BMJ Group

Putting evidence into practice: Palliative care

Klara Brunnhuber

Stephen Nash

Diane E. Meier

David E. Weissman

James Woodcock

Spring 2008

Funding

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Authors

Klara Brunnhuber, MD Clinical Editor, BMJ Publishing Group Limited

Stephen A. Nash, MD MPH Freelance Medical Writer, BMJ Publishing Group Limited

Diane E. Meier, MD (Appendix A: Toolkits) Director, Center to Advance Palliative Care; Director, Hertzberg Palliative Care Institute; Professor, Departments of Geriatrics and Medicine; Gaisman Professor of Medical Ethics, Department of Geriatrics, Mount Sinai School of Medicine, New York, NY

David Weissman, MD FACP Professor of Internal Medicine and Director of Palliative Care, Medical College of Wisconsin/Froedtert Hospital, Milwaukee, WI

James Woodcock, MSc Product Development Editor, BMJ Publishing Group Limited

Acknowledgments

Advisory board and peer review

Debra Barton, RN, PhD, AOCN Associate Professor, Oncology, Mayo Clinic, Symptom Management Research, Rochester, MN

Shirley H. Bush, MBBS, MRCGP, FAChPM Visiting Scientist, Department of Palliative Care and Rehabilitation Medicine, The University of Texas M. D. Anderson Cancer Center, Houston, TX; Senior Staff Specialist in Palliative Care, McCulloch House, Palliative Care Unit, Monash Medical Centre and Honorary Lecturer, Faculty of Medicine, Nursing and Health Sciences, Monash University, Clayton, Victoria, Australia

Ronald J. Crossno, MD FAAFP FAAHPM VistaCare Regional Medical Director, Temple, TX

Diane E. Meier, MD Director, Center to Advance Palliative Care; Director, Hertzberg Palliative Care Institute; Professor, Departments of Geriatrics and Medicine; Gaisman Professor of Medical Ethics, Department of Geriatrics, Mount Sinai School of Medicine, New York, NY

David Weissman, MD FACP Professor of Internal Medicine and Director of Palliative Care, Medical College of Wisconsin/Froedtert Hospital, Milwaukee, WI

Additional advisors

Eduardo Bruera, MD Director, Department of Symptom Control and Palliative Care, M. D. Anderson Cancer Center, University of Texas, Houston, TX

Nancy P. Lee, PharmD CDE Clinical Pharmacist, Drug Information Center, Department of Pharmaceutical Services, University of California, UCLA Medical Center, Los Angeles, CA

Joan Teno, MD MS Professor, Community Health and Medicine; Associate Director, Center for Gerontology and Health Care Research, Brown University, Providence, RI

Competing interests

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PART 1. BACKGROUND

Introduction

Diane E. Meier, MD
diane.meier@mssm.edu

Striking gains in life expectancy—for example from an average of 50 years in 1900 to 78 years in the United States today—have transformed human experience across the globe. Health care needs have followed suit. At the turn of the last century, most deaths followed an acute infectious illness afflicting young and old alike; today most deaths occur in older adults, following years of chronic illness. This trend toward chronic illness has been universally observed, but despite the prevalence and impact of this trend, the health care systems of the world have not kept pace. In the United States, for example, the health care system is structured around easy access to acute hospital care and does not support the community-based coordinated care required by the chronically ill. A growing body of evidence demonstrates high levels of suffering, dissatisfaction with, and overuse of health care resulting from the mismatch of patient and family needs with the health care system as it is currently structured. As a response to this trend, the new specialty of palliative medicine has grown rapidly in the last 10 years, winning American Board of Medical Specialties subspecialty status in 2006.

Palliative medicine is medical care focused on relief of physical, emotional, and existential suffering, and support for best possible quality of life for patients and their family caregivers. It is delivered at the same time as all other appropriate (i.e., likely to benefit the patient) medical care and should be offered simultaneously with curative, life-prolonging, or disease-modifying treatments. In practice, palliative care involves assessment and relief of troubling symptoms as well as skilled communication with patients and families about the goals of care and the treatment plan that will achieve these goals and attention to safe and well-coordinated care across the multiple settings that patients traverse during serious illness. Palliative approaches to care are a core responsibility of clinicians from all specialties, with expert consultation sought for intractable or especially complex problems.

This review from the BMJ Group synthesizes the evidence supporting key elements of palliative care: the control of common symptoms such as pain, dyspnea, and fatigue; communication and goal setting; and effective, efficient transition management. Following the synthesis of the best evidence are 4 Toolkits containing tools and technical assistance to support the busy clinician seeking rapid access to best clinical practices. We hope that these resources will help physicians as they seek to "Cure sometimes, relieve often, comfort always" (14th-century French proverb).

Demographics and disease burden

During the past century, progress in clinical medicine, public health and living standards has resulted in enhanced quality of life and a longer life expectancy for many.[1]

In 2007, average life expectancy in the U.S. was estimated to be 75 years for men and 81 years for women.[2] Currently, around 12% of the U.S. population is older than 65 years of age, with the aging of the baby boomer generation expected to increase this percentage to 20% by 2030.[1,3] Cause of death is now much less likely to reflect acute illness such as infectious diseases or trauma, and more likely to be due to the impact of chronic disease. As individuals age, their risk for disability rises; after the age of 85 years, 95% of individuals have reduced mobility and 50% suffer from memory loss secondary to dementia. Ninety percent of senior Medicare enrollees live with at least one of these illnesses in the year prior to death. As a consequence many people experience "end of life" not as a brief illness but as a prolonged period of months or years, during which they are treated for and have to cope with deterioration of their physical and mental functions.

Between 2004 and 2006, U.S. hospital costs rose by nearly 20%, primarily because of the larger numbers of patients seeking care in hospitals, and the increase in availability of costly life-sustaining interventions.[1] Hospitals now receive 75 cents of every Medicare dollar.[4] The medical costs incurred during the last years of life are high; over 50% of lifetime medical expenses occur after the age of 65, and 33% after 85 years of age. In the last year of life, an individual incurs about 30% of his or her lifetime Medicare expenditures. However, spending on palliative and hospice interventions accounts for a small percentage of this. Moreover, palliative medicine has been relatively neglected in the U.S. undergraduate curriculum, although this appears to be changing. A systematic review (search date 2006) found a considerable increase in the provision of palliative care training in U.S. medical schools between 1999 and 2006, and by 2005 there were 52 fellowships in hospice and palliative medicine.[5]

The care of patients with advanced illness is hindered by undertreatment of physical and emotional symptoms, psychological and physical debilitation of caregivers, conflicts over decision making, and diminution of family financial resources.[3] Patients often receive care that lacks continuity, with multiple care settings, multiple providers, confusing payment systems, and lack of critical services such as home and caregiver support.

Definitions

Palliative care has its roots in the hospice movement, which began in the 1960s in the U.K. and in the 1970s in the U.S.[4] It aims to relieve the suffering and improve the quality of life for patients and their families with advanced disease. In 1983, U.S. federal legislation created the Medicare Hospice Benefit, which has since provided palliative care services to more than 7 million terminally ill patients, usually within their homes. However, palliative care services can assist many patients with advanced chronic diseases who are not eligible for hospice benefits. In too many cases, comfort care measures are only introduced when death is imminent. This situation is exacerbated by the current structure of the U.S. health care reimbursement system with its two-tiered funding for curative

therapies (regular Medicare funds) and comfort care (Medicare Hospice Benefit).[3] Under current regulatory and compensatory Medicare Part A rules, patients are eligible for hospice if their physician states that death is likely within 6 months, and the patient is willing to shift the focus of care to "palliative care", which for reasons related to the funding stream to hospice agencies, means the patient must forego attempts at curative or life-prolonging treatments. The goal of this program is to enable families to care for their loved one at their home, with a focus on control of distressing physical and psychological symptoms and spiritual concerns.[4]

A systematic review (search date 2004) found that hospice utilization is on the rise in the U.S.; about 20% of patients now receive hospice care.[6] However, patients were being referred for hospice care at later phases in their diseases. The median length of time in hospice dropped from 29 days in 1995 to its lowest level (20.5 days) in 2001, and was at 23 days in 2003. In 37% of cases, death occurred within a week of the patient's enrollment. The review recommended hospice enrollment to lower hospitalization mortality rates, curtail the transfer to the hospital of dying nursing facility patients, and ameliorate suffering.

The WHO's definition of palliative care includes relief of suffering, enhanced quality of life, and support for patients and families. It enumerates the following goals and principles:[7]

● To regard death as part of life and a normal process

● Neither to hasten nor to delay death

● To use a team approach to address the needs of patients and their families, including bereavement

● To initiate palliative care early in a patient's illness, even when he or she is still receiving life-prolonging treatments such as chemotherapy or radiation therapy.

