheer and Yarbro, 1985].

MPE occur at an incidence of more than 150,000 annually in the US, adding significant distress and quality of life (QOL) impairment in an already frail population [Reddy et al., 2011]. Furthermore, these effusions usually reflect terminal conditions and are beyond cancer-directed therapy, due to disease progression and/or overall functional decline. The average survival of patients diagnosed with MPE ranges from 3 to 12 months, depending on the underlying malignancy [Roberts et al., 2010]. Despite many recent advancements in the diagnosis and treatment of pleural effusions in general, there still is no real consensus among practitioners regarding the optimal management of MPE, which remain subject to institutional biases and physicians' individual perceptions and expertise. In this chapter, we discuss the pathophysiology of fluid accumulation in the pleural space and the initial evaluation of MPE, and

review the different treatment strategies that are currently available to the practitioner. We finally give our own opinion regarding the management of MPE, based on our experience.

Pathophysiology of pleural effusions

Under normal conditions, the pleural cavity contains a small amount of fluid (estimated at 0.3 mL/kg body mass) that acts as a lubricant between the visceral and parietal pleura [Miserocchi, 1997]. The movement of pleural fluid between the pleural membranes is a continuous, dynamic process and studies on pleural fluid flow models have revealed that the lymphatic system plays an important role in the maintenance and homeostasis of fluid balance [Miserocchi et al., 1992]. However, the clearance of fluid within the pleural space is not fully understood but it is believed that most of the fluid accumulation during pathological conditions originates from the visceral pleura and is drained by the parietal pleura [English and Leslie, 2006]. In addition, scanning and transmission electron microscopy of human parietal pleura have revealed the presence of lymphatic pleural stomata located on the diaphragmatic surface of parietal pleura that serve to drain the pleural space of fluid and particles [Li and Jiang, 1993; Peng et al., 1994].

The mechanisms that lead to the development of malignant effusions are ultimately the result of interference in normal fluid clearance from the pleural space. Malignancies can in effect cause dysfunction of the pleural fluid flow dynamics and drainage by several means. For instance, the hydrostatic pressure of the interstitial tissue can increase due to obstruction of lymphatics or obstruction by enlarged mediastinal lymph nodes, therefore leading to

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an increased volume; similarly, tumor involvement of the visceral and parietal pleura can affect fluid absorption and induce an inflammatory response resulting in increased capillary permeability [DeCamp *et al.*, 1997]. Cancers can also propagate pleural effusions by the production of certain proliferative stimulants such as cytokines, neurotransmitters, and growth factors within a microenvironment that promotes cell survival and progression [Kassis *et al.*, 2005].

Clinical features and diagnostic assessment of the MPE

Patients who present with MPE most often have symptoms of dyspnea, cough, pleuritic chest pain, fatigue, and weight loss. Dyspnea is usually the result of intrapulmonary shunting, chest pain may signify tumor invasion of the parietal pleura into the chest wall, and weight loss usually correlates with the advanced stage of disease and the cachectic state. A malignant effusion from a lung primary underlines an advanced stage disease, and is currently considered stage IV (M1a) [Rusch, 2009]. A new MPE can also represent an extension of a known or remote extrathoracic tumor, or metastatic disease.

The most commonly used radiographic studies used to detect the presence of a pleural effusion include chest X-ray and computed tomography (CT scan) of the chest, which can determine if the fluid is loculated and guide the drainage procedure. A thoracentesis can be performed for both diagnostic and therapeutic purposes. In MPE, this fluid typically reveals an exudative effusion according to Light's criteria [Light et al., 1972]. Compared to cytology examination (62%) and needle biopsy (44%), medical thoracoscopy has a higher sensitivity (95%) in the diagnosis of MPEs, as shown by Loddenkemper and co-workers [Loddenkemper, 1998]. Video-assisted thoracoscopic surgery (VATS) is indicated when thoracentesis fails to confirm malignancy or when the histology of the tumor is in question. Thoracoscopy has become a more common diagnostic modality of MPE, replacing open pleural biopsy and medical pleuroscopy, with minimal associated morbidity [Light, 2006].

Treatment of the MPE

The majority of malignant effusions is symptomatic or will become so during the course of the terminal illness, with dyspnea occurring in 50-70% of patients [Hu *et al.*, 2004]. Even though some malignancies such as breast cancer or

lymphoma may be amenable to systemic treatment as we discuss later, management of MPE is generally based on local palliative procedures. Patient's performance status and overall prognosis should guide the management, but virtually all patients will benefit from palliative maneuvers. Determining the prognosis may not always be an easy task however, as only few clinical predictors are available. In a retrospective review of 278 patients who underwent surgical palliation of MPE, Pilling and colleagues found that preprocedural leukocytosis, hypoalbuminemia (≤35 g/L) and hypoxemia (PaO₂ \leq 71 mmHg) independently predicted a worse survival. Median survival was 42 days when all three factors were present, compared with 702 days when none of the factors were present (P<0.00001) [Pilling et al., 2010]. Additionally pleural fluid parameters such as low pH (<7.3) and low glucose levels (<60 g/L) have been shown to correlate with a worse prognosis when compared to effusions with higher levels of pH and glucose [Rodriquez-Panadero and Lopez-Mejias, 1989].

Thoracentesis

Thoracentesis is a useful tool to establish the diagnosis of MPE, with a sensitivity range between 40% to 87% and a potential for immediate relief of dyspnea [Jay, 1985; Toms *et al.*, 2000]. Even though the recurrence rate approaches 100% within a month [Antunes *et al.*, 2003], repeat thoracentesis may be considered in patients who demonstrate slow re-accumulation of pleural fluid and who have a short life expectancy. However, repeat thoracentesis can lead to adhesions formation and subsequent trapped lung, which can complicate the overall management and jeopardize the symptomatic relief of the terminally ill patient [Musani, 2009; Roberts *et al.*, 2010].

Indwelling pleural catheter

Indwelling tunneled pleural catheter (TPC) are being used with increased frequency in the treatment of MPE, due to their ease of placement and their ability to be used on an outpatient basis, as well as the avoidance of hospitalization and the administration of painful sclerosing agents. Two systems currently exist on the market, the PleurX[®] catheter (CareFusion, San Diego, CA, USA) which uses a vacuum bottle, and the less commonly used Aspira[®] pleural catheter drainage system (Bard Access Systems, Salt Lake City, UT, USA), which uses a low vacuum siphon pump. The advantages of indwelling catheters over bedside thoracostomy pleurodesis were demonstrated in one of the first and largest trial by Putnam and co-workers [Putnam et al., 1999], where patients were randomized in a 2:1 fashion and received doxycycline (n=45) or a PleurX[®] catheter (n=99). The degree of symptomatic improvement in dyspnea and the QOL was comparable in each group, but the median hospitalization was 1 day in the TPC group vs. 6.5 days in the doxycycline group. Twenty-one percent had a late recurrence of the effusion in the doxycycline group vs. 13% in the TPC group (P=NS). In another study, Ohm and co-workers demonstrated the effectiveness of TPC in managing patients with a trapped lung (n=34), compared to those with a normally expanding lung who underwent thoracoscopy with talc pleurodesis (n=7) [Ohm et al., 2003]. Patients who underwent placement of a TPC had a significantly shorter hospital stay, as most of them were initially seen on an outpatient basis. Another retrospective review of 250 TPC procedures by Tremblay and Michaud showed a significant improvement in dyspnea score in 38.8% of patients at two weeks, with complete resolution of dyspnea in another 50% [Tremblay and Michaud, 2006]; there were ten failed insertions only, and 43% of patients achieved spontaneous pleurodesis. More recently, the results of two multi-institutional prospective and randomized trials comparing TPC to bedside talc pleurodesis were published. The first one by Demmy and colleagues (CALGB 30102) [Demmy et al., 2012] was patterned after a prior trial, the CALGB 9334, had shown that bedside talc pleurodesis was equivalent to VATS talc poudrage [Dresler et al., 2005]. The new trial was terminated early due to insufficient accrual (58 patients were enrolled compared to an estimated 530 patients deemed necessary to show equivalency of the two treatment arms). Nevertheless, the authors found that combined success was higher with TPC than with bedside talc slurry (62% vs. 46%, OR 5, P=0.064), and that patients who underwent TPC had a better effusion control at 30 days compared to the pleurodesis group (P=0.024). The second trial is the U.K. TIME 2 prospective multiinstitutional study which randomized 106 patients to the two fore mentioned treatment options and focused on symptomatic relief of dyspnea, where the subjects had to fill a daily visual analog of dyspnea score over 42 days after either procedure [Davies et al., 2012]. The trial showed a statistically significant improvement in dyspnea in the TPC group at six months, but no difference in QOL.

While the above mentioned literature demonstrates an undeniable role for TPC in the management of MPE, there are potential complications. These include the risk of catheter track seeding with potential for local infection, empyema and metastases, catheter dysfunction or blockage requiring thrombolysis, the inconvenience of a chronic drain and visiting home nurses, the inability to achieve pleurodesis in all patients, and even possible fracture and retained material during bedside removal [Janes *et al.*, 2007; Fysh *et al.*, 2012]. Furthermore, no robust prospective data directly compares TPC to VATS pleurodesis, in terms of adequacy of lung expansion, patient symptomatic relief or cost-efficiency. In fact, even though the initial cost of TPC is lower compared to VATS pleurodesis, later costs related to visiting nurses and chronic drainage are not usually accounted for [MacEachern and Tremblay, 2011].

Pleurodesis

The ultimate goal of pleurodesis is to create a seal between the visceral and parietal pleura and obliterate the pleural space, preventing reaccumulation of the effusion. Pleurodesis can be performed mechanically during thoracoscopy or thoracotomy by inducing pleural abrasions. It is however not advisable from a surgical standpoint in the setting of MPE, as it is associated with bleeding and a higher morbidity in terminally ill patients with significant tumor burden. Pleurodesis can also be performed chemically, with a sclerosant which include adriamycin, tetracycline, doxycycline, bleomycin, talc and even iodine [Mohsen, 2011; Shaw and Agarwal, 2004]. Talc is the most commonly used agent as it is inexpensive and has been shown to be the most efficient sclerosant in a Cochrane meta-analysis of ten randomized trials that included 308 patients. Chemical pleurodesis can be achieved intraoperatively or at the bedside, through an indwelling catheter or a thoracostomy tube. For patients with a suspicious effusion who are undergoing surgery for diagnostic purposes, chemical pleurodesis is achieved after evacuation of the fluid by injecting the sclerosant into the hemithorax and leaving a chest tube in the pleural space to maximize approximation of the two pleural layers. This typically requires a hospitalization of a few days. For patients not undergoing surgery or those who already have a thoracostomy tube in place, pleurodesis can be performed at the bedside by instilling the chemical irritant via the chest tube. One relative contraindication to chemical pleurodesis is the inability of the lung to re-expand and fill the hemithorax after drainage, which typically results in less effective pleurodesis and can potentially cause further

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trapping and infection.

Comparing both methods of chemical pleurodesis, the CALGB 9334 trial showed that patients with a lung or a breast primary had a higher success rate with thoracoscopic talc insufflation, as opposed to thoracostomy talc slurry administration (82% vs. 67%) [Dresler *et al.*, 2005]. A single institution retrospective review of 109 patients with MPE showed that TPC was associated with a significantly shorter port-procedural length of stay and less ipsilateral pleural re-interventions compared to VATS talc poudrage [Hunt *et al.*, 2012].

Complications following pleurodesis do exist, and the most common adverse events after talc administration are fever (10-17%) and pain [Shaw and Agarwal, 2004; Viallat *et al.*, 1996]. These symptoms are self limiting and typically resolve within three days. Infectious Empyema is uncommon but can occur and often makes management of the patient very difficult. Acute respiratory distress syndrome has also been reported, but is usually rare, especially if less than 5 g of talc are administered.

Indwelling catheter and pleurodesis

Thoracoscopy and indwelling TPC are not mutually exclusive procedures, as both can be performed in order to achieve pleurodesis and potentially shorten the duration of hospitalization. A retrospective review of 30 patients who underwent medical thoracoscopy with talc poudrage and placement of TPC was recently published, and showed a median duration of hospitalization of 1.79 days. Pleurodesis was successful in 92% of patients, and the TPC was removed at a median of 7.54 days. The authors reported the occurrence of one empyema [Reddy *et al.*, 2011].

Pleurectomy

Pleurectomy/decortication is mainly indicated in the management of malignant mesothelioma, even more so since pleurodesis has been shown in some series to be less effective in controlling the malignant effusion in that setting [Bielsa *et al.*, 2011]. The procedure typically requires a thoracotomy and is associated with significant morbidity, requiring careful patient selection [Flores *et al.*, 2008; Nakas *et al.*, 2008]. Pleurectomy is otherwise not indicated in the management of MPE related to non small cell lung cancer, even if a partial decortication and adhesiolysis are performed to a certain degree in diagnostic/therapeutic VATS, in order to breakdown loculations and optimize lung

expansion [Murthy and Rice, 2013].