Hospitals are increasingly investing in palliative care services to improve patient care, enhance patient satisfaction, and reduce ICU and total bed days and costs.[4] In 2003, over 25% of U.S. hospitals had a palliative care program.[8] Overall, these programs have been found to be effective in facilitating patient transitions from acute, high-cost hospitals to more suitable settings, such as the home.[4]

Illness trajectories

Three disease trajectories can be used for categorizing most patients with advanced chronic illness, including:[9]

● Progressive disability and eventual death over a period of weeks or a few months, most often seen in patients with the most common solid malignances: accounting for about 20% of deaths over the age of 65 years

- Slow decline with acute exacerbations and often a sudden death, most often due to chronic organ failure (e.g., lung, kidney or heart failure): about 25% of deaths over the age of 65 years

- Long period of slow decline with worsening self-care ability; death often from an unpredictable intercurrent illness; the underlying condition is typically a chronic neurodegenerative disease such as dementia: about 40% of deaths over the age of 65 years[1,10]

Prognostic accuracy

Physicians' survival predictions are often inaccurate; in particular, they tend to be overoptimistic. A meta-analysis (search date 2000) of 8 studies in terminally ill cancer patients showed that median clinical prediction of survival (CPS) was 42 days, whereas median actual survival (AS) was 29 days.[11] Only 61% of expected survival estimates were accurate to within 4 weeks. Another review (search date 2006) identified a survey study in 258 physicians managing 300 cancer patients admitted to outpatient hospice programs and reported lengths of median "physician-communicated" survival prediction of 90 days, median "privately formulated" survival prediction of 75 days and median "actual" patient survival of 26 days.[12] Despite this, CPS and AS were strongly correlated (*P* less than 0.001) and studies have shown CPS to be a better prognostic factor than conventional tools such as performance status and symptoms and that it increases in accuracy in patients who are closer to death. A number of reasons may be responsible for clinician's over-optimism. Predicting the expected range of time in which death is likely to occur is a difficult skill to master.[13] A long-standing patient-doctor relationship may also influence their ability to prognosticate. The study noted that those who had not known the patient for long prior to the assessment scored better. Besides, physicians may want to preserve patients' hope.[14] Whereas oncologists seem to be in favor of providing prognostic information to patients with early stage disease, they find it more difficult to communicate prognosis and are less willing to give specific estimates of survival to patients with advanced cancer even if requested.[15]

Prognosis discussions with patients need to convey that uncertainty about the course of illness in individuals is to be expected. Although clinicians need to allow that patients are more likely to assume they are among those with the best prognosis.[16]

A review concluded that there was still further need for the systematic development of prognostic scales.[16] Studies including more than 1000 advanced cancer patients found the Palliative Prognostic Score (PaP) to be the best validated, simple, quick and commonly used indicator.[17] Its variables include dyspnea, anorexia, Karnofsky performance status, clinician prediction of survival (in weeks), total WBC count and lymphocyte percentage. It has been used to categorize patients with advanced cancer into 3 distinct prognostic groups (30-day survival probability: less than 30%, more than 70% or in between) and to offer quantitative guidance on the appropriateness of immediate referral into palliative care programs for this population.[16]

Figure 1. Typical illness trajectories for people with progressive chronic illness.[BMJ]

Short period of evident decline

Function — High / Low

Mostly cancer

Specialist palliative care input available

Death

Onset of incurable cancer

Often a few years, but decline usually over a few months

Time →

Long term limitations with intermittent serious episodes

Function — High / Low

Mostly heart and lung failure

Death

Sometimes emergency hospital admissions

2-5 years, but death usually seems "sudden"

Time →

Prolonged dwindling

Function — High / Low

Mostly frailty and dementia

Death

Onset could be deficits in functional capacity, speech, cognition

Quite variable – up to 6-8 years

Time →

Other validated palliative prognostic scales in advanced cancer included were the palliative prognostic index (PPI), Chuang prognostic scale, terminal cancer prognostic score (TCP), and Bruera's poor prognostic indicator. All scales were found to have limitations, but were significant improvements on any unadjusted clinician estimates.

Prognostication in nonmalignant disease can be even more difficult. A systematic review of 11 primarily prospective cohort and longitudinal studies suggested the lack of reliable prognostic models for this patient group contributed to the unfilled need for palliative care services for older patients with nonmalignant, life-threatening diseases.[18] The review identified generic predictors of survival for this population: increased dependency in activities of daily living, comorbidities, nutritional status and weight loss, and abnormal vital signs and laboratory tests. Although disease-specific predictors of survival are available further research is needed.

What patients know and what they want to know on prognosis

Both patients and caregivers require more information than is offered and there is a large discrepancy between patients/caregivers and health providers on the amount of information they believed had been given.[19] Most patients want accurate and detailed prognostic information, although a minority does not. In the SUPPORT study[20] around 1 in 5 would rather not discuss end-of-life options.[21] Therefore the clinician needs to plan how to elicit these patients' general preferences and designate an appropriate proxy. Even clinicians who believe they should disclose terminal diagnosis often fail to initiate discussion. Most patients prefer their physician to raise the subject.[22,15] Two studies identified by a systematic review found that many patients preferred their physician to ask them first if they wished to know their prognosis and in what detail.

Studies have identified cultural differences in expectation around provision of prognostic information.[16] Whereas most white and African American patients expect to be provided with full information to make informed decisions, in some other cultures (e.g., Asian, Navajo, African, Central and South American and Eastern European cultures), nondisclosure of bad news or use of nonverbal means is expected. However, preferences vary and assumptions based on ethnic background can be misleading, so prior discussions on appropriate levels of information are always indicated.

Patients' care needs and preferences during advanced illness

Patients' values and preferences should guide life-sustaining care but observational studies report lack of knowledge of individual patients' preferences by physicians/caregivers.[23] Early consideration of preferences increases the likelihood that care will be consistent with these later on.

Physicians can help patients with life-threatening diseases to identify their needs and preferences for care, and examine areas of doubt or conflict around these preferences. One review identified the following 3 domains of patient perspective that influence preferences for care: feelings about their disease, level of suffering, and circumstances of death.[24] In discussing these issues, physicians need to take into account that patients vary in their interest in curing, modifying or monitoring their underlying disease. Patients' perceived level of suffering is dependent upon the quality of symptom control, available emotional support and overall quality of life. Preferences regarding the circumstances of death may include decisions on when to limit or withdraw interventions, where to die and the desire to hasten death. By assessing these domains, the care team can guide and assist with the development of a patient-centered plan of care.

Another systematic review identified 11 qualitative studies exploring spirituality from the perspective of patients. It found spiritual concerns to be centered on three main themes: a sense of spiritual/existential despair, with associated feelings of alienation, loss of self, and uselessness; spiritual work such as forgiveness, self-exploration, reconciliation, and acceptance; and the sense of spiritual well-being, demonstrated by feelings and thoughts of wholeness, connection, and satisfaction.[25]

The U.S. Patient Self Determination Act of 1991 confirmed that patients have the right to refuse life-sustaining treatments. The law also requires health care facilities/agencies to discuss and provide assistance in the completion of advance care planning documents.[26] State-specific documents and detailed guidance are available at http://www.caringinfo.org. When patients are unable to make their own medical decisions ('incapacity'), depending on the state, either a patient-appointed surrogate decision maker, or next-of-kin surrogates are authorized to make decisions. Both types of surrogates predict patients' treatment preferences in about 68% of cases.[27] Most patients expect their family to play a role in making decisions and a review found moderate evidence from 3 RCTs that interventions aimed at surrogates or patients improved understanding of wishes.[8] Another review identified found 3 further RCTs, which provided low-quality evidence that a facilitated discussion with terminally ill patients and their surrogates may result in patients being less likely to undergo life-sustaining treatment.[28]

One systematic review (search date 2003) of mainly small, nonrandomized and uncontrolled studies found that African American people were more likely to request life-sustaining therapies at the end of life than white people, and less likely to seek physician-assisted suicide or adopt advance care planning.[29] Strong spiritual beliefs and regular attendance at prayer activities in other ethnic groups were also associated with these care preferences.

Site of death
Recent surveys have shown that most cancer patients in the U.S. express a preference to die at home.[30,31] Despite this, about 75% of Americans with

chronic illnesses die in a hospital or nursing home setting, although there are large regional differences.[32] Between 1989 and 2001 the overall rate of home deaths increased (from 16% to 23%), hospital deaths decreased (from 62% to nearly 50%) and the likelihood of dying in nursing homes rose from 19% to 23%.[33] A systematic review (search date 2003, 66 observational studies) identified a multitude of factors influencing the location of death for people with chronic diseases.[32] These included clinical considerations, individual and community-based sociodemographic characteristics, the availability of health care resources, and local reimbursement policies. It found that being white, native-born, married, of higher socioeconomic status, and living farther away from a university health center is associated with home death, whereas being black, Latino or other nonwhite increased likelihood of hospital death.

A systematic review (search date 2004) including 58 studies and totaling over 1.5 million patients from 13 countries, primarily the U.S., U.K., Australia and Canada, evaluated the influence of different factors on location of death for cancer patients.[34] It identified 6 factors associated with home death location: low functional status, a stated desire for home death, a shared living arrangement with family, the support of an extended family, home care and its frequency. Another systematic review (search date 2003) reported that cancer patients more frequently died at home compared with other causes of death.[32] Measures of hospital use intensity (number of hospital beds, average hospital length of stay, hospital days per capita) were positively associated with increased hospital death, and age, gender, and caregiver ability and availability were also likely to play a part. The U.S.-based SUPPORT study showed hospital bed capacity to be the strongest predictor of hospital death: the larger the number of available hospital beds in a community, the more likely the patient was to die in hospital.[35] This study found little or no impact on location of death from patient and family preferences, physician preference, and advance care planning.