Pleuro-peritoneal shunt

Pleuroperitoneal shunting is rarely used anymore in the management of MPE, especially since the advent of indwelling catheters [Little *et al.*, 1986]. Nevertheless, they can still be performed via thoracoscopy with reasonable morbidity and can provide palliation in the majority of a properly selected population. However, shunt related problems are common (up to 15%) and include occlusion, infection, and metastatic seeding of the tract, often requiring revision or replacement of the shunt [Genc *et al.*, 2000; Tsang *et al.*, 1990].

Non surgical treatment: chemotherapy, radiation and medical management

Chemotherapy is typically helpful in controlling malignant effusions caused by certain malignancies, such as breast cancer, small cell carcinoma of the lung, germ cell tumors and lymphoma [Weick *et al.*, 1973; Livingston *et al.*, 1982]. Radiation therapy may also help managing effusions caused by bulky lymphatic involvement which accompanies the latter condition. Furthermore, a recent phase I trial of intrapleural administration of docetaxel showed promising results with complete radiographic response in the majority of patients, and was associated with minimal systemic toxicity [Jones *et al.*, 2010]. Opioids have also been shown to relieve the sensation of breathlessness in cancer patients with dyspnea and may be used as an adjunct to more definitive treatment modality of MPE [Abernethy *et al.*, 2003; Jennings *et al.*, 2002].

Summary

Generally speaking, the authors feel that there is no single right or wrong way to manage a MPE. Each case requires its own considerations and patient discussions [Beyea *et al.*, 2012]. For patients who have a definitive diagnosis of MPE and where the focus is palliation, maximizing QOL and avoiding hospitalization, placement of an indwelling TPC is ideal. Although some may be reluctant to having a chronic drain, it is our overwhelming experience that patients who have had a TPC placed are typically satisfied. For those younger patients who complain of the catheter and who are responding well to the systemic treatment of their malignancy, nothing precludes a change in the course.



Figure 1 Treatment algorithm for palliation of malignant pleural effusion.

Options would then include pleurodesis through the TPC or via thoracoscopy. In the setting of trapped lung, the indwelling TPC is without question the best management tool. Not only does it avoid operative complications such as failure of pleurodesis, infection, or prolonged air leak from a parenchymal lung injury, it can also eliminate the space over time and lead to further symptomatic improvement.

In our practice, we typically reserve pleurodesis for inpatients who are not suitable for immediate discharge, patients who already have a chest tube in place, and those who need to undergo a diagnostic or staging procedure. A proposed treatment algorithm is shown in *Figure 1*.

Finally, the majority of MPE patients can have improvement with drainage. Even if some pleural effusions may not be successfully palliated, we caution the clinician not to assume this without at least one attempt at drainage, as not to miss a precious opportunity in improving the patient's life.

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Part IV

Evaluation and management of pleural conditions

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Controlled sedation for refractory symptoms in dying patients

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Introduction

A subset of terminally ill patients at end of life may experience intolerable suffering, despite best efforts for symptom control and the goal of a peaceful death may appear unobtainable. The patient's suffering causes family members to also suffer and ultimately to survive with the memories and guilt of the patient's last days. In cases where suffering is refractory to treatments, one effective means of alleviating this suffering is sedation [Cherny, 2006]. This palliative practice has been used for years with a variable incidence, ranging from 2% to 52% [Cowan and Walsh, 2001]. Acute palliative care units tend to have a relatively high rate of sedation likely secondary to the acuity, the vigorous monitoring of suffering, and the decision making and communication algorithms in place [Mercadante *et al.*, 2009].

However, what is done in the acute palliative care unit may not reflect what is done in other settings. In fact, there are even wide variations in frequency to choose sedation across different centers, due to diverse attitudes of doctors and policies of the institution. State and national legislation may also affect decision making. Thus, sedation in terminally ill patients is a complex issue because of the ethical, cultural, legal and technical implications. The aim of this chapter is to provide information on indications, management, and ethical issues regarding sedation in endof-life care and its relationship with survival.

Indications

Terminal sedation has been defined by the European Association of Palliative Care (EAPC) as the use of a sedative medication to relieve intolerable suffering in the last days of life [Materstvedt *et al.*, 2003]. An expert panel provided detailed recommendations for terminology and

definitions, indications and conditions, decision-making and informed consent, cultural issues, ethical aspects, type of sedation and drugs, outcomes and monitoring, nutrition and hydration [Cherny, 2006].

More recently, the term "controlled sedation for intractable symptoms in dying patients" has been proposed as an alternative description. It is more accurate as it includes the modality, the aim, the need, and the context, respectively. Specifically, "controlled" speaks to whether mild, deep, intermittent or continuous sedation is administered, how it is monitored, and who has the expertise to administer it. The term "sedation" is implicit, and is defined as the administration of drugs to decrease the level of consciousness (controlled). "Intractable symptoms" refer to a clinical condition that did not respond to standard palliative care drugs and are inducing severe suffering in patients, for whom sedation is the last resort. Finally, "dying patients" is used to identify the context of an otherwise initiated process, excluding other indications (noxious procedures) or confusing terms (terminal, palliative). This implies that the team looking after the patient has enough expertise to judge the symptom as refractory and that there is consensus on this subject [Mercadante et al., 2009].

When a clinician perceives that there is no other treatment capable of relieving intolerable symptoms refractory to standard approaches, he or she should assess the severity of the problem, the limitations of available treatments, and expected course of the last days of life, without a specific intervention requiring the lower the level of consciousness. This is separate from transient sedation, which can be necessary in certain circumstances to allow short-lived painful procedures. A typical situation for "controlled sedation for intractable symptoms in dying patients" is represented by a patient who has a continuously distressing symptom that persists beyond a reasonable time and is assumed to be refractory after trying available treatments unsuccessfully.

Agitation and dyspnea are the most common symptoms requiring end-of-life sedation [Mercadante *et al.*, 2009; Elsayem *et al.*, 2009; Fainsinger *et al.*, 2000]. In these cases, the clinical need for sedation and its rational and ethical foundations should be shared with the staff involved in the ongoing care. The involvement of multiple health care providers is of paramount importance. All members of the team should be able to explain to patient, or more likely to the family members, the change in therapeutic strategy. In these cases, the requests often directly arise from relatives and rarely from the patients themselves. In fact, less than half of the palliative care patients not receiving sedation have been found to be unable to achieve complex communication five days before death [Fainsinger *et al*, 1998].

The decision should be based on an open discussion with family members regarding the need to start the treatment, taking into account any physical, spiritual, and psychosocial issues as well as the context. Informed consent and documentation of the decision making process must be exemplary to minimize misunderstandings about the intent of sedation. Patients approaching end of life may suffer from existential issues and anxiety, often associated with physical symptoms. The presence of these symptoms does not necessarily indicate that the patient is dying, making the decision to start the treatment often quite difficult. This dilemma is complex and the designation of such symptoms should only be done following a period of repeated assessment, also considering trials of routine approaches for anxiety, depression, and existential distress. Using psychological and existential distress alone as an indication for sedation is a controversial issue. In these cases, sedation should be initiated only under exceptional circumstances and only after careful consultation [Kohara et al., 2005]. This sedation should be initiated on a respite basis with an intermittent treatment, hoping for breaking a cycle. As psychological distress usually accompanies the physical symptoms, intermittent therapy will often be transformed into a traditional continuous sedation.

There are some conditions that may require a respite intervention to provide symptom relief while waiting for a more definitive treatment in patients who are not imminently dying. In these cases, sedation can be considered intermittent for a short period or reversible, allowing for re-assessment of whether patients could sustain an acceptable condition once sedation is stopped. In other conditions, a reversible sedation could be restarted in a definite way because symptoms are not relieved without lowering the patients' level of consciousness.

In some situations, dying patients may present overwhelming symptoms that require an immediate emergency decision to be made and acted upon. Examples include patients who have sudden-onset dyspnea, massive bleeding, agitation or delirium. In these cases decisions must be immediate and may require more intensive treatment. These situations may be tempered if potential emergencies are anticipated to the extent possible and discussed with the patient and family members prior to their occurrence [Cherny, 2006].

Management

The retrospective nature of most studies leads to insurmountable limitations in assessing intention, monitoring, application of protocols, and collecting data due to the poor information commonly retrieved from clinical notes and diverse indications [Fainsinger et al., 2000; Miccinesi et al., 2006; Rjetjens et al., 2006]. Another issue is that different populations, including cancer and non cancer patients, are often included in the same analysis [Cherny, 2006; Fainsinger et al., 1998; Miccinesi et al., 2006; Bielsen et al., 2006; Morita et al., 2001; Morita et al., 1996]. Multicenter studies have provided information about cultural differences [Miccinesi et al., 2006; Bielsen et al., 2006], and questionnaires provide information about physicians' attitudes in clinical practice [Morita et al., 2001; Morita et al., 1996]. A few prospective studies have shown that palliative sedation is an effective measure to control refractory symptoms at the end of life [Maltoni et al., 2009] despite differences in outcome, with a minority of patients not responding to treatment or having complications related to sedative agents [Fainsinger et al., 1998].

How sedation is given can vary accordingly to patients' needs. Sometimes patients require increased sedative doses at night or intermittently during the day. Patients with acute unsuspected and potentially mortal problems, such as sudden and profuse bleeding or massive pulmonary embolism, tend to be sedated quickly, or more commonly the patient may die before any attempt is made to offer sedation. The most frequent pattern is represented by patients for whom death is seen as impending and inevitable. In the last hours of life, patients are cognitively impaired and may present with dyspnea, agitated delirium

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and/or pain. At this point, the patient's consent is usually unavailable.

Once a decision has been made, practical aspects should be considered [Cowan and Walsh, 2001]. Different drugs with sedative properties have been used. Midazolam, a benzodiazepine, is the most commonly used agent. The short half-life allows rapid dose titration and use of a subcutaneous or intravenous route. After priming with doses of 2-3 mg to achieve an initial level of sedation, a continuous infusion calculated on the effect obtained with the bolus can be started. Generally 30-45 mg/day is the starting dose, which is then changed according to the level of sedation required to control symptoms. The goal is to provide comfort by lowering the level of consciousness. Despite careful titration to achieve symptom control only, impaired communication capacity may result [Mercadante *et al.*, 2009].

Many observations in palliative care setting have reported a mean dose of midazolam prescribed in the final days of 22-70 mg/day, with a maximum of 240 mg/day [Mercadante et al., 2009; Miccinesi et al., 2006; Morita et al., 2000]. Most patients have a good symptom control, with variable levels of unconsciousness with 90 mg/day. Sometimes, it is necessary to titrate the doses up to more than 100 mg/day, especially in younger patients, pre-exposure to midazolam, after several days consisting of prolonged periods of sedation [Fainsinger et al., 1998; Chater et al., 1998] and/or being close to death. This could be attributed to tolerance [Chater et al., 1998], although metabolite accumulation in patients with a reduced renal function may reinforce sedation [Bauer et al., 1995]. The use of midazolam combined with opioids achieved no significant increase in predicting survival.

Patient reassessment is mandatory in order to change the infusion rate based on clinical needs. The depth of sedation that is required to achieve adequate symptom relief is highly variable from one individual to the next and sometimes provisions for emergency boluses for breakthrough symptoms are necessary, at least in a hospitalhospice setting. For some patients, a state of conscious sedation may provide adequate symptom relief without total loss of cognitive function [Bauer *et al.*, 1995]. This approach is often desired by relatives when sedation is started, although these changes are more likely to be performed in a structured and continuously monitored environment. Refractoriness has a temporal component, from both the patient's and the system's perspective. The practice of intermittent or temporary sedation recognizes that either a symptom might respond to continued or future therapy, or that the patient's ability to tolerate the symptom may be improved following the rest and stress reduction provided by sedation [Morita *et al.*, 2005]. For example, in a palliative care unit, 23% of patients who were sedated during

admission were discharged alive [Elsayem et al., 2009].