Desire to die requests
One systematic review (search date 2005) in people with terminal cancer found that many desire-to-die requests were expressions of psychological distress.[36] Among those specifically seeking information or assistance with hastened death, the main reasons were fear around being a burden, loss of dignity and independence, and unrelieved pain. The review recommended psychosocial interventions, psychiatric care for patients wishing to die, and better training for clinicians. Unfortunately obtaining psychiatric care for patients with highly advanced disease can be extremely difficult.

Patient–caregiver relationship
Primary lay caregivers, often the patient's spouse, frequently play a major role in the home care of patients with cancer, dementia, strokes and AIDS, particularly in advanced stages.[37] A systematic review (search date 2004) reported that surveys indicate that 20% of caregivers provide full-time or

24-hour care, 20% quit their regular positions or sustain other major life transitions, and 31% lose significant portions of or even all their savings.[6]

Social pressure can mean that those who feel unable to care effectively may be reluctant to indicate this. Lack of skills, limited functional capacity, additional family or employment responsibilities, and the symptom burden may all restrict the ability to provide care. The quality of the patient-caregiver relationship is a major predictor of willingness to care. Having had the opportunity to adjust gradually to the caregiving role increases the likelihood of caregivers to continue providing care in the event of a crisis, although caregiving refusal can occur at any point.[37]

The perception of not having a choice and reports of being stressed are associated with impaired health outcomes among caregivers. Prospective cohort studies have demonstrated adverse effects on the emotional health of the caregiver including depression and anxiety.[38] Cohort studies have also identified increases in physical stress and even mortality among caregivers.[39] Psychosocial care is important for the patient and family. This goes beyond the psychological symptoms of the patient to helping the entire family to cope. Increasing numbers of interventions designed to improve the well-being of caregivers are being developed but most have not been adequately studied.[40] Most caregiver interventions are focused on decreasing the work load or improving coping skills without addressing the added stress of watching a loved one suffer.[41] Additional research is needed but many experts recommend screening caregivers for stress, with a focus on those who feel trapped.

Higher caregiver stress levels are associated with an increase in the patient's symptoms.[6] If people are pressured into a caring role this is associated with worse clinical outcomes in patients, more frequent institutionalization, and reduced quality of care.[37] A further review found that elderly patients nearing the end of life are at heightened risk for abuse, resulting from caregiver stress, patients' dependency, and weak social support networks.[42] Abuse can be physical, emotional, sexual or financial. Neglect was identified as the most common type of elder victimization at the end of life. The overwhelming majority of abuse occurs in the home and is committed most commonly by the patient's spouse (58%) or child (47%), irrespective of socioeconomic status and ethnic background. Ready availability of professional care services such as multidisciplinary palliative or hospice care teams can be used to assess the potential for, and hopefully prevent, abuse, although high-quality evidence is lacking.

For many patients nearing the end of life, their self-perceived burden to others is a major concern. A review (search date 2005) suggested self-perceived burden was associated with anxieties over dependency, hopelessness, guilt, loss of dignity and control, and of having a "bad death".[43] In some cases, it might motivate the patient to decline life-sustaining treatments, even spark a desire for a hastened death.

Barriers to delivering effective palliative care

Despite an increased understanding of the factors necessary for optimal palliative care, there are numerous obstacles. We provide an overview of these building on a conceptual framework in a systematic review (search date 2002) of end-of-life cancer care.[44]

1. Societal attitudes

● *Mass media portrayal of the end-of-life period:* Focus on physician-assisted suicide and stories of individual cancer patients may instill fear of a painful death, reduce expectations for quality of life, and prevent pursuit of adequate quality of life in the course of illness. Media focus on relatively unusual cases provides a skewed picture of typical end-of-life scenarios.

● *Technological advances and increases in hospitalization:* These factors may lead patients and their families to assume that intensive medical intervention is appropriate in all situations.

2. Health care system

● *Rapid changes in the health care delivery system:* Increased medical spending and resulting cost containment efforts have led to competition between health plans to attract healthy patients, and reduced insurance benefits and innovation in chronic disease and palliative care. The reimbursement climate has also put physicians under increased time pressures to increase patient encounters resulting in less time for patients' psychosocial and spiritual issues.[45]

● *Limited availability of palliative care services:* Hospice care is available for patients with a prognosis of 6 months or less who are willing to give up insurance coverage for curative or life-prolonging treatments. Patients whose prognosis is indeterminate or those who wish to pursue life-prolonging therapies are ineligible for hospice services. Nonhospice palliative care is available at an increasing number of U.S. hospitals, but remains difficult to access in nursing homes and community settings.

● *Medicare organization:* Over 80% of hospice care in the U.S. is provided through Medicare. Medicare regulations inhibit use of the skilled nursing benefit combined hospice care.

● *Fragmented coverage by insurers at the end of life:* Content and coverage of coverage varies widely between insurers and figuring out eligibility for an individual patient can be complicated and time-consuming for health care providers. Outside managed care, services not covered by insurers (including most prescription medications such as oral analgesics), co-pays and deductibles may all lead to financial barriers.

● *Increased reliance on informal caregiving:* Due to fragmented care and shorter lengths of hospital stay, family members and friends may need to provide complex care without formal training, which can lead to physical, financial and emotional stress, and suboptimal care.

- *Regulatory restrictions:* Although state laws regulate prescribing opioids (including dosages and complicated prescribing requirements) in terminal illness in most states, the regulatory requirements for the care of terminal patients are not as big a barrier as they are perceived to be. Information on state pain policies is provided at http://www.painpolicy.wisc.edu/states.htm.

- *Off-label prescription:* With some newer drugs, "off-label" reimbursement by third-party payer (insurance) may be an issue.

3. Health care provider

- *Poor communication with patients and families, and between providers:* Physicians are typically reluctant, lack the requisite time, or are poorly prepared to communicate with patients and their families. Health care providers may fail to transmit information about patient preferences to each other.

- *Underreferral to palliative care specialists or services:* In addition to unrealistic prognostication and patient desire for life-sustaining treatments, delay in palliative care referral may be due to physicians' lack of knowledge about palliative care or hospice, or their services, discomfort with the subject, and service availability.

- *Limited ability to recognize and appropriately treat common symptoms:* Providers often undertreat pain due to physician–patient discrepancy in the rating of patient pain. A systematic review (search date 2006) identified further physician-related barriers to pain management with opioids in cancer patients.[46] These included concerns about side effects, underdosing, and inadequate treatment of side effects from opioids. Physicians may fail to detect psychological distress, anxiety and depression, or to distinguish associated symptoms from side effects of treatment.

- *Lack of training in palliative care:* Formal palliative care training in medical schools, residencies and fellowships remains poorly coordinated and of variable quality.

4. Patient and family

- *Patient's ability to confront death:* Fear and unwillingness to accept prognosis can lead to lack of acceptance of terminal disease.[47]

- *Patient's attitudes toward the sick role:* Some patients may feel the need to be stoic leading to undertreatment of pain, nausea and depression; others may underreport symptoms for fear of hospitalization, or because of fear of distracting the physician from curative or life-prolonging efforts.

- *Patient's attitudes toward palliative treatments:* A systematic review (search date 2006) identified patient-related barriers to appropriate management with opioids in cancer patients.[46] Patients may see morphine as comfort for dying patients rather than a legitimate treatment for pain.[48] Family members may not realize that improved pain control can be achieved.[49] Both patients and their families have inaccurately inflated estimates of the risk of psychiatric addiction from opioids analgesia.

- *Inadequate or lack of insurance coverage:* Real or perceived inadequacies of insurance coverage may delay or prevent access to palliative care services.

- *Other factors:* Men and patients in rural communities are slower to enroll in hospice.[50] Language and culture differences may lead to disparities in hospice care access and use.[51]

Noncancer diagnoses

- The role of palliative care in patients with chronic illnesses other than cancer is often not recognized.[52] For patients with heart failure, prognostication may be especially difficult and doctors need to be better at integrating patient preferences into goals of care.[21] In the SUPPORT study, only 25% of patients hospitalized with heart failure recalled discussions with physicians about resuscitation and 20% changed preferences after discharge.

- Similarly, patients with advanced COPD often do not receive palliative care services despite their poor prognosis, dyspnea, disability, anxiety and depression.[53] Only 32% of COPD patients report having had a discussion about end-of-life care with their physician.[54] One review indicated that only a minority of patients with moderate to severe COPD have discussed treatment options with their physicians.

- Dementia is rarely viewed as a terminal illness, which means that patients with dementia often receive inadequate or no palliative care and live and die in pain.[55]

Communication

Good communication is essential to effective palliative care. Key skills for clinicians include:

- communicating bad news

- conducting a goal setting meeting with patients and their families

- discussing advance care planning including artificial nutrition and hydration and DNR issues.