Palliative sedation (PS) can be performed at home. PS was found to be an effective method of relieving terminal suffering in the last days of a dying patient, especially for relatives who considered it effective and satisfactory treatment for relieving suffering. The decision was made after clear explanation about the clinical need for PS and in about one/third of cases the relatives elicited this explanation. Recent studies show PS used in of 13-35% home palliative settings [Mercadante et al., 2011a], confirming varying degrees of PS reported previously [Mercadante et al., 2011b]. The large variability suggests a lack of appropriate criteria adopted for the use of PS. For example, in a multicenter Italian study the range varied between 0% and 60%. It is likely that information implies a lack of consensus on definition of PS among the centers involved [Peruselli et al., 1999]. The figures seem to be lower than the rate reported by hospital-based palliative care units or hospice [Cherny, 2006; Miccinesi et al., 2006; Rjetjens et al., 2006; Maltoni et al., 2009], with the highest rate reported in acute units [Mercadante et al., 2009]. The difference could be attributed to the fact that hospitalized patients tend to have a greater symptom burden than those who remain at home and/or are admitted to hospital as an emergency because of the development of impeding symptoms close to death [Mercadante et al., 2011a]. Alternately, the home environment may inhibit PS, due to a lack of a continuous bedside presence, family cooperation, time for planning, and/or ability to make decisions in emergency conditions [Mercadante et al., 2011b].

Hydration and nutrition

In most patients, hydration and nutrition are already lessened due to different reasons, including anorexia, difficulty in swallowing and cognitive impairment, typically present in the last days of life. Hunger is rare and transient symptoms of dry mouth and throat usually respond to assiduous mouth care.

Once the decision to start a definitive palliative sedation is taken, hydration should be discontinued or given in minimal amounts [Mercadante *et al.*, 2009]. Most patients are already unable to swallow or are coughing, and as the level of consciousness is lowered, this ability will further decrease. About half of patients will present with death rattle before dying, and this may contribute to the severe distress of patients and their family members. Patients with lung and brain cancer are more likely to develop death rattle [Stone *et al.*, 1997]. For these reasons, it is recommended to start anticholinergic drugs or diuretics to decrease pharyngeal and bronchial secretion. Anticholinergic drugs should be started pre-emptively before secretions accumulate. Gentle aspiration may be useful before giving anticholinergic agents [Mercadante *et al.*, 2011c].

Monitoring

Palliative sedation is a complex issue that is clearly distinct from slow euthanasia or ambivalence [Claessens et al., 2011]. The expected side effect of sedation is the loss of communication but not death; thus, great care must be taken especially in very fragile patients. Careful monitoring is required in order to obtain the best outcome. The depth of sedation needs to be adapted to the required level of symptom control to limit under- or over-sedation. Symptoms should be assessed continuously. The Glasgow coma score lowers once sedation is initiated and gradually decreases up until the day of death [Claessens et al., 2012]. This tool, however, is more frequently used in intensive care environments, and is difficult or unethical to apply in this group of patients as the evaluation of some responses is based on a painful stimulus. In a dying patient, this approach may have clinical consequences and compromise the level of sedation achieved. Different tools have reported the use of observational scales to monitor the effects of palliative sedation, including the Richmond Agitation Sedation Scale, the Ramsay sedation scale, five-point Likert scales, and the community capacity scale. Timing and frequency of monitoring varies and should be adapted on the individual's situation and environment. Among these tools, the Richmond Agitation Sedation Scale seems to be less time consuming, clearer, and easier to use [Arevalo et al., 2012].

Communication issues

Informed consent is provided by family members, as the patient is often unable to participate due to his or her reduced cognitive function. Family members may report guilt, helplessness, and physical and emotional exhaustion when patients are going to be sedated. Relatives are often concerned about whether sedated patients experience distress. Clinicians should understand families' emotional distress and reassure them that symptoms are truly refractory, providing support and information to help families prepare for patient death. With skilled personnel, it is possible to have a low level of conflicts with relatives and acceptance of sedation as last resort to allow a peaceful death [Mercadante *et al.*, 2009]. This holds true even in Mediterranean culture, where paternalism and conspiracy of silence prevail [Centeno-Cortes and Nunez-Olarte, 1994], living will is rarely expressed, and relatives are making decisions, which often requires intensive treatment even in desperate situations.

Ethical considerations

The concept of sedation, when used to relieve intractable suffering, is generally accepted from the legal point of view. However, controversy still surrounds the use of sedation due to confusion with euthanasia [Morita *et al.*, 2001]. The difference relies on the intent. Euthanasia is defined as the administration of drugs with explicit intention of ending the patient's life, at the patient's explicit request [De Graeff and Dean, 2007]. In euthanasia a hastened death is the aim of the procedure. The intent of sedation is to relieve suffering. Palliative sedation should have no intention of ending a patient's life, but rather should aim to reduce the distress of refractory symptoms and uncontrolled suffering [De Graeff and Dean, 2007].

Palliative sedation generally follows the principles of double effect, proportionality, and autonomy. While the double effect theory provides moral reassurance, its ambiguity may induce the suspicion that death is being hastened and may act as a deterrent to the provision of good symptom control [Morita *et al.*, 2004]. As survival of sedated patients is longer than survival of non-sedated patients, there is no need for the doctrine of double effect to justify sedation from an ethical point of view [Mercadante *et al.*, 2009; Maltoni *et al.*, 2009].

While opioids are a first choice for the treatment of pain and/or dyspnea, even during sedation, regretfully, opioids have been found to be administered alone as sedative agents in general practice [Bielsen *et al.*, 2006; Morita *et al.*, 1996]. Parallel to the modern concept of anesthesia, where specific agents have substituted ether and are used with specific indications, i.e., anesthesia versus analgesia, opioids role in palliative sedation should be well-defined. Specifically, they should be used for pain or dyspnea. When used for

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sedation, they may have detrimental consequences, as required doses may have unwanted, or unpredictable lifeshortening effects, as reported in EURELD studies [Bielsen *et al.*, 2006; Morita *et al.*, 1996]. Another multicenter survey revealed that a small number of patients experienced fatal complications related to sedation from opioids [Fainsinger *et al.*, 1998]. Opioids are not appropriate for relieving suffering from exhaustion, delirium, anxiety, agitation, and psychological suffering. Rather, they may serve to aggravate delirium [Fainsinger *et al.*, 1998].

In appropriate hospice settings, opioids were given in combination with midazolam in almost all patients for palliative analgesia [Mercadante et al., 2009; Rjetjens et al., 2006]. In these cases, patients receiving sedation tend to receive higher opioid doses in the last week of life than those who did not receive sedation, likely secondary to patients' complex symptoms, including dyspnea and pain severity [Bauer et al., 1995]. In fact, there are no significant differences in survival between patients who received higher doses of opioids [Morita et al., 2000] and those in whom opioids doses were unchanged after starting sedation [Hardy, 2000]. Further, a Japanese study in which 80% of patients were received stable doses of opioids after starting sedation (mostly lower than 300 mg of oral morphine equivalents), meaning that this drug class was administered with the purpose of providing analgesia rather than sedation [Morita et al., 2000]. Thus, opioid administration should be continued once sedation is initiated, as there is no tangible evidence that patients do not experience pain.

Sedation and survival

The majority of studies of interventions with potent drugs, including high dosage opioids and sedatives to treat suffering in the last days of life, were unable to show sedation hastens death if carefully administered by skilled people [Fainsinger *et al.*, 2000; Morita *et al.*, 2000]. The relatively short period of time between start of sedation and death is consistently reported in the range of 24-72 hrs [Mercadante *et al.*, 2009; Fainsinger *et al.*, 2000; Miccinesi *et al.*, 2006; Rjetjens *et al.*, 2006], indicating that the need for sedation is an indicator of impeding death rather than a cause of premature death. Sedated and non-sedated patients did not differ in survival after admission [Cherny, 2006]. This was confirmed by a specific study with intent performed in two matched cohorts of hospice patients, one patient receiving palliative sedation and the other managed as per routine practice.

Survival was found to be longer in patients who received palliative sedation [Maltoni *et al.*, 2009]. Although doses of opioids were significantly increased in sedated patients, the dosage increases prevalently observed in sedated patients were performed before starting sedation with the purpose of treating concomitant distressing symptoms, such as dyspnea [Mercadante *et al.*, 2010].

In a study performed in an acute palliative care unit, the median sedation-death time was about one day, with only one patient sedated for more than four days [Mercadante *et al.*, 2009]. Patients who were sedated had a longer survival time when compared to not sedated patients. Moreover, most patients had already stopped eating, were unable to swallow or cough, and had severe fatigue, so that in these conditions sedation cannot be said to hasten death through dehydration or starvation [Morita *et al.*, 2000].

Summary

- Palliative sedation is defined as the use of specific sedative medications to relieve intolerable suffering from refractory symptoms by a reduction in patient consciousness;
- The most frequent intractable symptoms are delirium and dyspnea occurring in the last days of life;
- Palliative sedation is distinct from euthanasia because of the different intent;
- The decision should be shared with patients when possible, or more likely with relatives as most patients are incompetent at time of decision;
- Palliative sedation should be performed by skilled professionals with experience use of sedatives for refractory symptoms and with the use of careful monitoring;
- Initial doses of sedatives should be usually small and titrated proportionally to achieve the desired effect;
- Definitive sedation should be taken into consideration when smaller doses are ineffective and death is imminent;
- Midazolam is the drug of choice;
- Opioid doses should be continued or increased without the intention of sedating, especially in patients who receive opioids for treating dyspnea;
- Hydration should be limited and anticholinergic drugs should be administered to patients in the presence of poor laryngeal and pharyngeal reflexes in order to reduce death rattle.

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Part IV

Controlled sedation for refractory symptoms in dying patients

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Palliative radiotherapy

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Introduction

Radiotherapy is effective in palliating symptoms for patients with advanced malignancies. Different dose-fractionation schedules and techniques are used worldwide, but resources are limited in developing countries and palliative radiotherapy may not be readily available. Therefore, hypofractionated schemes, or even single fraction (SF), are advocated as they provide quick relief of symptoms, minimize the number of visits and save machine time. This chapter serves as a reference for physicians who work in developing countries or in centers with limited resources. The most cost-effective techniques and dose-fractionation schedules for individual body sites will be discussed. We hope this chapter can aid physicians in delivering radiotherapy more efficiently, allowing a greater number of patients to benefit from treatment.

General principles of palliative radiotherapy

Palliative radiotherapy aims at palliating symptoms like pain or bleeding in patients suffering from advanced malignancies. Given the limited life expectancies of these patients, a balance must be struck between quality of life and treatment length and morbidity.

Radiotherapy works by causing both direct and indirect

DNA damage. Direct DNA damage occurs through base deletions and single and double strand breaks. Indirect damage occurs when radiation ionizes water molecules and produces free radicals, which in turn damage DNA. Dividing the total dose of radiation into a number of smaller fractions delivered over time allows normal tissues to repair their DNA. Cancer cells, on the other hand, are usually less capable, causing cancer cell death with preservation of normal tissues. Radiation dose is measured in Gray (Gy). One Gy is one joule of absorbed energy per kilogram, while one centigray (cGy) is equivalent to 0.01 Gy (or one rad in the old system of measurement). Hypofractionated schedules are usually advised in developing countries. It reduces the number of patient visits, reducing the travelling time and burden to patients and their families. It also makes better use of the scarce resources, allowing more patients to receive treatment.

Radiotherapy can be delivered via external beam (Teletherapy) or via radioactive sources implanted or inserted into a body surface, tissue or cavity near the tumor, or into the tumor itself (Brachytherapy). External beam radiation therapy (EBRT) can be delivered with high-energy gamma rays produced by a linear accelerator, or X-rays produced by a radioactive cobalt source. This chapter primarily focuses on EBRT with linear


Figure 1 Example of palliative radiotherapy portal for head and neck cancers above the shoulders (cancer of tongue).

accelerators. A simple technique as well as anteriorposterior (AP) opposing fields is most commonly used. Physicians can simply draw their field on a simulation XR film. Patients usually lie supine on the couch comfortably, and laser beams from three dimensions are used for reproducing treatment positions. Six millivolt photon for opposing fields is usually adequate for thorax or head and neck region. Higher energy photon e.g., 8 or 10 MV may be needed in abdomen or pelvic region where separation is greater. Special points to note at each body site would be discussed in detail in the following sessions.

Head & neck

Radiotherapy in treatment of head and neck cancers is complicated due to the complex anatomy. A number of important organs are at risk because they are in close proximity to the tumor. However, it is of less concern in palliative radiation since the dose is usually below organ tolerance. The aim of treatment is to obtain tumor control of reasonable duration in order to facilitate eating, swallowing and airway patency. A radiation field covering the gross tumor with a margin of 1-2 cm is usually adequate for palliation. In general, the field arrangement above the shoulder can be dealt with a lateral opposing pair and that below the shoulders with a single anterior field. If tumor and lymph nodes extend from above to below the shoulders, matching of the two fields with a half beam block can be used (*Figures 1,2*). Occasionally, wedge pairs can be used



Figure 2 Example of palliative radiotherapy portal for head and neck cancers below the shoulder (matching field with *Figure 1*).

for a lateralized tumor to avoid organs at risk and minimize toxicities.

For dose fractionation, various schedules have been investigated. Kancherla et al. [2011] from United Kingdom investigated a split course treatment with 20 Gy in five fractions for two times with a 2-week gap. The maximum acceptable spinal cord dose was 30 Gy (equivalent dose in 2 Gy per fraction of 37.5 Gy for late effects using an α/β ratio of two), with the posterior field border moved anterior to the cord as necessary. Outcomes including symptomatic improvement, complete tumor response, and partial response were reported to be 79%, 39% and 33% respectively. Median overall survival was nine months and progression-free survival at one and two years was 35% and 25%, respectively. Treatment was generally well tolerated, with Radiation Therapy Oncology Group grade 3 skin toxicity in only one patient, grade 3 mucosal toxicity in two patients, and grade 3 esophageal toxicity in three patients. Admission for nasal-gastric feeding and/or supportive care was required in only 6 out of 33 patients. It is reasonable to start the first part of the treatment with 20 Gy in five fractions. The patient can be reassessed two weeks later for another course of 20 Gy in five fractions, if patient can tolerate further treatment and tumor response is documented.

Porceddu *et al.* [2007] reported the "Hypo Trial" regimen of 30 Gy in five fractions at twice per week, at least three days apart, with an additional boost of 6 Gy for small volume disease (\leq 3 cm) in suitable patients. Overall

Table 1 Comparison of outcomes of various fractionated palliative radiotherapy to lung tumors				
Reference	No. of patients	Fractionation schemes	Symptom response	Survival/months
Simpson	409	30 Gy/10 Fr/2 weeks	Overall 69%, no difference	6
<i>et al</i> ., 1985		40 Gy/20 Fr/4 weeks	between the 3 arms	6
		40 Gy/20 Fr/6 weeks (Split, 2 weeks apart)		
Teo <i>et al</i> .,	29	45 Gy/18 Fr/3.5 weeks	71%	5
1988		31.2 Gy/4 Fr/4 weeks	54%	5
MRC, 1991	369	17 Gy/2 Fr/8 days	65-81%	6
		27 Gy/6 Fr or 30 Gy/10 Fr/daily except weekend	56-86%	6
MRC, 1992	295	17 Gy/2 Fr/8 days	48-75%	3
		10 Gy/1 Fr	55-72%	4
Abratt et al.,	84	35 Gy/10 Fr/2 weeks	68%	8.5
1995		45 Gy/15 Fr/3 weeks	76%	8.5
Macbeth et al.,	509	17 Gy/2 Fr/8 days	More rapid palliative with	7
1996a		39 Gy/13 Fr/2.5 weeks	17 Gy/2 Fr	9
Rees et al.,	216	17 Gy/2 Fr/8 days	No difference	6
1997		22.5 Gy/5 Fr/1 week		6
Plataniotis	92	17 Gy/2 Fr/8 days	39%	5.8
<i>et al.</i> , 2002		22.25 Gy/5 Fr/1 week	36%	5.8
Bezjak <i>et al</i> .,	52	10 Gy/1 Fr	Better control with 20 Gy/5 Fr	4.5
2002		20 Gy/5 Fr/1 week		6
Sundstrøm	53	17 Gy/2 Fr/8 days	No difference in symptom	8.2
<i>et al.</i> , 2004		42 Gy/15 Fr/3 weeks	response or toxicity	7
		50 Gy/25 Fr/5 weeks		6.8
Kramer et al.,	297	16 Gy/2 Fr/8 days	Better response for 30 Gy/10 Fr/2	10.9%
2005		30 Gy/10 Fr/2 weeks	weeks at 22 weeks post treatment	19.6% at 1 year
Senkus-Konefka	100	16 Gy/2 Fr/8 days	No difference	8
<i>et al.</i> , 2005		20 Gy/5 Fr/1 weeks		5.3
Erridge et al.,	149	10 Gy/1 Fr	77%	22.7
2005		30 Gy/10 Fr/2 weeks	92%	28.3

objective response rate was 80% with grade 3 mucositis and dysphagia in 9/35 (26%) and 4/35 (11%) respectively. Improvement in quality of life and pain was noted in 62% and 67% respectively. The median time to progression and overall survivals were 3.9 and 6.1 months, respectively.

Dose fractionation recommendation: (I) 20 Gy in five fractions over one week, then assess for another course of 20 Gy in five fractions over one week after two weeks gap; (II) 30 Gy in five fractions over 2.5 weeks.

For tumor recurrence after high dose radiotherapy, studies concerning re-irradiation with high dose are emerging. The challenge will be organs at risk especially the brain, brain stem and spinal cord. In a palliative setting, the tumor can be controlled with a more fractionated radiotherapy dose e.g., 30 Gy in ten fractions over two weeks. The organs at risk should be shielded as much as possible.

Thorax

Non-small cell lung cancer

There were 13 prospective trials in the past two decades comparing outcomes of fractionated palliative radiotherapy to lung tumors (*Table 1*). Chemotherapy was not included



Figure 3 Typical radiotherapy field covering the tumour causing SVCO and also including right supraclavicular fossa in this patient. The larynx is shielded to avoid mucositis.

in most of these trials. All 13 studies reported patients with significant symptoms including: dyspnea, hemoptysis, cough, and pain. Many of them showed similar symptom relief and survival with 16 or 17 Gy in two fractions over seven days compared with a more prolonged course. Ten Gy in one fraction had been used in the MRC trial showing 55-72% response rate and four months medial survival in patients with poor performance status (WHO 1979 2-4). Even though it was shown to be inferior in survival compared with 20 Gy in five fractions in patient with good performance status [Bezjak et al., 2002; Erridge et al., 2005], it is still a convenient and effective treatment to be considered in areas where radiotherapy is not easily accessible. Toxicities, including WHO grade 3 dysphagia, were seen in 5% of patients [Lupattelli et al., 2000] when debilitated patients underwent 16 Gy in two fractions one week apart. There was no significant toxicity observed in other studies with shorter doses/other fractionation schemes.

Dose fractionation recommendation: (I) 16-17 Gy in two fractions over eight days; (II) 10 Gy in one fraction.

Small cell lung cancer

Long term survival is usually dismal in patients with extensive stage small cell lung cancer. For patients fit for chemotherapy, platinum doublet is the mainstay of motherapy palliat

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treatment. For patients not fit for chemotherapy, palliative dose/fractionation used in non-small cell lung cancer (NSCLC) can be implemented [Radiotherapy Dose-Fractionation, 2006].

Superior vena cava obstruction (SVCO)

Rowell and Gleeson [2002] conducted a systematic review on the treatment of SVCO in 2002. Three randomized and 98 non-randomized studies were reviewed, of which 2 and 44, respectively, met the inclusion criteria. Ten percent of patients with SCLC and 1.7% of patients with NSCLC presented with SVCO at diagnosis. Radiotherapy was helpful in 77.6% of patients. For dose fractionation, Rodrigues et al. reported 96% response with hypofractionated radiotherapy 24 Gy/3 Fr/3 weeks [Rodrigues et al., 1993]. The first fraction was delivered with parallel opposed fields via AP and posterior-anterior (PA) fields, and the next fractions were delivered with an AP field and posterior oblique field sparing the spinal cord. Three-dimensional simulation will be superior in sparing the cord, but this may not be available in many developing countries. Donato et al. reported similar symptom relief of 73.9% with 20 Gy/5 fractions/1 week and in 75% with 30 Gy/10 fractions/2 weeks [Donato et al., 2001]. Once again, shorter fractionation schemes are effective in symptom relief. Simple 2-D simulation can be used with the two beforehand mentioned dose-fractionation schemes (Figure 3). Steroid coverage with dexamethasone, prescribed at 4 mg four times a day alongside an antacid/ proton pump inhibitor, is recommended as radiation can cause transient tumor swelling, which may aggravate symptoms initially.

Dose fractionation recommendation: (I) 24 Gy in three fractions over three weeks (note field arrangement); (II) 20 Gy in five fractions over one week.

Radiation myelitis in thoracic radiotherapy

Radiation myelopathy is an uncommon, but serious, side-effect in patients receiving thoracic radiotherapy. Macbeth *et al.* evaluated the risk in 1,048 patients in three randomized trials of palliative thoracic radiotherapy, conducted by Medical Research Council Lung Cancer Working Party [Macbeth *et al.*, 1996b]. Five patients were reported to suffer from radiation myelitis. The estimated cumulative risk of radiation myelitis by two years was 2.2% (3 out of 524) in patients receiving 17 Gy in two fractions over eight days and 2.5% (2 out of 153) in patients receiving

39 Gy in 13 fractions over 17 days. None was reported in patients receiving other fractions including 27 Gy in six fractions over 11 days (47 patients), 30 Gy in six fractions over 11 days (36 patients), 30 Gy in ten fractions over 12 days (88 patients) and 36 Gy in 12 fractions over 16 days (86 patients). From their data, the best estimate of α/β of spinal cord is less than 3 Gy and close to 2 Gy. They suggested the spinal cord dose should not exceed 48 Gy in terms of the total doses that would have an equivalent biological effect if given in 2 Gy fractions (assuming $\alpha/\beta = 2$). The 17 Gy in two fractions regimen could be modified either by reducing the midplane dose to 16 Gy or by shielding the cord from the posterior field for the second fraction, which would reduce the cord dose to 14-16 Gy without compromising the dose to most of the symptomatic tumor away from the midplane.

Macbeth further pointed out that by keeping the spinal cord dose below 48 in 2 Gy fractions, the risk of radiation myelopathy would be less than 1% and acceptable [Macbeth, 2000]. Two more salient points were to be noted. The spinal cord dose would be 5-10% higher than the midplane dose with parallel opposing fields, depending on the photon beam energy and separation. Many patients have a sloping chest from the superior to inferior borders of the radiation field. Therefore, the anterior field should be appropriately wedged to prevent the spinal cord from being over-dosed.

Breast

It is not uncommon for patients in developing countries to present with advanced breast cancer. Chemotherapy and hormonal treatment provide effective palliation to tumours that are large or fungating. There are few trials evaluating the optimal radiation dose for advanced breast cancer. For a fungating or bleeding breast mass, it is commonly treated with 20 Gy in five fractions or 30 Gy in ten fractions in tangential opposing fields. For frail patients, a SF of 6 Gy can effectively palliate symptoms. Reassessment after one week for repeating another 6 Gy up to a total six fractions can be considered [Barrett *et al.*, 2009].

Dose fractionation recommendation: (I) 20 Gy in five fractions over one week; (II) 30 Gy in 10 fractions over two weeks; (III) 6 Gy weekly up to six fractions.

Esophagus

Many of the patients suffering from esophageal cancers are elderly and are often frail with significant weight loss. Palliative radiotherapy provides up to 80% of symptom relief. Simulation is simple. The tumor can be localized by barium swallow to look for the narrowed site on XR films. A margin of 3 cm from superior and inferior aspect of the tumor is adequate to account for respiratory movement and set up error. AP opposing fields are usually used. A typical dose of 20 Gy in five fractions or 30 Gy in ten fractions is prescribed. High dose rate 192Ir brachytherapy of Intraluminal doses of 6 Gy delivered at 1 cm for two treatments with or without external beam radiotherapy (65% with brachytherapy alone and 35% with both) have been reported to be effective in relieving 48% of obstruction and maintaining 41% of pretreatment swallowing status [Sharma et al., 2002]. Another large trial involving 219 patients echoed with the beneficial use of combining external beam radiotherapy and intraluminal brachytherapy 8 Gy prescribed at 1 cm from source centre [Rosenblatt et al., 2010]. Brachytherapy was shown to be more effective in long-term relief of dysphagia compared with stenting [Homs et al., 2004].

Dose fractionation recommendation (External Beam radiotherapy): (I) 20 Gy in five fractions over one week or 30 Gy in ten fractions over two week with or without HDR brachytherapy fractions over one week after two weeks gap; (II) 6-8 Gy in one fraction prescribed at 1 cm from source centre.

Abdomen & pelvis

Stomach

Palliative radiotherapy is usually employed for obstructive symptoms or for a haemostatic purpose. A schedule with 20 Gy in five fractions is commonly used. In patients with very poor performance status, a SF of 8-10 Gy can stop bleeding. Barium swallow is frequently used to visualize the stomach. AP opposing fields are usually adequate to cover the tumor (*Figure 4*).

Dose fractionation recommendation: (I) 20 in five fractions over one week; (II) 8-10 Gy in one fraction.

Bladder

The Medical Council Research B09 trial demonstrated equivalent efficacy of symptom relief with a dose of 21 Gy in three fractions over alternate weekdays in a week versus 35 Gy in ten fractions over two weeks in advanced bladder cancers [Duchesne *et al.*, 2000]. For frail patients, a single



Figure 4 Patient with stomach cancer was asked to have barium swallow to visualize the stomach.

dose of 6-8 Gy is also an acceptable option as recommended by the UK College of Radiologist 2006. Radiotherapy portal covering the true pelvis with AP opposing fields is usually adequate to include the bladder.