Few high-quality RCTs exist on the effectiveness of training to improve communication skills or the effects of different communication approaches in palliative care. Most recommendations and reviews are based on focus groups, patient surveys and expert opinion.[16]

Good communication requires preparing for the encounter, creating a supportive environment, active listening, appropriate awareness of nonverbal behavior, and expressing empathy.[16] Clinician's should be open to exploring emotion and meaning.[56] It is important to evaluate the patient and family's knowledge of the current situation and desire to learn new information about prognosis and what the future holds, and to communicate in a manner appropriate to their culture and education. Bad news may be followed by acceptance or denial and appropriate strategies for both situations should be prepared.

There is moderate-quality evidence that:

- Intensive education improves clinician communication skills

- Provision of prompt cards to patients improves communication.

Approximately 70% of family physicians who provide palliative care have no training in communication skills.[57] A systematic review (search date 2005) of residents' end-of-life decision-making with adult hospitalized patients identified 26 studies of mixed designs and found residents unprepared to handle patient end-of-life decision-making.[58] Another systematic review (search date 2005) identified 18 low-quality, heterogeneous studies.[57] These suggested some benefit from a multifaceted, interactive approach to palliative care training for primary care physicians, as opposed to traditional didactic teaching. A review suggested that clinicians find discussions most difficult with elderly patients, but there is little good evidence on improving those skills.[59]

A systematic review (search date 2001) identified one large RCT, which found that training oncologists in communication during a intensive 3-day course increased rates of focused questions (34% increase, P less than 0.005), focused and open questions (27% increase, P = 0.005), expressions of empathy (69% increase, P greater than 0.005) and appropriate cue responses (38% increase, P less than 0.05) at follow-up.[60] An additional RCT demonstrated significant benefit from the provision of question prompt lists to patients prior to consultation, which were then used by the physician during the consultation.[61] It found that patients asked significantly more questions (relative risk [RR], 2.3; 95% CI, 1.7 to 3.2), discussed more end-of-life issues (30% vs. 10%; P = 0.001) and had longer consultations (average, 38 minutes vs. 32 minutes) with the intervention.

Evidence on interventions to increase utilization and completion of advance directives

There is moderate-quality evidence that:

- Multifaceted interventions increase completion of advance directives and the likelihood of adherence to patient preferences

- Providing a trained facilitator increases decisional competence

- Forms designed for those with low literacy increase completion rates

- Peer mentoring increases advance directive completion rates among African Americans

Our literature search identified 3 systematic reviews and 3 subsequent RCTs on advance care plans.[8,62,63,64,65,66] The first review (search date 2007) found moderate evidence that multicomponent interventions yielded more advance directives than limited strategies.[8] The second review (search date 2005) identified 25 studies (both RCTs and observational) and reported that didactic interventions (clinical mailings, education or information programs) did not appear to increase uptake of advance directives, but interactive measures were

more effective (23% to 71% increase in completion).[62] This finding was confirmed by a subsequent RCT (469 adults with psychiatric disorders) that compared an opportunity to meet individually with a trained facilitator to create a psychiatric advance directive vs. a control group receiving written materials about advance directives.[64] The third review (search date 2005) identified 18 RCTs and observational studies in primary care.[63] It concluded that interventions (mostly patient-directed interventions such as educational mailing, information at visit, discussion with social worker, single-group lecture, or physician-directed interventions such as group education of physicians or reminders to discuss) increased take up of advance directives. However, results were poorly reported and not broken down by kind of intervention. A second RCT found that a redesigned form to meet the literacy level of most adults produced higher acceptability ($P = 0.03$) and completed more advance directives.[65] The third RCT (297 people admitted to hospital) compared routine care vs. a scripted intervention.[66] It found 13% in treatment group advance directive completion versus 1% in the control group (P less than 0.01).

Advance care planning

Although observational studies and expert opinion have indicated support for advance care planning from patients, caregivers and physicians and desire of patients to participate in decision-making, advance directives still have a low prevalence even among at risk populations. The most cited reason by clinicians is insufficient time, but another issue may be lack of reimbursement. Patients should feel advance care planning is part of routine care and their values are important for decision making.[67] Completion of advance directives is a process and there is a higher likelihood with repeated contact. The well-equipped office should include state-approved advance directive forms and a checklist in the patient chart to ensure that it is filled out. A team approach involving other qualified health professionals is recommended. Once completed, they need to be revisited regularly as patients' preferences have been shown to change over time. Plans should be revisited at diagnosis, following frequent hospitalizations and on declining functional status. Many forms are insufficiently detailed and poorly implemented. The goal should be genuine understanding, not just completing a document. Observational studies have shown a lack of transmission of information about patient preferences between providers, a concern considering the high rate of care transitions in late life. Two observational studies found no evidence of benefit from portable health records.

There is a need to move from an exclusive focus on advance care directives to a more comprehensive approach to advance care planning, with systems in place that ensure the wishes of the patient are actually honored. All stakeholders need to be aware of and involved in the plan. Advance care information needs to be available to the right people, at the right time, with services organized to provide the chosen level of medical intervention. One important approach is the Physician Orders for Life-Sustaining Treatment (POLST) form and program, and related programs Physician Orders for Scope of Treatment

(POST) and Medical Orders for Life-Sustaining Treatment (MOLST).[68] Information about the program and sites across the U.S. are available at http://www.ohsu.edu/polst/professionals.shtml. Key elements include: a protocol outlining policies and procedures for transferring information about preferences across health care settings; distinctive and prominently displayed form that details specific wishes on medical interventions; education of all those involved (patients, families, and health care professionals); revision of the template forms based on feedback and a system to monitor distribution of forms, education and quality improvement.

DNR orders

The self-reported prevalence of DNR policies in U.S. nursing homes has risen substantially.[69] However, DNR orders are frequently misunderstood, rarely discussed, and poorly implemented.[16] Patients may overestimate the prognosis following in-hospital resuscitation, with most surveys reporting that less than 15% of people survive to discharge. A systematic review (search date 2005) found that many residents misinterpreted the terms "DNR" and "futility".[58] The SUPPORT study included patients with life expectancy less than 6 months and reported that only 47% of physicians knew their patients' CPR preferences, 46% of DNR orders were written within the last 2 days before death, and 38% of these patients had spent more than 10 days in an ICU, on a ventilator, or in coma before dying.

Mechanical ventilation

Ideally, mechanical ventilation should be performed only if consistent with patients' treatment goals. The SUPPORT study found that ventilator withdrawal patterns vary substantially, with communication being the main predictor of whether ventilation was withdrawn.[23] Another study demonstrated that 15% of clinicians almost never withdraw ventilation.

Enteral and parenteral nutrition

One recent review found that nutritional support was overused and that education, guideline implementation, and shared decision making could reduce its use.[70] Another found that gastrostomy tube feeding varies is as high as 90% in some states among patients with advanced dementia, despite a lack of evidence that it improves outcomes.[23] Many patients would not want life-prolonging tube feeding, but this decision is often made after incapacity. Furthermore, one study reported that 15% of patients had feeding tubes placed despite a recorded preference against them. One pre-post study found that physician education plus palliative care consultation halved feeding tube placement rates.

Coordination and delivery of care

We found moderate-quality evidence that specialized palliative care services improve family satisfaction but evidence on patient satisfaction, quality of life, and symptoms control was less clear-cut.

A recent systematic review of specialized palliative care (search date 2008) found 22 RCTs.[71] Problems with study implementation or analysis were common. Insufficient power, including high withdrawal rates, typically limited the potential for finding a positive effect. Lack of allowance for cluster design, potential for contamination between groups, and inadequate specification of primary outcomes or use of appropriate outcome measure was common. Heterogeneity precluded meta-analysis. The best evidence of effectiveness was for family satisfaction, with 7 out of 10 studies finding a positive effect. It found some evidence of improved satisfaction with care, with 4 out of 10 studies finding a significant benefit. Four out of 13 trials found significant improvements in quality of life. The review identified no good evidence that specialist care improved symptoms.

Despite the poor quality of trials, use of specialist care teams is increasingly common and knowing when and how to refer to specialist palliative care services is important. Indications that usual care is not sufficient include patient and/or family distress, symptoms not responding to usual management or needs becoming sufficiently complex to require specialist input.

Social workers

A systematic review on the role of social workers in palliative care underlined their important role within multidisciplinary teams and emphasized how they have traditionally contributed to psychosocial and spiritual concerns, completing advance directives, counseling, and advocacy.[72] The review identified inadequate education and role conflicts as major barriers to more effective social worker involvement.

Nursing homes

The role of hospice services within nursing homes has also been studied. One RCT (205 nursing home residents) found that use of a structured interview designed to identify nursing home patients appropriate for hospice care increased hospice referrals, improved family ratings of the care and decreased utilization of acute care resources compared with usual care.[73]

Volunteers

A systematic review found that the work of palliative care volunteers benefited dying patients and their families, health care professionals, and the volunteers themselves.[74]

Discrepancies in service delivery in patients with advanced chronic disease

A recent review from the U.K.[53] identified 1 large retrospective study of differences in care between people with COPD and lung cancer (1,490 had COPD, 349 had lung cancer, and 110 had both lung cancer and COPD, all of whom died in the previous 6 months).[75] It demonstrated that patients with COPD had twice the odds of being admitted to the ICU and higher medical

costs, but received fewer opiates and benzodiazepine. The review concluded that palliative care was not available for people with advanced COPD, despite having poor prognosis with greater disability, lower quality of life, and worse depression than lung cancer patients and greater use of ICUs.