Dose fractionation recommendation: (I) 21 Gy in three fractions, alternate day over one week; (II) 6-8 Gy in one fraction.

Prostate

Radiation is useful in relief of urinary obstruction and haematuria. Kawakami *et al.* found that the optimal dose is around 30 Gy [Kawakami *et al.*, 1993]. Another scheme suggested by Kynaston *et al.* with 8 Gy for 1-3 fractions weekly dose attained a 88% of relief in urinary obstruction and 100% of relief in haematuria, although it was reported together with another scheme of 35 Gy in 15 fractions over three weeks [Kynaston *et al.*, 1990]. However, in developing countries, a hypofractionated scheme is preferred.

Dose fractionation recommendation: 8 Gy ×1-3 fractions weekly.

Gynecological cancers

Gynecological cancers can be well covered with anteriorposterior opposing fields. Physical examination can assist the oncologist in defining the lower border, and the vaginal introitus can be marked with a ring marker (*Figure 5*). Halle *et al.* reported that a SF of 10 Gy to the



Figure 5 Cervical cancer treated with radiotherapy using anteriorposterior opposing fields covering mainly the true pelvis. The black line just below the pubis is the ring marker locating the vaginal introitus.

pelvis for patients with advanced carcinoma of cervix or endometrium yielded a 60% cessation of bleeding, 22% complete pain relief and 28% complete tumor resolution [Halle *et al.*, 1986]. The dose was recommended for frail patients with life expectancy less than one year. Boulware *et al.* attempted a fraction of 10 Gy and repeated when feasible within 3-4 weeks interval [Boulware *et al.*, 1979]. They found that patients with three treatments attained the best palliation, and two treatments were more effective than one. However, it has to be highlighted that significant late bowel toxicities may occur. A more fractionated treatment regimen e.g., 30 Gy in ten fractions or 20 Gy in five fractions is recommended to avoid bowel toxicity.

Dose fractionation recommendation: (I) 30 Gy in 10 fractions over two weeks; (II) 20 Gy in five fractions over one week; (II) 8-10 Gy in one fraction, weekly up to three fractions if tolerated (frail patients with limited life expectancy).

Rectum

In rectal cancer, the lower border of tumor can be located with physical examination or with proctoscopy. The anus can be marked for better sparing. There is little evidence regarding the optimal dose of palliative radiotherapy to rectal cancer. A hypofractionated scheme with 30 Gy in six fractions over three weeks with two fractions given per week

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Figure 6 Palliative radiotherapy portal for brain tumors.

combined with continuous 5 FU infusion was reported to stabilize symptoms in 75% of patients [Janjan *et al.*, 2000]. More fractionated schemes with 30 Gy in ten fractions or 20 Gy in five fractions may avoid bowel toxicity if patient has fair life expectancy. Hatfield and Sebag-Montefiore [2003] reviewed the radiotherapy dose to rectum and commented that a dose of 6-8 Gy in one fraction can be recommended for frail patients.

Dose fractionation recommendation: (I) 30 Gy in ten fractions over two weeks; (II) 20 Gy in five fractions over one week; (III) 30 Gy in six fractions over three weeks (two fractions per week) (combined with 5 FU infusion) if chemotherapy facilities available); (IV) 6-8 Gy in one fraction in frail patients.

Central nervous system (CNS)

Brain

Palliative radiotherapy to the brain can be delivered with lateral opposing fields covering the majority of the meninges above Reid's line. The orbital globes are usually spared (*Figure 6*).

Brain metastases

A review by Tsao *et al.* [2012] analyzing data from 39 randomized control trials including 10,835 patients showed similar overall survival using 30 Gy/10 fractions/2 weeks

versus 20 Gy/5 fractions/1 week. British Royal College of Radiologists trial [Priestman *et al.*, 1996] suggested a 39% of response rate when using a dose fractionation of 12 Gy/2 fraction/2 days versus 44% in 30 Gy/10 fractions/2 weeks, though a marginal survival benefit was observed in the 30 Gy arm. For patient with poor performance status, the 12 Gy/2 fraction/2 days scheme is a good option for symptom relief.

Dose fractionation recommendation: (I) 20 Gy in five fractions over one week; (II) 12 Gy in two fractions over two days.

Primary malignant glioma

High grade glioma is usually infiltrative. Upfront surgery plus post-operative concurrent chemo-radiotherapy was shown to have survival benefit. However, for patients with poor performance status, hypofractionated radiotherapy was shown to be beneficial [McAleese *et al.*, 2003]. Patients treated with hypofractionated partial brain radiotherapy of 30 Gy/6 fractions/2 weeks had a median survival of five months with a 1-year survival rate of 12% from diagnosis. The median survival of case-matched controls treated with 60 Gy/30 fractions/6 weeks was estimated to be 2.5-4.5 months longer. However, if conformal radiotherapy is not available, a palliative dose to the brain as implemented in multiple brain metastases is widely used.

Dose fractionation recommendation: (I) 30 Gy in six fractions over two weeks (partial brain radiation); (II) 20 Gy in five fractions over one week or 12 Gy in two fractions over two days (whole brain radiotherapy).

CNS lymphoma

The primary treatment of CNS diffuse large B cell lymphoma is high dose chemotherapy. Whole brain radiotherapy is used for consolidation. The dose is recommended to be 24-36 Gy/1.8-2 Gy per fraction [NCCN guideline, 2013 v2]. For patients with poor performance status, steroid treatment alone or with whole brain radiotherapy can be considered, but is expected to be less effective. Shorter dose fractionation schemes like 20 Gy in five fractions can be considered if performance status of the patient is poor. The median survival was shown to be better with steroid plus radiotherapy versus steroid alone in HIV patients in a small series [de La Blanchardière *et al.*, 1997]. Studies for this group of patients are limited.

Dose fractionation recommendation: (I) 24-36 Gy/1.8-

Palliative radiotherapy

2 Gy per fraction; (II) 20 Gy in five fractions over one week in frail patients.

Lymphoma

Hodgkin's lymphoma

Advanced Hodgkin's lymphoma is usually managed with chemotherapy followed by radiotherapy to initial bulky sites or residual diseases. A dose of 30-36 Gy in 1.5-2.0 Gy per fraction over 3-4 weeks is recommended [Radiotherapy Dose-Fractionation, 2006; NCCN guideline 2014 v1; Eichenauer *et al.*, 2011].

In palliative cases, 30 Gy in ten fractions over two weeks to 7-8 Gy in SF can be offered [Radiotherapy Dose Fractionation. RCR 2006]. In regions where radiotherapy access is limited, a SF of 8 Gy is a reasonable option.

Dose fractionation recommendation: 8 Gy in one fraction (if multiple sites are involved and can be encompassed in a tolerable radiation portal, a more fractionated regime is still recommended for more favorable toxicity profile).

Non-Hodgkin's lymphoma

Low grade lymphomas

A large multi-centre phase II trial [Haas *et al.*, 2003] recruited 109 patients with the majority having follicular lymphoma (n=98), some extranodal marginal-zone lymphomas of mucosa-associated lymphoid tissue-type, and lymphoplasmacytoid lymphomas (n=9 and 2 respectively). Patients were given radiotherapy with 2 Gy for two fractions as palliation. The response rate was high up to 92%, with 61% complete response and 31% partial response. The median time to progression was 14 months. Therefore, it becomes a standard dose/fractionation for palliative cases. It can be repeated in cases of disease progression in later course of disease.

Dose fractionation recommendation: 4 Gy in two fractions.

Intermediate to high grade lymphomas

There are few papers discussing the optimal dose of palliative radiation in intermediate to high grade lymphoma. However, the United Kingdom Royal College of Radiologist suggested a practical dose-fractionation for this entity.

Dose fractionation recommendation: (I) 20 Gy in five fractions over one week; (II) 8 Gy in one fraction.

Cutaneous lymphoma

Large scale randomized trials for this entity are lacking. A Dutch trial by Neelis et al. [2009] on 18 patients with low grade cutaneous B cell lymphoma and 44 symptomatic sites found that tumors treated with a dose of 4 Gy in two fractions attained a complete response rate of 72%. In the same study, 31 patients with mycosis fungoides were treated at 82 symptomatic sites with a dose of 8 Gy in two fractions and attained a complete response rate of 92%. Those who progressed were retreated with 20 Gy in eight daily fractions, and all had a rapid complete response. A recent American trial reviewed the records of 58 patients with cutaneous T cell lymphoma (CTCL), primarily mycosis fungoides, treated with a SF of 7-8 Gy in a period of 20 years, found a complete response rate of 94.4% over a mean follow up of 41.3 months [Thomas et al., 2013]. However, primary cutaneous large B-cell lymphomas, leg type (PCLBCLs, LT) is a more aggressive entity with relapse rate of 63% and 5-year survival rate of only 44% with a median dose of 40 Gy (range, 20-46 Gy) [Senff et al., 2007]. A higher dose may be recommended for this entity.

Dose fractionation recommendation: 8 Gy in 1-2 fractions; Retreatment: 20 Gy in eight fractions over 1.5 week.

Bone metastases

Bone metastases can be divided into uncomplicated and complicated bone metastases. Complicated bone metastases are those with pathological fractures and/or spinal cord compression. Radiotherapy to bone provides a partial pain response in 50-80% of patients and a complete response in up to one third of patients [Chow *et al.*, 2007]. A recent meta-analysis has demonstrated equal efficacy between SF and multiple fractionation (MF) [Chow *et al.*, 2011], although retreatment rate is higher in the SF arm. Further, even after accounting for the higher re-treatment rate using initial SF radiotherapy (8% versus 20%), the cost is still lower than performing initial SF and retreatment with MF radiotherapy [van den Hout *et al.*, 2003].

The American Society for Therapeutic Radiation Oncology (ASTRO) has been involved in guideline development. A Task Force of recognized experts from radiation oncology (private practice, academic, and residency programs), neurosurgery, and palliative medicine convened to offer their perspective on the literature. With regard to fractionation schemes, they determined, on the basis of several well-designed prospective randomized trials, that there was no difference in effectiveness between SF and MF [Lutz *et al.*, 2011]. However, SF offered a more cost-effective method of delivering treatment that was more convenient and less burdensome to patients and their caregivers. Re-irradiation is also efficacious with response rate of 58% in a meta-analysis [Huisman *et al.*, 2012].

For radiotherapy technique, treatment can be delivered with AP opposing fields covering the painful site with margins for non-axial bones. A posterior field covering 1-2 vertebrae above and below the painful site with 8 cm width with 6-8 MV photons prescribed at cord depth) is usually used to cover spinal process for axial bones.

Metastatic spinal cord compression (MSCC)

Spinal cord compression is an oncological emergency as it can cause permanent disability with paraplegia and double incontinence. Detection and treatment should be prompt. For clinical suspicion for spinal cord compression, steroids should be prescribed to reduce cord edema (e.g., Dexamethasone 4 mg four times a day per oral or intravenous). MRI should be performed to confirm diagnosis, if facilities are available.

Radiotherapy is effective in the treatment of MSCC. However, it is important to choose the appropriate dose fractionation in different scenarios. It was also shown that multi-fractionated long-course radiotherapy results in better re-calcification and fewer recurrences of spinal cord compression within the irradiated spinal region [Rades et al., 2010, Rades, 2010]. On the other hand, a phase III Italian trial [Maranzano, 2009] investigated the efficacy of SF 8 Gy compared with 8 Gy ×2 in one week in patients with MSCC having unfavourable histologies which have a short life expectancy due to the natural history of the tumor itself, or patients with favourable histologies, neurological symptoms and/or low performance status, factors that are generally associated to a short life expectancy. Outcomes were measured in terms of symptom control (i.e., back pain, motor and sphincter function), duration of response, and survival. There was no difference in terms of response in the two arms. Median duration of response was 5 and 4.5 months for short-course and single-dose radiotherapy (P=0.4), respectively. The median overall survival was 4 months for all cases. Toxicity was mild with 7% patients with grade 1 oesophagitis/dyspepsia, 1% patients with grade 3 oesophagitis treated in the thoracic area, 2% patients with grade 1-2 diarrhea in the SF arm. Similar rate of grade 1-2 vomiting was recorded in the two arms, with 17.5% in patients given

antiemetic prophylaxis and 6% in patient who did not (as the treated spines were not at risk. It concluded that SF with 8 Gy achieved minimal toxicity and inconvenience to MSCC patients. An updated systematic review and practice guideline of Cancer Care Ontario [Loblaw *et al.*, 2012] analyzed available data published from January 2004 to May 2011 made a conclusion of the following few points:

- If not medically contraindicated, steroids are recommended for any patient with neurologic deficits suspected or confirmed to have metastatic extradural spinal cord compression;
- Surgery should be considered for patients with a good prognosis who are medically and surgically operable;
- Radiotherapy should be given to nonsurgical patients.
 - o For those with a poor prognosis, a SF of 8 Gy should be given;
 - o For those with a good prognosis, 30 Gy in 10 fractions could be considered.