PART 2. EVIDENCE REVIEW: SYMPTOM ASSESSMENT AND MANAGEMENT

Symptom assessment

Bringing relief of suffering to people with advanced illness is largely dependent upon the early identification and assessment of pain and other problems, physical, psychosocial and spiritual, as implied by the WHO definition of palliative care.[7] In addition to improving patient/family care, regular assessment helps to identify those in need of referral to specialist palliative care services. The high incidence of cognitive impairment, fatigue and comorbidities make ease of comprehension and speed of completion desirable qualities in an assessment tool in this population.[76] Many seriously ill patients are simply too unwell to complete detailed instruments.

Multidimensional tools assess a variety of symptoms, rather than assessing an individual symptom—e.g., pain—in isolation. One example of a practical and simple multidimensional assessment tool that can be incorporated into busy daily practice is the Edmonton Symptom Assessment System (ESAS): 10 visual analog scales covering physical and psychological symptoms, and global sense of well-being).[77] A multisymptom tool, the Memorial Symptom Assessment Scale (MSAS): 32 physical and psychological symptoms, is a more thorough but much longer instrument that has been validated in cancer and noncancer patients.[78] Although regular use of these tools helps to build up a clinical profile of symptom severity over time, they do not provide complete symptom evaluation in themselves and need to be incorporated into a holistic clinical assessment of the patient. Assessment tools focused on specific symptoms are mentioned in the introductory sections of the symptom chapters below.

For physicians or health care institutions interested in an overview of the best available symptom assessment and outcome measurement tools, the Toolkit project has developed an evidence-based online resource, which provides access to an authoritative bibliography of over 200 reviewed instruments for 11 palliative care domains.[79] Building on this work, a recent systematic review (search date 2005) identified 64 further measures of outcomes in end-of-life care and evaluated their use in intervention studies.[80] Compared with the Toolkit, this review places a greater emphasis on specific measures of palliative care or end-of-life care, especially those with psychometric aspects. Another valuable resource is the City of Hope Pain and Palliative Care Resource Center web site at http://www.cityofhope.org/prc/.[81] Although most of the evidence base for outcome measures in palliative and end-of-life care comes primarily from the area of cancer, there is still a need for reliable and valid measures in certain areas within cancer (e.g., depression in cancer), but most urgently in other chronic conditions.[82] In addition, most current measures have been tested in just a single setting, whereas most seriously ill patients are managed at multiple sites of care.[80] Measures, therefore, should be more longitudinally oriented and be applicable across settings. Few measures have been evaluated for use in an outpatient setting, although this is the most frequent location for

care.[82] Culture has been found to have an impact on patient and caregiver experience of serious illness, but ethnicity-specific measures are also lacking.[80]

Symptom prevalence at the end of life

Recent systematic reviews have evaluated the prevalence of symptom distress in patients with incurable cancer[83] as well as far advanced chronic disease.[84] The first review (44 studies, 25,074 patients with incurable cancer) identified 37 symptoms assessed in at least 5 studies. Five symptoms occurred in >50% of patients (pooled prevalence): fatigue (74%), pain (71%), lack of energy (69%), weakness (60%) and appetite loss (53%).[83] During the last 2 weeks of life, weight loss (86%) was found significantly more often than earlier in the course of illness, whereas pain (45%), nausea (17%) and urinary symptoms (6%) were less frequent during the last 1 to 2 weeks of life. In these final 2 weeks, fatigue (88%), weight loss (86%), weakness (74%) and appetite loss (56%) were noted in >50% of patients. The second review (64 studies) compared the prevalence of 11 common symptoms among end-stage patients with cancer, AIDS, heart disease, COPD and renal disease.[84] Although the prevalence of these symptoms varied widely between studies, the overall distribution among the 5 diseases was homogenous, indicating a common pathway toward death for cancer and noncancer diseases. Pain (34% to 96%) and fatigue (32% to 90%) were present in greater than 50% of all patients. Breathlessness was also common overall, but was most consistently present among patients with COPD (90% to 95%) and heart disease (60% to 88%).

Pain

Pain—one of the most feared and debilitating symptoms among patients—is common in people with cancer and other advanced chronic conditions. Pain prevalence was 35% to 96% in 19 cancer trials involving 10,379 participants (search date 2004); 63% to 80% in patients with AIDS (3 trials, 942 people), 41% to 77% in patients with heart disease (4 trials, 882 people), 34% to 77% in patients with COPD (3 trials, 372 people), and 47% to 50% in patients with renal disease (2 trials, 370 people).[84]

Pain assessment

Pain assessement needs to be performed daily and, in its simplest form, using a numeric rating scale (0 to 10 or 0 to 3) as it is directly linked to adequate pain management. The literature provides a wide range of more elaborate pain assessment tools of varying detail and content.[85] An expert panel prioritized the following pain dimensions identified by a systematic review of instruments in the palliative care of advanced cancer (search date 2003):

1. Pain intensity

2. Temporal pattern

3. Treatment and exacerbating relieving factors

4. Pain location

5. Pain interference.

The temporal facet of pain was rated as particularly important in palliative care because of the high prevalence of breakthrough pain. The review concluded that the optimal assessment tool for the palliative care setting should be precise (high validity and reliability), brief, and have the flexibility for use in different populations and situations. A robust/vigorous computerized tool was preferable to a paper questionnaire.

The Toolkit recommends the McGill Pain Questionnaire (MPQ) and its short form (SF-MPQ: 11 questions on sensory quality of pain; 4 questions on affective dimension of pain; 4-point scales) as well-used, valid, and manageable pain scales, and both the Edmonton Symptom Assessment System (ESAS), and Memorial Symptom Assessment Scale (MSAS) for assessing pain as part of a multidimensional instrument.[86]

Pain assessment can be particularly difficult in people with dementia.[87] However, a prospective study of 160 dementia patients in a hospital setting found that more than 90% of people with mild or moderate dementia and 40% of the 15 patients with severe dementia were able to complete at least 1 of 4 evaluated self-assessment scales. Pain was mainly musculoskeletal and rates were similar in all three dementia severity groups. There was only a moderate correlation between self-assessment scales and an observational pain scale, which underestimated patients' estimate of pain. The City of Hope Pain and Palliative Care Resource Center web site provides access to a wide range of instruments and a comparison of 10 pain assessment tools in nonverbal older adults.[88]

Cancer pain management

Organic causes of cancer pain may be directly linked to the tumor itself (e.g., through infiltration and/or compression of nervous roots or visceral tissue, bone involvement), indirectly related (e.g., muscular contracture, lymphedema, para-neoplastic syndrome) or due to treatments (e.g., mucositis secondary to radiochemotherapeutic interventions, postoperative pain).[89] The pathophysiology of cancer pain is also very complex, including nociceptive, somatic, visceral and neuropathic components. The therapeutic approach may need to reflect the multidimensional character of this type of chronic pain through the use of different drug classes, often in combination, to increase efficacy and minimize toxicity.

Best practice in the use of analgesics is led by the following principles:[90]

- giving the right analgesic at the right dose and the right time

- administering by the most appropriate route (preferably oral)

- increasing to the maximum dose before moving to a new agent

- always considering coanalgesics

- managing adverse effects

- one clinician taking the lead role in the prescribing of opioids.

The extensively validated WHO analgesic ladder offers a stepwise approach to the use of analgesic drugs. It suggests starting with a nonopioid (acetaminophen, NSAIDs or aspirin) and if pain is insufficiently controlled, progressing to a combination opioid (e.g., codeine or oxycodone plus acetaminophen) and, if required, to a strong opioid (e.g., morphine, hydromorphone, buprenorphine, hydrocodone, tramadol, fentanyl, methadone). Acetaminophen is contraindicated in patients with liver disease and 4 g/day is the dose limit. NSAIDs increase the risk of renal failure and GI bleeding, and are particularly risky in the elderly for whom opioid analgesics are usually a safer option. Analgesics may be combined with adjuvant drugs such as corticosteroids, anticonvulsants, tricyclic antidepressants, or bisphosphonates for specific pain syndromes.[89] If used correctly, the WHO ladder has been shown to lead to adequate control of cancer-related pain in 70% to 100% of patients.[90] However, this needs to be regarded as one part of a comprehensive strategy for managing cancer pain, integrating analgesic pharmacotherapy with disease modifying treatment and nondrug measures. Consultation with a palliative care specialist or anesthesiologist is indicated for the subset of patients in whom the WHO ladder does not lead to effective pain relief.[91]

NSAIDs have also been successfully used in combination with opioids for the treatment of moderate to severe pain and have demonstrated a relevant opioid sparing effect.[90] Another approach used in advanced cancer is to "jump start' analgesia using strong opioids, as in 1 RCT (100 patients with mild to moderate pain), which demonstrated their superior analgesic efficacy and reduced need for treatment changes compared with treatment according to the WHO ladder.[92]

A recent systematic review (search date 2007) found high-quality evidence for treating cancer pain with opioids and NSAIDs, metastatic bone pain also with radiotherapy and radionuclides.[8] Less-consistent evidence supports the use of multidisciplinary teams in managing cancer pain and the use of bisphosphonates for bone pain or painful complications (e.g., fracture) from bone metastases.

Opioids in cancer pain
Opioids are the cornerstone of adequate analgesia in moderate to severe cancer pain. Their activity is due to the interaction with a variety of receptors in CNS areas along the sensory pathways of pain.[89] Unfortunately, mistaken beliefs and concerns about the risk of addiction, respiratory depression and excessive sedation still cause patients and health care professionals to avoid using opioids or to use them in suboptimal doses.[90] Clinical experience has shown that psychological addiction (continued compulsive use despite harm to self or others) is highly unlikely if opioids are used to manage pain responsive to opioids, and in doses titrated to the degree of pain. Long-term opioids will need to be tapered before discontinuation, but the withdrawal symptoms of physical dependence should not be confused with psychological dependence (addiction). Respiratory depression is unlikely at recommended doses.

Morphine is most commonly used for managing moderate to severe cancer pain due to its proven analgesic efficacy and cost effectiveness.[90] Despite lack of large, robust clinical trials, morphine remains, to date, also the most tested opioid for this indication. A systematic review (search date 2006) identified 54 RCTs (3,749 people) evaluating the use of oral morphine for cancer pain.[93] It found that morphine was an effective analgesic, with no significant difference in efficacy between oral immediate (used for dose titration) and modified release morphine (used for maintenance treatment). An increasing number of other effective opioids are now available but the evidence is lacking to demonstrate the clear superiority of fentanyl, hydromorphone, methadone, oxycodone, hydrocodone or tramadol over oral morphine in terms of analgesic benefit and tolerability.[94]

Table 1 outlines the principles of opioid use for the management of cancer pain.

Table 1. Opioid treatment in cancer pain

Starting dose	● Usually 10 mg oral immediate-release morphine every 4 hours ● Previous analgesic requirements also taken into account ● Lower doses may be sufficient in the elderly and those with renal impairment
Dosing intervals	● Short acting products are usually taken every 4 hours; a systematic review (search date not reported) found that dosing frequency predicted onset to analgesia independently of baseline dose (2 RCTs, 6 single-arm and 1 retrospective trial with a total of 877 patients);[95] time to adequate analgesia after initiating oral morphine ranged from 6 hours to 2.3 days ● Longer dosing interval may be needed for people with renal impairment ● Next dose is given based on half-life, before the effect of the previous one has worn off ● Although not formally investigated, a double dose at bedtime is a widely adopted practice of preventing sleep disruption through pain
Insuffi-cient pain control	● Pain control is reassessed regularly ● If pain not sufficiently controlled, dose can be increased by 50% for moderate or 100% for severe pain; in 54 RCTs identified by a systematic review, the daily doses ranged from 25 mg to 2000 mg with an average of between 100 mg and 250 mg.[93]

	• In case of breakthrough pain (transient pain characterized by rapid onset, severe intensity, and is in most cases self-limiting after an average duration of 30 minutes) during 4 hourly standard-release morphine, 10% to 15% of the 24-hour morphine total dose are usually given as "rescue medication" and repeated every hour if necessary
	• A recent systematic review (search date 2005, 4 RCTs, 393 participants) found moderate evidence that oral transmucosal fentanyl citrate (OTFC) was more effective than placebo or normal-release morphine in reducing breakthrough pain intensity.[96] A subsequent RCT (87 patients) found buccal fentanyl also to be effective in the management of breakthrough pain in cancer patients.[97] Due to reports of death and adverse events, buccal preparations should not be substituted with the same dose of OTFC and fentanyl only be used in people tolerant to opioids.[98] More trials are urgently needed on the use of other opioids to improve the evidence base for current practice
High doses	• Morphine and its derivatives have no ceiling dose; the right dose is the one that controls the pain without untoward or unmanageable side effects.
Stable dose	• Once adequate pain control with a stable dose has been maintained for 48 hours using immediate-release morphine, the medication can be converted to a sustained-release morphine preparation (given every 12 or 24 hours)
	• Changes to a long-acting oral opioid dose should not be be made more frequently than every 24 hours; 72 hours for methadone and transdermal fentanyl
	• Rescue immediate release morphine equivalent to 10% to 15% of the morphine daily dose is also prescribed for breakthrough pain
Alter-native routes of adminis-tration	• An excellent alternative to oral opioids, when a parenteral route is required, is intermittent or continuous subcutaneous morphine; both subcutaneous and IV morphine are around 3 times more potent than oral morphine, so for conversion the 24-hour dose or oral morphine is divided by 3 (for example 120 mg total daily oral morphine is equivalent to 40 mg subcutaneous morphine in 24 hours)

	• A systematic review (search date 2002) provided limited evidence from 6 small randomized controlled or crossover studies (150 people) that continuous subcutaneous infusion of opioids (CSIO) is effective and safe, and should be considered when the oral route is problematic or has failed, the patient has limited intravenous access, adequate supervision of the CSIO is present, and CSIO will not unduly limit the functional activity of the patient.[99] • Intramuscular opioid injections are not recommended (painful, unreliable absorption) • Rectal administration of morphine has similar bioavailability and duration of effect to oral morphine and does not require dose conversion • Transdermal fentanyl is a noninvasive alternative for opioid-tolerant patients who require stable opioid doses; it should not be used in an opioids-naïve patient • In intractable pain, opioids can also be given centrally, administered via intracerebroventricular (ICV), epidural (EPI) or subarachnoid (SA) routes (± a local anesthetic or clonidine). A systematic review (search date 2003) found no RCTs on the use of centrally given opioids.[100] However, 72 uncontrolled studies in 2,402 patients demonstrated excellent pain relief in 73% of ICV, 72% of EPI, and 62% of SA patients, with unsatisfactory pain relief reported to be low in all treatment groups. Adverse effects such as persistent nausea, persistent and transient urinary retention, transient pruritus, and constipation occurred more frequently with EPI and SA, whereas respiratory depression, sedation and confusion were most common with ICV.
Adverse effects	• Important to counsel patients and caregivers about opioid toxicities • Nausea and vomiting: Occurs in up to two-thirds of patients starting morphine and lasting up to 7 days; unlikely once dose is stable; effective treatment with antiemetics (see Nausea and vomiting below) • Constipation: Very common (in up to 90% of patients) and persistent effect; therapy with softening and stimulating laxatives (see Constipation below); increased risk of bowel obstruction with bulk laxatives when there is insufficient oral liquid intake • Drowsiness: Common at start of treatment; usually wears off after a few days

	• Cognitive impairment: Minimal in most patients on stable dose; tolerance develops over a few days; driving not significantly impaired in alert patients on stable dose • Delirium: see Delirium below • Dry mouth: Preventative measures include good mouth hygiene, regular sips of water and sugar-free chewing gum • Urinary retention and pruritus: Uncommon; may occur with spinal opioids • Respiratory depression: dose, drug and route dependent; most often seen with rapid IV infusion or rapid dose escalation of methadone; other risk factors include renal failure, limited pulmonary reserve, and concomitant use of sedating drugs such as benzodiazepines
Poor analgesic response	• Occurs in 10% to 30% of patients • Currently, no indicators known to predict in whom this will occur • Possible to rotate to other opioids (e.g., oxycodone, hydrocodone, methadone, or fentanyl) • Success of rotation is variable and unpredictable; in a prospective study 20% of patients needed 2 or more switches prior to adequate analgesia • Opioid rotation is always an indication for consultation with palliative care specialist or anesthesiologist[91]
Opioid rotation	• Hydromorphone (extended or immediate release):[101] 5 to 10 times more potent than oral morphine • Oxycodone:[102] 1.5 to 2 times more potent than oral morphine[90] • Fentanyl (a lipid-soluble synthetic opioid): 50 to 100 times more potent than oral morphine; transdermal delivery for up to 72 hours; similarly effective in equivalent dosing but lower risk of constipation and daytime drowsiness compared with oral morphine;[94] however, stable serum levels achieved only after 12 to 24 hours and due to inflexible dosing with patch, not recommended in opioid-naïve patients or those whose dose requirement has not stabilized • Methadone:[103] complex pharmacokinetics and long half-life; regular monitoring; administered in consultation with experienced physicians only

Other drug treatments

1. NSAIDs and acetaminophen

A systematic review (search date 2003) found high-quality evidence from 7 out of 8 RCTs that NSAIDs reduced cancer pain compared with placebo, without

increasing the rates of side effects.[104] Nine out of 13 RCTs found no significant difference in efficacy between different NSAIDs, but studies in people with musculoskeletal pain have demonstrated important differences in adverse effects.[105] Reduction in ulcers with cyclooxygenase-2 (COX-2) inhibitors needs to be weighed against an increase in cardiovascular risk compared with the older NSAIDs. Ten RCTs compared NSAIDs versus opioids and found no clinically significant difference between treatments but demonstrated that NSAIDs were associated with significantly fewer adverse effects (OR = 0.38).[104] Four of 8 RCTs found low to moderate evidence that adding a (weak) opioid to an NSAID increases efficacy but also rates of side effects. Five of 6 RCTs identified by the review and one additional small RCT[106] showed that adding an NSAID to an opioid may reduce opioid use and escalation. A second additional RCT found that adding acetaminophen to morphine did not increase analgesia. [107] The review and an additional RCT[108] demonstrated no significant difference between different NSAID/opioid combinations. Renal insufficiency and risk of bleeding can be significantly worsened by NSAIDs. This is of particular concern in the geriatric population, many of whom have underdiagnosed or underappreciated renal insufficiency and are at higher than average risk of abnormal bleeding in association with NSAIDs.[109]