Spinal cord tolerance in re-irradiation

When considering re-irradiation, careful calculation of equivalent dose at 2 Gy per fraction EQD2Gy should be carried out. Linear quadratic equation should be employed.

EQD2Gy = $Nd(\alpha/\beta+d)/(\alpha/\beta+2)$ (d, dose per fraction; N, number of fractions)

Concerning the late complication of radiation myelopathy, Schutheiss and Stephens [1992] suggested an α/β of 2 Gy best fit the model. Radiation myelopathy would increase when total EQD2Gy exceeds 48 Gy [Macbeth *et al.*, 1996]. However, a more recent study [Nieder *et al.*, 2006] suggested a much higher EQD2Gy up to 135.5 Gy (when interval is longer than six months) for cord tolerance. It should be noted that an initial small dose per fraction and newer radiation techniques such as conformal radiotherapy or intensity-modulated radiotherapy were used. For palliative radiotherapy, EQD2Gy 48 Gy as maximum cord tolerance is still recommended.

Neuropathic pain

Neuropathic pain is caused by nerve root compression in bony metastases. It causes a great burden to patients and is often difficult to treat. The use of analgesics according to WHO analgesics ladder in combination with antidepressants (e.g., Tricyclic antidepressant) and anticonvulsants (e.g., pregabalin, gabapentin) may not

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be adequate for pain relief. Radiotherapy is an important treatment modality for relieving pain. In the past, it was believed that more fractionated schemes provided better result. A randomized trial by TROG 96.05 investigated the efficacy of 8 Gy in one versus 20 Gy in five fractions in treatment of neuropathic pain [Roos et al., 2005]. No statistical difference was found in overall response rate, estimated median time to failure, rate of retreatment, cord compression and pathological fracture by arm. Authors concluded that SF 8 Gy was not shown to be as effective as 20 Gy in five fractions, nor was it statistically significantly worse. Dennis et al. [2001] reviewed current treatment of neuropathic pain with radiotherapy. They suggested that treatments today are different with those in TROG 96.05, as neuropathic pain is more strictly defined with validated screening and measurement tools. More results are awaited to validate the efficacy of different dose fractionations. However, as concluded by TROG 96.05 trial, SF would still be appropriate for patients with limited expected survival or a poor performance status, or for departments operating with limited resources.

Dose fractionation recommendation

- (I) Uncomplicated bone metastases: 8 Gy in one fraction (initial and retreatment).
- (II) Complicated bone metastases/Spinal cord compression:
 (i) 20 Gy in five fractions over one week or 30 Gy in ten fractions over two weeks (good performance status and survival);
 (ii) 8 Gy in one fraction (poor performance status and survival).
- (III)Neuropathic pain: 8 Gy in one fraction (poor performance status and survival).

AIDS related Kaposi sarcoma

Raju *et al.* [1990] reported that 20 to 24 Gy in 10 to 12 fractions over two weeks gave good symptom relief for 37 of 39 treated sites in eight patients. However, in patients with anticipated survival for a few months, a dose of 8 Gy in one fraction is useful in palliation [de Wit *et al.*, 1990].

Dose fractionation recommendation: (I) 20-24 Gy in 10-12 fractions over two weeks; (II) 8 Gy in one fraction for frail patients.

Summary

This chapter serves as a simple guide for radiation oncologists in developing countries in delivering cost effective palliative radiotherapy. These parameters may be modified by individual oncologists based on availability of local resources. In general, hypofractionated radiotherapy provides rapid symptomatic relief of symptoms which is beneficial in patients with limited life expectancy. Radiotherapy, which is more fractionated, should be reserved for patients with good performance status and more favorable histology.

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Introduction

The future of neuromodulation shows incredible potential and will likely demonstrate greater integration of various techniques as adjunctive therapy to already accepted standard of care management. In addition to further study on current applications such as movement disorders, neuromodulatory techniques are undergoing investigation for a number of conditions-depression, obsessive-compulsive disorder, impulsivity disorders, addiction, eating disorders, obesity, tinnitus, blood pressure control and traumatic brain injury.

Neuromodulation has a potential role in the palliative care population as this sector often suffers from significantly distressing refractory symptoms which have a common basis to those mentioned above. Neuromodulatory techniques could alleviate these symptoms in an effort to facilitate a better quality of life and peace for the remaining time. This chapter will discuss the potential roles of neuromodulation in the treatment of dyspnea, gastrointestinal (GI) dysfunction, motor recovery, mentation and sleep dysfunction in the palliative population.

Deep brain stimulation

Current use

Deep brain stimulation (DBS) is known for its treatment effects in movement disorders, specifically on PD, essential tremor and dystonia by targeting the subthalamic nucleus (STN), ventralis intermedius (VIM) nucleus of the thalamus and globus pallidus internus (Gpi) respectively. Lives of selected patients with these disorders have been greatly improved by this technology. DBS is now also approved for the treatment of obsessive-compulsive disorder and in clinical trials for the treatment of major depression and Alzheimer's dementia.

The precise mechanism of action continues to elude the scientific community. Multiple hypotheses have been suggested: (I) depolarization block by inactivating generation of action potentials in efferent nerve endings; (II) synaptic modulation by way of activating nerve terminals to excite and/or inhibit efferent outputs; (III) synaptic depression by depleting neurotransmitter supply in terminals of efferent outputs; (IV) network jamming/ modulation by facilitating anti-oscillatory action on basal ganglia circuitry; and (V) synaptic facilitation by enhancing sustained neurotransmitter release.

All hypotheses however acknowledge that the effects of DBS occur at various levels from local changes in the stimulated brain nuclei affecting changes in efferent outputs and further affecting subsequent changes in the target nuclei [Lee *et al.*, 2009]. The other facets however seem contradictory-involving activation, inhibition and concomitant activation, and/or inhibition at the electrode site [Shah *et al.*, 2010].

Essentially, DBS targets structures that are deep in the brain and because of this deep targeting one must have adequate localization. This is done primarily with thin cut T1 with gadolinium and T2 weighted MRIs. From there, frame-based stereotaxy (*Figure 1*) then allows mapping out of vector coordinates for the target based on MRI. After careful consideration to avoid vasculature and other eloquent structures, the neurosurgeon may continue with



Figure 1 Intra-operative photograph from deep brain stimulation (DBS) procedure. This photo demonstrates a patient's head within a stereotactic frame, with a cannula through the microdrive depicting the entry point and trajectory of stereotactic placement of the DBS electrode.

the craniotomy and electrode implantation. Microelectrode recording is performed to assess neuronal activity and optimize physiological placement. Intra-operative testing with the macroelectrode is then utilized to determine thresholds of stimulation without causing side effects. Though the main goal of DBS in movement disorders is treating motor symptoms, a number of other benefits have been appreciated. We hypothesize that these unexpected benefits would be of particular help to palliative patients.

Gastrointestinal disturbances

Dysphagia, acid reflux and constipation can significantly impede quality of life in the palliative care population. GI dysfunction certainly offers a worthwhile target to address in an attempt to ameliorate daily life activities. Our current insight into management of GI dysfunction has been provided through our experience with patients with PD who underwent STN DBS. An improvement in gastric emptying was seen in 12/15 PD patients who underwent STN DBS while no PD patients treated medically showed any improvement [Arai *et al.*, 2012]. A group of 14 subjects had improved swallowing of solids and preparation to swallow thin liquids with STN-DBS in the "ON' condition compared with "OFF" as measured with videofluoroscopy at pre-intervention, 3 and 12 months [Silbergleit *et al.*, 2012]. Patients also reported subjective improvements in swallowing on the Dysphagia Handicap Index, a 25-item questionnaire that addresses physical, emotional and functional aspects into the total score [Silbergleit *et al.*, 2012]. A number of other series and case reports support the amelioration of dysphagia with STN-DBS [Asahi *et al.*, 2012, Wolz *et al.*, 2012].

The cause of GI dysfunction in PD patients may be different than that seen in patients without PD. The hypothesis in PD is that there is deficient control of the intramural intestinal plexus and the dorsal vagal nucleus that likely leads to slowed gastric emptying and hence the associated refractory symptoms [Del Tredici *et al.*, 2002]. Whether STN DBS would aid in patients without PD remains to be assessed.

Also important to note is a potential role for STN DBS in treatment of cachexia. An incidentally observed benefit of STN DBS in one study was weight gain. Thirty patients with advanced Parkinson's disease underwent STN-DBS and were found to have an increase in weight gain of 2.7 kg (P=0.028) at the one-year follow-up assessment [Ford et al., 2004]. Another group reported an average of 5.9 kg weight increase in patients with bilateral STN-DBS at three months post-stimulation [Moghaddasi and Boshtam, 2010]. Further evaluation comparing unilateral STN-DBS with staged bilateral STN-DBS demonstrates a trend toward greater weight gain with bilateral implantation, however it did not achieve statistical significance [Lee et al., 2011]. Weight gain with STN stimulation appears to be sustained over the long term [Foubert-Samier et al., 2012]. A crosssectional study in STN-DBS PD patients from 1996-2006 revealed a mean weight gain of 7.2±8.1 kg (P<0.001) and a mean BMI gain of 2.7±3.0 kg/m² at approximately 4.7 years follow-up. The mechanism of weight gain remains unclear and may be a consequence of amelioration of GI symptoms.

Alternatively, the alteration of the interaction between the STN and hypothalamus may affect appetite and enhance food enjoyment and consumption [Arai *et al.*, 2012]. This could prove helpful in the palliative care population as cachexia plagues a fair proportion of patients. Additional etiologies for poor food intake such as nausea and vomiting must be considered for possible intervention. Further investigation into stimulation of the hypothalamus may also yield beneficial information. In a feasibility study, stimulation of the ventromedial hypothalamus using typical DBS programming parameters demonstrated increased food intake in two monkeys [Lacan *et al.*, 2008].

Further preclinical study in a rodent model examined

the impact of nucleus accumbens (Nac) stimulation on food directed behavior. Stimulation of the Nac shell, but not core, resulted in increased feeding behavior and lateral shell stimulation decreased sucrose reinforcement properties [van der Plasse *et al.*, 2012]. This study lends interest in further investigation of the medial shell of the Nac as a target inducing feeding behavior and consumption. In four patients with severe refractory anorexia nervosa, Nac DBS led to an average of 65% increase in body weight at 38 months [Wu *et al.*, 2012]. Other potential targets for treatment of anorexia/cachexia for patients, potentially including palliative patients, are the bed nucleus of the stria terminalis, subgenual cingulate cortex and the anterior limb of the internal capsule [Israël *et al.*, 2010; McLaughlin *et al.*, 2012].

Dyspnea

Another frequent complaint in the palliative population is dyspnea [Gilman and Banzett, 2009]. The American Thoracic Society defines dyspnea as "the subjective experience of breathing discomfort," that can be comprised of three distinct sensations: air hunger, tightness, and work/ effort of breathing [American Thoracic Society, 1999]. The experience of dyspnea is a wholly unique one that is subjectively described in response to the threat of one of the most primal biological drives. Dyspnea often arouses strong aversive emotions to the fear of the feeling of "suffocating."

Two main pathways modulate respiratory sensations to the cerebral cortex. The first pathway begins at the level of the respiratory muscle afferents that is then relayed to the brainstem medulla with further synapses in the ventroposterior thalamus and projecting to the primary and secondary somatosensory cortices and modulating the sensory or intensity aspects of dyspnea [Von Leupoldt and Dahme, 2005; Birbaumer and Schmidt, 2003; Price, 2000]. The second pathway mostly consists of vagal afferents arising from the lungs and airways that synapse in the brainstem medulla before projections ascend to the amygdala and medial dorsal region of the thalamus along the pathway to the insular and cingulate cortices [Von Leupoldt and Dahma, 2005]. Further study on this pathway may implicate contributions from other prefrontal regions, putamen hippocampus, and operculum in the processing of affective perception in dyspnea [Guz, 1997; Davenport et al., 1995]. Neuroimaging studies implicating specific regions of the limbic system-the right anterior insular cortex and to a lesser extent the amygdala-give credence

to this theory [Gilman and Banzett, 2009; Von Leupoldt and Dahme, 2005]. DBS and cortical stimulation of these regions may lead to a reduction in the fear and anxiety that frequently accompany dyspnea.