2. Corticosteroids

There is very low-quality evidence from 1 RCT including 76 people with limited survival that adding dexamethasone to conventional opioid therapy may not increase analgesia but reduce the incidence of GI adverse effects.[110]

3. Ketamine

A systematic review (search date 2007) identified 2 RCTs including 30 people and concluded that there was insufficient evidence to draw conclusions on the benefits and harms of ketamine as an adjuvant to morphine in the treatment of cancer pain.[111]

4. Neurolytic celiac plexus block

This intervention has only been evaluated in people with unresectable pancreatic cancer. In this population, 5 RCTs including 302 patients found that neurolytic celiac plexus block (NCPB) reduced pain compared with standard treatment with NSAIDs/opioids at 4 and 8 weeks (search date 2005).[112] NCPB significantly decreased opioid consumption by mean 40 to 80 mg/day and rates of constipation compared with standard treatment but increased the risk of intractable diarrhea. There is very limited evidence that bilateral splanchic nerve blockade may reduce pain and opioid usage more than NCPB.[113]

5. Neuropathic pain in cancer

Neuropathic pain is caused by nerve damage due to a wide range of etiologies and is regarded to be less responsive to opioids than other types of pain.

- *Antidepressants*

A systematic review (search date 2005, 61 RCTs, 3293 people) demonstrated that neuropathic pain could be treated with antidepressants, independently of any effect on depression.[114] One in three patients benefited from tricyclic antidepressants (amitriptyline, desipramine, imipramine) and the newer drug venlafaxine. The review found only limited evidence from four small RCTs for the effectiveness of SSRIs (fluoxetine, paroxetine, citalopram) and insufficient data to assess effectiveness for other antidepressants such as St Johns Wort and L-tryptophan. Only three small RCTs assessed antidepressants for the treatment of postoperative neuropathic pain after breast cancer surgery and radiotherapy, and found that amitriptyline significantly relieved pain, and venla-faxine reduced chronic pain and analgesic use in this population. Cardiovascu-lar adverse effects (e.g., postural hypotension, heart block and arrhythmias) limit the use of tricyclic antidepressants, especially in older patients. Most common side effects include sedation and anticholinergic effects such as dry mouth, constipation and urinary retention). SSRIs have a better toxicity profile and are free of cardiovascular adverse effects.

- *Anticonvulsants*

A systematic review found that one in four patients with neuropathic pain benefited from gabapentin or pregabalin but reported a lower efficacy with topiramate.[115] Another systematic review of anticonvulsants in neuropathic pain found little or no clinical benefit from lamotrigine, except in HIV patients receiving neurotoxic antiretrovirals.[116] Rash was sufficiently serious and fre-quent (7% incidence), so that its use cannot be recommended unless all other options have failed. One RCT (63 cancer patients) provided very low-quality evidence that adding gabapentin to opioids may reduce neuropathic pain more than opioid treatment alone.[117]

- *Opioids*

A systematic review (search date 2005, 23 RCTs in 727 patients with neuro-pathic pain) found mixed results from short-term trials (14 RCTs, <24 hours) using morphine, alfentanil, fentanyl, meperidine or codeine found in the man-agement of neuropathic pain.[118] However, intermediate-term trials (9 RCTs, median = 28 days; range = 8 to 70 days) using morphine, oxycodone, methadone, or levorphanol demonstrated opioid efficacy for spontaneous neuropathic pain. Opioids reduced pain intensity scores compared with placebo in seven RCTs. Three RCTs showed tramadol to be effective in patients with painful polyneuropathy or postherpetic neuropathy.[115] A systematic review evaluating the use of buprenorphine in neuropathic pain (search date 2006) identified 2 RCTs comparing transdermal buprenorphine versus placebo in people with chronic pain, including 52/294 participants with neuropathic pain.[119] Both suggested that buprenorphine may improve quality of sleep and reduce the need for rescue medication in this population.

- *Systemic administration of local anesthetics*

A systematic review (search date 2004) identified 30 RCTs in people with neuropathic pain due to injury and cancer, and found that lidocaine and

mexiletine significantly reduced neuropathic pain compared with placebo, and were equally effective as carbamazepine, amantadine, gabapentine or morphine in terms of efficacy or adverse effects.[120]

● *Spinal cord stimulation*

Spinal cord stimulation (SCS) is commonly used in patients with neuropathic pain accompanying partial lesions of nerves, nerve roots and the spinal cord in chronic pain but evidence in palliative care patients is lacking (search date 2003).[121]

Nondrug treatments

1. Cognitive behavioral therapy

Psychoeducational care has been shown to benefit adults with cancer in relation to pain but found it problematic to determine the most effective of the various types of psychoeducational care.[122] Two additional RCTs in 368 cancer patients with or without chemotherapy showed that CBT (five weekly 50-minute sessions or 10-contact, 20-week, nurse-administered cognitive-behavioral intervention focusing on symptom management) reduced pain severity compared with usual therapy.[123,124] Whereas tailored CBT was better in the short term (at 1 month), standard CBT (proved to be more effective at 6 months. In breast cancer patients, 7 studies including 484 women found that CBT techniques reduced pain in 69% of participants compared with control groups (search date 2004).[125] Interventions included relaxation (± visualization, cognitive restructuring, coping skills training, problem solving, or imagery) and hypnosis. Individual CBT did not produce larger effect sizes, and amount of patient contact was not significantly correlated with effect size.

2. Reminders

A large RCT (over 300 nurses managing 637 people with cancer in a home care setting) found that nurse-targetted, patient-specific, 1-time email reminders highlighting 6 pain-specific clinical recommendations significantly improved patients' pain intensity scores compared with controls.[126]

3. Complementary and alternative medicine

Use of complementary and alternative medicine (CAM) is common among cancer patients. Among advanced cancer patients enrolling into phase I trials, 90/102 (88%) used at least one CAM modality; 93% and 53% used pharmacologic and nonpharmacologic CAM, respectively; and 47% used both modalities.[127] Vitamin (especially vitamin E and C) and mineral preparations constituted 89% of all pharmacologic CAM used. Seventy-one percent of respondents took nonvitamin/mineral agents, with green tea (30%), echinacea (13%), and essiac (10%) being the most popular. Prayer and spiritual practices were the most commonly used nonpharmacologic CAM (52%) and chiropractors the most frequently visited nontraditional medicine practitioners (10%). CAM modalities were used more frequently by women (54% vs. 40% in men). In another survey (212 advanced cancer patients enrolling into phase I trials) increased CAM use

was associated with younger age, worse stated prognosis, and poorer quality of life.[128] CAM use had no affect on survival.

The majority of patients are reluctant to disclose their use of CAM to their physician, so it is advisable for health care providers to initiate a discussion about CAM in order to maintain an open and honest patient–doctor relationship, encourage adherence to conventional treatment, and monitor adverse effects and interactions with cancer drugs. The evidence base is growing but consists mostly of low-quality, small, and poorly reported studies.

Systematic reviews and additional RCTs found promising results for massage with or without aromatherapy, reflexology, hypnosis, imagery, support groups, acupuncture, healing touch, and EMG biofeedback-assisted relaxation sessions but study quality overall was too low to draw definite conclusions. [129,130,131,132] Another systematic review (search date 2006) identified 41 RCTs of low quality, which found no significant difference between Chinese herbal medicines and analgesic drug treatment.[133]

Metastatic bone pain

Metastatic bone cancer is a frequent and serious complication of advanced disease that occurs in approximately 70% of people with prostate and breast cancer, and 30% of cases of thyroid, lung and bladder cancer.[134] Metastatic bone lesions are radiographically classified as either osteolytic (e.g., in breast cancer), or osteoblastic (e.g., in prostate cancer).

The mechanism of metastatic bone pain is uncertain, but generally has three distinct clinical patterns:

● Background pain: deep and aching in quality; increasing in intensity with disease progression

● Spontaneous, often intense pain

● Pain associated with physical movement.

The principal complications of bone metastases are severe pain, spinal cord compression, and pathologic fractures.

Patients with metastatic bone pain need to be managed using an individualized and multidisciplinary approach with local external beam radiotherapy, supportive care with analgesics (opioids and/or NSAIDs/acetaminophen) and biphosphonates, systemic treatment (hormone or chemotherapy), and in selected patients radionuclides. The ideal therapy remains a subject of considerable debate among palliative care physicians.