Hyam et al. sought to investigate whether the PAG and STN, regions recognized to influence cardiovascular autonomic function, play a role in the electric circuitry of breathing and whether stimulation of these sites effects a change in lung function. Testing consisted of ten patients with DBS of the STN and ten patients with PAG, as well as ten patients with Gpi and seven patients with sensory thalamus as controls. Random testing of patients in a blinded fashion was done three times on stimulation and three times off stimulation. Patients with stimulation of the STN and PAG had a significant increase of 14% in peak expiratory flow rate compared with no significant increase in respiratory performance in patients with control nuclei stimulation [Hyam et al., 2012]. This study is particularly interesting in that it examines multiple brain regions, thereby having an internal control. Additionally, it examines both chronic pain and PD patients and thus the findings are likely not unique to one disease state or another.

Sleep

DBS may play a role in facilitating better nighttime sleep and less daytime sleepiness. A study evaluating 43 PD patients 24 months after bilateral STN DBS showed increased total sleep time and decreased subjective sleep problems [Lyons and Pahwa, 2006]. Another case report of a PD patient after STN DBS revealed a reduction in hours of daytime sleep with fewer naps, lower Epworth Sleepiness Scale score and subjective perception of more deep sleep at night and less sleepiness during daytime activities [Lopiano *et al.*, 2001]. These results contradict each other with the lack of sufficient evidence for the role of DBS in sleep, however it warrants further investigation as a potential target to improve sleep patterns in patients at end of life.

Delirium

Patients that have an acute alteration in their cognitive abilities or perceptual differentiation that disturbs their level of consciousness are said to be in a state of delirium. Three clinical subtypes of delirium exist—hyperactive, hypoactive and mixed. Hypoactive delirium is often misdiagnosed as depression or dementia and mixed delirium contains features of alternating periods of hyperactive and hypoactive episodes [Trzepacz *et al.*, 2002]. Patients may be distractible and unable to focus on external stimuli, inattentive, irritable, anxious, restless and have difficulty sleeping. In the delirious state, orientation, executive planning, memory and language may be affected. Patients may experience hallucinations or illusions [Meagher *et al.*, 2000].

Delirium is often difficult to diagnose and treat but it can cause significant morbidity in ill patients. Diffuse abnormality at the cellular and synaptic level rather than a focal disruption may cause delirium [Gunther et al., 2008]. Delirium is a functional brain disorder with the interplay of abnormal neurochemical concentrations, perception of external stimuli, physiological stressors and disturbances of the sleep-wake cycle [Yokota et al., 2003]. Serotonin, dopamine, acetylcholine and gamma aminobutyric acid (GABA) disturbances likely play a role in the pathogenesis [Gunther et al., 2008]. The interaction between acetylcholine deficiency and dopamine excess appear to be particularly critical in the final common pathway of causing delirium [Trzepacz et al., 2002]. A study conducted with xenon-enhanced computed tomography scans revealed a 42% reduction in global cerebral blood flow (CBF) in ten patients diagnosed with hypoactive delirium. Occipital and subcortical areas had more marked reductions in CBF compared to other regions [Yokota et al., 2003]. Neuroimaging also demonstrated abnormal cerebral perfusion of the frontal or parietal regions in six patients that underwent 99mTc HMPAO single photon emission computed tomography (SPECT) scans during a delirious state compared with scanning after resolution of delirium [Fong et al., 2006].

Various cerebral hypoperfusion patterns occur in patients with hepatic encephalopathy, including reduced cerebral perfusion in the temporal, frontal, parietal, occipital lobes, anterior cingulate gyrus, basal ganglia and thalamus [Jalan et al., 2003; Yazgan et al., 2003; Strauss et al., 1999]. However, some of these studies were statistically underpowered and likely attribute to the inconsistent perfusion patterns. Based on current available research, the most popular hypothesis for the neural circuitry of delirium includes the thalamus, basal ganglia, and the prefrontal, fusiform, and posterior parietal cortices [Trzepacz, 2000; Trzepacz, 1994]. Diffusion tensor imaging (DTI) has been used to study white matter and thalamic abnormalities in patients after cardiac surgery to predict those who may be vulnerable to developing delirium post-operatively [Shioiri et al., 2010]. Pathology in the temporal lobes (right greater than left), fusiform gyri, lingual gyri, caudate nuclei and anterior cingulum may predispose patients to hyperactive delirium, most commonly manifested as hyperactive agitation [Caplan, 2010]. Postmortem anatomical analysis of nine cases with delirium and six age-matched controls without delirium demonstrated an association of astrocytes, microglia and interleukin-6 (IL-6) in the pathogenesis of delirium [Munster *et al.*, 2001]. Although delirium is not treated with DBS currently, as research continues, it is plausible that DBS may have some potential in this field, targeting the regions functional imaging support.

Depression

Another venue for DBS is in the treatment of refractory depression. Depression is a worldwide disease with the majority of patients deriving benefit from antidepressant medications, psychotherapy and electroconvulsive therapy (ECT). However, approximately 10-20% of people who suffer from depression are refractory to conventional treatment modalities. There has been substantial effort into researching targets for DBS in treatment refractory depression (TRD). Cognitive and limbic circuits are intertwined between the prefronto-basal ganglia system with particular involvement of the anterior cingulate cortex, the orbital prefrontal cortex, Nac, and the thalamus. The amygdala, serotonergic neurons and midbrain dopaminergic cells contribute to the aforementioned network to process reward-based learning and executive decision making as well as being implicated in depression, addictive behaviors and pathological risk-taking [Haber and Brucker, 2009].

Based on the current hypothesis for the pathophysiology of depression, four regions of the brain have been identified as potential targets for DBS-subgenual cingulated cortex (SCC), Nac, inferior thalamic peduncle, and lateral habenula. Studies with small sample sizes have been conducted on humans with DBS implantation in the Nac, SCC, and inferior thalamic peduncle. Although further research is necessary, results from initial studies are promising in efficacy as well as safety [Hauptman et al., 2008]. Early and progressive benefits were found in 20 patients undergoing DBS of the SCC (Figure 2) when utilizing the Hamilton Rating Scale for Depression (HSRD-17) [Lozano et al., 2008]. Thirty-five percent of patients had at least a 50% reduction in the HSRD-17 and 10% went into remission at one month, with 60% and 35% respectively at six months. Adjunctive investigation with PET scans in the same study revealed a change in the metabolic activity in the cortical and limbic circuits described in the pathogenesis of depression. Implantation and programming of the subcallosal cingulate



Figure 2 Subgenual cingulate cortex (SCC) and depression. Improved mood, sleep pattern, and anxiety are seen in depressed patients who show reduced activity in cingulate-connected limbic regions and increased activity in dorsal prefrontal regions after effective therapy with antidepressants of SCC stimulation.

gyrus was well tolerated with few significant adverse effects and no permanent issues [Lozano *et al.*, 2008]. A phase 3 study is on-going.

Bilateral stimulation of the Nac in 11 patients with TRD also proved to be beneficial for 5/11 of the patients (45%) [Bewernick et al., 2012]. At one year, five patients were classified as responders and remained responders until the last follow-up time point at four years. The authors found that the sustained responders had no worsening of their symptoms over time and that stimulation of the Nac was effective as an antidepressant and anxiolytic as well has improving measures on the QoL. Comprehensive neuropsychological testing on ten patients with TRD pre- and one year post Nac DBS revealed significant improvements on cognitive performance in addition to antidepressant and anxiolytic effects [Grubert et al., 2011]. Patients measured better on learning and memory, attention, visual perception and executive functions. Rat studies further support the anxiolytic effects of Nac stimulation. A continuous stimulation paradigm was also found to decrease tyrosine hydroxylase, dopamine and norepinephrine in the prefrontal cortex [Falowski et al., 2011].

Motoric symptoms

Lastly, a few studies have been conducted on patients who suffer motor deficits after stroke. Stimulation of the left lenticular fasciculus in a man with Benedikt syndrome after suffering a stroke resulted in significant tremor improvement [Bandt *et al.*, 2008]. Two patients with Holmes tremor as a result of upper brainstem lesions underwent VIM DBS with marked improvement in symptoms [Nikkhah *et al.*, 2004]. A man with debilitating right upper extremity pain after stroke underwent PAG DBS of the periventricular gray matter of the third ventricle in hopes of pain amelioration [Phillips and Bhakta, 2000]. The patient derived slight



Figure 3 Mapping sensory and motor cortex. Intra-operative photograph of an eight contact epidural grid being used to assess phase reversal between motor and sensory cortex to aid in proper placement of MCS. Abbreviation: MCS, motor cortex stimulation.

analgesic effect, however he noted significant improvement in motor function of his paretic upper and lower extremities. Using the rat model for three-vessel occlusion cerebral ischemia and the Montoya staircase task, it was found that contralateral stereotactic implantation of bipolar electrodes into the lateral cerebellar nucleus with low frequency stimulation resulted in improved motor recovery in rats after ischemic strokes, encouraging further research into animal stroke models for eventual further applications in motor recovery in humans after stroke [Machado *et al.*, 2009].

Motor cortex stimulation

Current use

Motor cortex stimulation (MCS) for pain syndromes has garnered attention, but remains off-label. Previously it was believed that MCS physiologically operated via stimulating primary somatosensory cortex evoked potentials (SSEPs). However, the contrary has been shown in rat models; MCS actually suppresses SSEPs [Chiou *et al.*, 2012]. The basis of MCS is now focused on fMRI based corticothalamic connections that increase thalamic blood flow and subsequent PAG opioid production [Garcia-Larrea and Peyron, 2007; Peyron *et al.*, 2007; Peyron *et al.*, 1995; Pirotte *et al.*, 2005; Saitoh *et al.*, 2004].

Preoperatively, patients undergoing MCS require a thin slice functional MRI to identify the correlated painful area of the motor strip. After using frameless neuronavigation to guide appropriate craniotomy landmarks, physiological monitoring for phase reversal confirms the location of the precentral and postcentral gyrus (*Figure 3*). Once the motor cortex is intraoperatively localized, epidural electrodes, often the same paddle electrodes used for SCS, are sutured to the dura either parallel or perpendicular to the motor cortex [Stadler *et al.*, 2011].

Dysphagia

As with other neuromodulatory techniques, MCS may have an extended role in palliative care to address other distressing symptoms in addition to pain, such as dysphagia or other GI issues. A patient with neuropathic facial pain with components of trigeminal neuralgia, glossopharyngeal neuralgia and dysphagia underwent implantation of a MCS system and found dramatic amelioration of her facial pain with significantly improved swallowing [Anderson *et al.*, 2009]. Interestingly, electrophysiologically similar noninvasive techniques support this finding.

Transcranial magnetic stimulation (TMS) over the esophageal cortex for ten minutes five days a week improved post-stroke dysphagia symptoms in 14 patients when compared with 12 sham TMS patients and these results persisted through two months [Khedr *et al.*, 2009]. Further study of TMS on post-stroke dysphagia, specifically lateral medullary infarction and other brainstem infarctions, revealed improved symptoms in patients with TMS compared with sham TMS with the results being maintained to two months from stimulation [Khedr and Abo-Elfetoh, 2010].

Transcranial direct current stimulation (tDCS) has been investigated to treat post-stroke dysphagia. tDCS uses an electrode pad over the area of interest and a reference pad in the neck or shoulder region to pass constant low electrical current. Anodal stimulation depolarizes and excites the cortex while cathodal stimulation hyperpolarizes and inhibits it. Sixteen patients were randomly assigned to swallowing training plus anodal tDCS or swallowing training plus sham stimulation and after the intervention both groups had improved functional dysphagia scale scores [Yang et al., 2012]. At three months post-intervention, the anodal tDCS group had greater improvement in the functional dysphagia scale score compared with the sham stimulation group [Yang et al., 2012]. While TMS uses a rapidly changing magnetic field to induce changes in electrical current, tDCS uses direct physical electrical current as the name implies. TMS does not require physical contact of the device to the scalp as tDCS does. Appropriate preparation and placement of the electrode pads can significantly affect the results of tDCS. tDCS is less topographically specific than TMS [Edwardson

et al., 2013].

Michou and colleagues studied paired associative stimulation (PAS) by combining peripheral pharyngeal stimulation with cortical stimulation, first in healthy individuals with virtual lesioning and then in patients with post-stroke dysphagia. They found that PAS induced behavioral responses and short-term bilateral changes in the brain that warrants further investigation as a rehabilitative modality for post-stroke dysphagia [Michou *et al.*, 2012].

Motor recovery

Repetitive TMS (rTMS) also appears to have benefited when applied to the affected hemisphere in stroke patients and may provide an effective and safe technique to rehabilitate cerebral function and motor recovery. The cortical activity of the affected hemisphere is disrupted due to the actual infarct, although, overall cortical function may also be affected by unopposed inhibition of the unaffected, contralateral hemisphere through an imbalance of transcallosal inhibitory pathways between both hemispheric cortices [Corti et al., 2012]. In a retrospective analysis of 60 patients, those with less cortical injury and preservation of the corticospinal tract derived greater motor recovery with cortical stimulation [Nouri and Cramer, 2011]. Research shows that the human brain exhibits neuroplasticity and animal studies support that stimulation can enhance those properties.

This finding as well as anecdotal evidence in patients undergoing MCS for pain with recovery of function led to a randomized, controlled study six patients underwent MCS in addition to physical rehabilitation for three weeks. When compared to the four control patients receiving physical rehabilitation alone, the stimulation group had significantly better motor recovery of the upper extremity according to the Upper Extremity Fugl-Meyer (P=0.003) and hand function score of the Stroke Impact Scale (P=0.001) [Brown *et al.*, 2008]. tDCS of the affected hemisphere and cathodal tDCS of the contralateral unaffected hemisphere both produced improvement in hand function in ischemic stroke patients when compared with control sham stimulation [Fregni *et al.*, 2005].

Recovery of function after stroke can be facilitated by enhanced activation of the affected hemisphere and suppression of activity of the contralateral hemisphere, thereby reducing the transcallosal inhibition between the two motor cortices [Fregni *et al.*, 2005]. There is also some suggestion that patients with chronic stroke, fixed focal



Figure 4 Fluoroscopic intra-operative image from a spinal cord stimulation procedure. This image shows SCS electrodes placed at T8-9 for bilateral coverage of back and lower extremities.

deficits for at least six months, may benefit from cortical stimulation. One of the two cases reported had left middle cerebral artery infarction with associated motor and language deficits for 18 months. The second case report had a subcortical infarct of the internal capsule and motor weakness for eight months prior to study investigation. Both patients had epidural implantation of unipolar electrodes over the contralateral premotor and motor cortex and an additional electrode over Broca's area in the patient with language disturbance. After cortical stimulation and physical rehabilitation for four months, both patients revealed improvement of motor function. The patient with speech impairment did derive benefit in language function as well [Kim *et al.*, 2008].

In summary, current studies support MCS potential for refractory pain and stroke rehabilitation. Data from TMS and tDCS may aid in selection of new disease processes and locations amendable to MCS. Evaluation of optimal stimulation parameters and development of MCS specific technology may demonstrate greater clinical significance across the population. For example, the same paddle leads are used for MCS and SCS although affecting different anatomy [Levy *et al.*, 2010]. Combining peripheral and central nervous system stimulation poses an interesting question. Dual stimulation to address one indication could possibly lead to potentiation of effects and ultimately a better response than either modality alone.

Spinal cord stimulation

Spinal cord stimulation is the most commonly used and most familiar type of neuromodulation across pain practices. SCS procedures either involve placement of a percutaneous or paddle electrode. Generally, a trial of SCS is performed using a percutaneous lead inserted to the level corresponding to the patient's painful region. The device is turned on and the patient is asked if they have paresthesias in the appropriate spot. The location is fine-tuned based on patient response. In cases where pain is adequately relieved, patients then go onto permanent implantation with a paddle lead in our practice (*Figure 4*). We use electrophysiological intraoperative monitoring to further refine placement.

Motor recovery

SCS is currently also being investigated for control of PD symptoms. A case report describes a 61-year-old male who had been successfully treated with a SCS implanted at the T9-10 level for treatment of symptoms associated with FBSS. He then developed tremor predominant PD at the age of 69 with symptoms affecting the right side. The impact of SCS on his ability to move was evaluated with the Unified Parkinson's Disease Rating Scale (UPDRS-III) motor score. This score was assessed while the patient was off medications in both the OFF- and ON-stimulation and with him on medication both OFF and ON stimulation. His score improved 50% with SCS ON in the absence of PD medication, with results similar to medications alone. Furthermore, with SCS ON and medication ON, a further improvement was seen. This report suggests that downstream neuromodulation in PD may be of benefit and that movement may be improved with SCS, which may have effect in certain palliative patients. Of note, however, another SCS report showed no effect [Thevathasan et al., 2010] despite suggestion by rodent PD model studies [Fuentes et al., 2009].

Regulation of vasculature

Change in cerebral hemodynamics was a noted effect during SCS chronic pain [Hosobuchi, 1985]. Cervical SCS in ten patients incidentally demonstrated increase in CBF as measured by SPECT in the ipsilateral hemisphere to the induced paresthesia. In subsequent years, Meglio *et al.* studied 36 patients to reproduce previously reported effects of CBF changes with SCS as well as to test reliability between SPECT and transcranial Doppler (TCD) [Meglio *et al.*, 1991]. They also evaluated changes in cerebral hemodynamics as a function of the level of SCS. Cervical SCS was correlated with increase in CBF while thoracic SCS showed a possible reduction in CBF. Another study revealed that SCS could increase, decrease or have no effect on cerebral hemodynamics [Visocchi, 2006].

In a novel SAH animal model, double hemorrhage was induced in 56 rats that had SCS applied at the C-1 level [Lee et al., 2008]. SCS after SAH revealed a CBF increase in the cerebellum from 62-76% to 91-115% and in the cortex from 69-70% to 115-118% when compared with controls (P<0.01). The effects in increased CBF resulted from increase in diameter and cross-sectional area of the basilar artery [Lee et al., 2008]. One study of SCS implantation in humans for cerebral vasospasm [Takanashi and Shinonaga, 2000] vielded inconclusive results due to its small sample size and significant neurological morbidity of the ten patients (Hunt Hess 3-4). The Hunt Hess scale is a tool to measure clinical symptomatic presentation of patients suffering from non-traumatic subarachnoid hemorrhage. These patients had SCS at C1-2 and were stimulated continuously for 10-15 days, starting on day 5 after SAH. CBF did increase significantly in the MCA distribution as measured by xenon CT and diagnostic angiography when compared by pre and post-stimulation.

The mechanism of action of change in cerebral hemodynamics as a result of SCS remains undetermined. Some support the role of the autonomic nervous system and others have postulated the role of humoral factors that the cerebral vasculature releases or others support autoregulation [Visocchi *et al.*, 2011]. Despite lack of information on precisely how SCS affects cerebral vasculature, various investigators are examining the role of SCS on traumatic ischemic brain injury, ischemic stroke and SAH and arterial vasospasm. High cervical SCS could pose as a 'functional' revascularization modality [Visocchi *et al.*, 2011].

Peripheral nerve stimulation

Though currently PNS is employed for the treatment of pain and treatment of bladder dysfunction, recent work suggests that many more symptoms may respond. Transcutaneous electrical stimulation (TENS) may provide a means of assessing which symptoms may respond to implantable PNS. It has been used to some avail in both dysphagia and dyspnea and may be able to provide some relief to palliative patients suffering with those complaints.

Dysphagia

Eleven patients suffering from oropharyngeal dysphagia after stroke underwent one hour of submental TENS for five days with swallowing evaluations completed before and after the week of treatment. The dysphagia handicap index questionnaire revealed an improvement in oropharyngeal dysphagia symptoms and videofluoroscopy demonstrated reductions in laryngeal aspiration and pharyngeal residue with improved swallowing reaction time [Gallas *et al.*, 2010].

Dyspnea

TENS has also been investigated for use in alleviating the symptoms of dyspnea. As with pain, dyspnea can cause significant distress to individuals and is highly influenced by surrounding circumstances. Negative affect is associated with increased subjective reports of pain and dyspnea [Bogaerts *et al.*, 2005]. An individual's pain threshold can be correlated to their dyspnea threshold, however there is a lack of correlation between pain tolerance and dyspnea tolerance [Nishino *et al.*, 2010]. Cortical processings of both pain and dyspnea have similar pathways, particularly the anterior cingulate and insular cortices [Apkarian *et al.*, 2005].

A double-blind, randomized controlled trial of 44 subjects with chronic obstructive pulmonary disease (COPD) with TENS versus placebo-TENS on Dingchuan (EX-B1) acupuncture point for 45 minutes revealed improved forced expiratory volume in one second (FEV1) and was as well as increases in levels of beta-endorphin after TENS [Jones *et al.*, 2011]. Dingchuan acupuncture point is below the spinous process of C7 and 0.5 cm lateral to posterior midline.

In patients with COPD, transcutaneous neuromuscular electrical stimulation (NMES) treatment can produce clinically significant improvements in dyspnea scores [Sillen *et al.*, 2009]. In NMES, electrodes are placed strategically over the desired muscle groups and electrical current is applied. NMES stimulates muscle contractions for strength and conditioning while TENS delivers electrical current to block or modulate pain signaling. Both low-

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frequency (15 Hz) and high-frequency (75 Hz) NMES may offer rehabilitative methods on patients with COPD with comparable effects on dyspnea, fatigue and lowerlimb function [Sillen *et al.*, 2011]. The adjunct of NMES in addition to the usual rehabilitation protocol for underweight patients with COPD has resulted in greater improvements in lower limb function, extent of dyspnea and daily tasks than in standard rehabilitation alone.

Previously the comment about PNS and MCS/SCS working synergistically was raised, however the implication of using NMES in conjunction with PNS or MCS/ SCS could be more promising. Although all are forms of electrical stimulation, NMES enhances physical muscular contractions directly while interaction of electrical currents with SCS/MCS affects changes indirectly. Direct stimulation of muscular contraction at the peripheral level on an already stimulation enhanced central level (indirectly with MCS/SCS) could likely facilitate potentiation of effects. Indirect MCS/SCS with direct NMES with manual physical rehabilitation could achieve optimal outcomes. In addition to motor effects of MCS/SCS, its effects on pain could also allow greater propensity of rehabilitation if pain is improved and allows tolerance of therapy.

Depression

The utility of TENS as a treatment for TRD was performed in a pilot study. Thirty-seven patients with TRD were randomized into stimulation (five times per week for two weeks) and sham groups [Hein et al., 2013]. Head sets with electrodes were placed in outer ears for transauricular TENS to affect the fibers of the ramus auricularis nervi vagi. Patients in the stimulation group had statistically significant improvement over the sham group. Another form of PNS, i.e., vagal nerve stimulation (VNS), was tested more extensively in TRD. Three hundred thirtyone patients were randomized into a double-blind study across multiple centers and over 50 weeks (long-term phase) with evaluation at 22 weeks (acute phase) [Aaronson et al., 2012]. Patients were randomized into a LOW, MEDIUM or HIGH stimulation arms. All arms of the study revealed statistically significant improvement of depression by the end of the acute phase, and sustainment of amelioration through the long-term phase. Patients in the MEDIUM and HIGH arms showed greater durability of VNS response and were less likely to relapse than those in the LOW stimulation arm. Unfortunately however, there is great difficulty despite this data with insurance companies covering the device for this FDA-approved indication.

VNS has also been shown to improve function by reducing the frequency and quantity of seizures in a subset of patients. The traditional VNS delivers continuous stimuli regardless of brain activity—whether normal or not. At this time clinical trials for closed loop systems, such as RNS (Responsive neurostimulation, NeuroPace, Inc., Mountainview, California), are evaluating the safety and efficacy of these new stimulators that can detect abnormalities in brain electrical activity and deliver small impulses to suppress developing seizures at appropriate times, i.e., closed loop technology.

Limitations

Given the current applications of neuromodulation, some may already consider it as another modality of treatment for palliation of symptoms that detract from daily quality of life. The cost of a neuromodulatory device and its accessories poses a hurdle in the palliative care population since time of survival greatly impacts cost-effectiveness. All neuromodulatory devices have expensive up front costs that may range from \$15,000-35,000 depending on the device. The internal pulse generator (IPG) or battery that generates the electrical stimulation comprises most of that cost. Technology needs to develop low-cost but effective device systems in order to play a substantial role in palliative care. Reuse of external components and using antenna-receiver/ external battery stimulators could significantly reduce costs [Blomstedt and Hariz, 2010]. A recent study examined re-implantation of donated pacemakers after proper sterilization and found a lack of significant complications at almost two years follow up [Kantharia et al., 2012]. Another obstacle is the lack of MRI compatibility of the devices. Patients with DBS can have MRI of the brain with specific settings and body MRI is contraindicated [Henderson et al., 2005]. MRI with SCS and PNS, with the exception of one device, remain contraindicated.

Summary

Though some limitations need to be overcome, the potential for neuromodulation in the palliative populations seems unlimited. Many of the advances in functional neurosurgery have come from unintended benefits while treating other conditions and we suspect that use of neuromodulation to treat pain in the palliative care population will result in similar findings of relief for other symptoms. It is an exciting time to be involved in neuromodulation as we look to improving quality at end of life.

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