Analgesics

According to the WHO ladder, analgesics are the first-line treatment of metastatic bone pain, although the RCT base for this approach is limited.[135] In people receiving radiotherapy, an RCT (460 people with bone metastases) found that transdermal fentanyl offered more effective pain relief and a lower overall rate of side effects than codeine plus acetaminophen.[136]

External beam radiotherapy

A systematic review found high-quality evidence for the effectiveness of palliative radiotherapy from 16 RCTs involving 5,000 cancer patients and comparing multiple fraction 30Gy radiotherapy versus single fraction radiotherapy.[137] A meta-analysis of the results indicated no significant difference in complete pain relief or overall bone pain relief between the 2 treatment groups.

Radiopharmaceuticals

Radioisotopes or radiopharmaceuticals (Strontium 89 [148 MBq IV], Samarium 153 [37 MBq/kg IV], Rhenium 186 [1295 MBq IV]) are administered by IV injection or locally in areas of active bone turnover, and emit beta particles that result in cytotoxic irradiation of adjoining malignant cells.[134] High-quality evidence from RCTs demonstrated that strontium 89 (with or without radiotherapy) and Samarium 153 reduced metastatic bone pain compared with placebo and should be considered in people with multiple active bone lesions when pain control with analgesics is unsatisfactory.[138] The most common side effects in the studies were thrombocytopenia and neutropenia, which were usually slight and reversible. Further RCTs are required to evaluate newer radiopharmaceuticals and combination treatments with other systemic therapies.

Biphosphonates

Biphosphonates are specific inhibitors of osteoclast-mediated bone resorption. In addition to alleviating bone pain, they reduce hypercalemia and the risk of subsequent fractures. Biphosphonates require long-term therapy and, according to a systematic review, should be considered where analgesics and/or radiotherapy are inadequate.[139] An additional RCT of women with metastatic bone cancer found low-quality evidence of less pain but more severe adverse reactions with ibandronate (2 mg and 6 mg dosages) compared with placebo.[140] Another systematic review specifically in patients with advanced prostate cancer with bone metastases found that clodronate and sodium etidronate are more likely to produce a pain response and decrease analgesic use than placebo.[141]

Radiofrequency ablation

A systematic review[142] identified very low-quality evidence that radiofrequency ablation (RFA) produced significant pain relief for cancer patients after failed standard treatments.[143]

Hormonal therapy and chemotherapy

Hormonal therapy is effective in patients with breast or prostate cancer.[135] Tamoxifen and aminoglutethimide relieve metastatic bone pain in about 1 in 2 breast cancer patients, and antiandrogens, estrogens and orchiectomy (surgical or chemical) can dramatically decrease bone pain within 24 hours in patients with prostate cancer. Chemotherapy can reduce tumor volume and pain in a wide range of cancers. The analgesic impact from chemotherapy is dependent on the timing of response to treatment; for most patients who are

chemotherapy responders, a positive effect is noted within 2 weeks and may last for many months. Unfortunately, with both hormonal and chemotherapy pain recurrence is common as patients tend to become refractory to treatment.

Calcitonin
Calcitonin, a hormone produced by the thyroid gland, lessens the amount of bone resorption and thus slows the rate of bone destruction.[144] A systematic review identified 2 small RCTs that found no significant decrease in total pain reduction with calcitonin compared with placebo.[145]

Noncancer pain in advanced chronic illness
Opioids are increasingly used in the management of chronic noncancer pain. They showed good short-term efficacy in 15 RCTs including 1,145 people with noncancer neuropathic or musculoskeletal pain conditions, with a mean decrease in pain intensity in most studies of at least 30% (search date 2003).[146] Adverse events were experienced by around 80% of participants, the most common ones being constipation (41%), nausea (32%) and somnolence (29%). There was insufficient data to draw conclusions on long-term effects of opioid treatments such as tolerance and addiction. We found no evidence addressing pain management in other advanced chronic conditions. However, variable literature indexing for advanced chronic illness and palliative care may have limited the comprehensiveness of our searches, so conclusions about interventions not supported by high-quality evidence need to be regarded with caution.

Dyspnea
Dyspnea (breathlessness) is a common and disabling symptom in advanced cancer, COPD, and heart failure, and tends to increase in patients approaching death.[147] A number of interventions are available, but may be underused. A study of late-stage cancer patients reported that >60% had been dyspneic for >3 months, and that most had not received any treatment.[148]

Assessment of breathlessness
The lack of a universally accepted measurement scale for breathlessness hinders clinical practice and research aiming to appraise the efficacy of interventions. Most dyspnea assessment scales identified by systematic reviews (search dates 2005) had been evaluated only in chronic respiratory disease, but not in cancer or palliative care.[149,150] The unidimensional Visual Numeric Scale, Numerical Rating Scale (NRS), and modified Borg Scale were noted as most suitable for measurement of severity in clinical practice, whereas the Japanese Cancer Dypsnea Scale (CDS) was found to be valuable for assessment of the quality of breathlessness.

Management of dyspnea
Many of the studies reported in this section were identified and presented in a systematic review by Lorenz and colleagues (search date 2005; literature

surveillance up to January 2007), which reported the published evidence for interventions aimed at palliation at the end of life.[8]

Oxygen

High-quality evidence from 20/22 RCTs showed that oxygen improved symptoms during short-term exercise in COPD, but there was only weak evidence of any benefit in patients with COPD at rest, heart failure, or cancer (3 small studies and 1 subsequent RCT[151]).[8] Another systematic review found weak evidence and mixed results from small studies in patients with advanced cancer, most of whom were hypoxic at the outset.[152] However, a recent review has suggested that even in hypoxic patients, both oxygen and air can improve dyspnea in patients with cancer, and that before either of these is tried, the patient may be offered a fan.[153]

Opioids

There is high-quality evidence of a benefit from opioid use in COPD (12 RCTs), but poor-quality evidence of benefit in cancer (2 RCTs), according to a systematic review with a search date of 1999.[154] A meta-analysis of 9 studies found that oral or parenteral opioids reduced dyspnea compared with placebo, but 3 studies found no benefit from nebulized opioids. Subsequent RCTs in patients with COPD and advanced cancer confirmed the benefit from oral morphine for improved subjective dyspnea and sleep, without compromising respiratory function.[155] The most common side effects of opioids reported in the reviews were constipation, nausea and vomiting. Clinicians might be wary of prescribing opioids in palliative care, because of a theoretical effect of respiratory depression, but this does not appear to be supported by the literature.

Anxiolytics

Although not supported by RCT evidence, low-dose phenothiazines and benzodiazepines are widely used in patients with breathlessness requiring sedation or anxiolysis.[153] They should be given in combination with nonpharmaceutical anxiety-reduction interventions. Phenothiazines (e.g., 6.25 mg oral levomepromazine) are often preferred to benzodiazepines as the evidence base is even weaker. The long half-life of oral anxiolytics may lead to accumulation and prolonged sedation. A small RCT of terminally ill cancer patients reported that subcutaneous midazolam (5 mg every 4 hours) might be a safe and effective adjunct to morphine in the treatment of dyspnea.[156] The starting dose used in the RCT was higher than recommended by other sources (5 to 10 mg in 24 hours subcutaneously; titrated according to the patient's wishes with 2.5 to 5 mg as needed). Midazolam has a half-life of 5 hours and no active metabolites. High-quality trials are urgently required evaluating the effectiveness of anxiolytics on dyspnea in palliative care.

Nondrug and complementary therapies

Apart from high-quality evidence from a meta-analysis of 20 RCTs showing a benefit from pulmonary rehabilitation in advanced COPD,[157] there appears to be a paucity of evidence across other interventions (e.g., supervised exercise or

muscle training, care delivery interventions, nursing interventions and programs, nutrition, psychotherapy, reflexology) and other palliative care conditions. A systematic review demonstrated weak evidence from 11 RCTs and 2 controlled clinical trials, and was unable to produce any recommendations in respect of a range of alternative therapies.[158] Two RCTs evaluating acupuncture, one in advanced cancer, the other in advanced respiratory disease (cystic fibrosis, COPD and pulmonary fibrosis) found low to moderate evidence and mixed results.[159,160] There is a need to undertake more and better research into the effectiveness of complementary and alternative therapies in palliative care situations.

Radiotherapy

Palliative radiotherapy has been evaluated for relieving respiratory symptoms in patients with lung cancer and mesothelioma only. There is moderate evidence of symptomatic benefit for dyspnea, cough and hemoptysis for people with nonsmall-cell lung cancer. Two reviews, covering mainly the same RCTs, did not identify any regimen that provides optimal palliation, although there was a tendency for both more harms (in particulare esophagitis) and increased benefits to result from higher doses.[161,162] They concluded that "the majority of patients should be treated with short courses of palliative radiotherapy, of 1 or 2 fractions". Our literature search found insufficient evidence in mesothelioma[163] and no evidence in other lung malignancies. No patients with mesothelioma who were treated at a dose of 20 Gy had adverse effects attributed to radiation, whereas in contrast, most of those receiving total doses of 38.5 to 71 Gy suffered severe and progressive injury to the irradiated lung.

Malignant pleural effusion

Malignant pleural effusion develops in approximately 50% of patients with metastatic cancer— particularly breast and lung cancer—and causes morbidity such as cough and dyspnea. Management is usually with pleurodesis, which prevents reaccumulation of the fluid and thereby reduces symptoms.[164]

Five RCTs (228 patients) found that the use of sclerosants (mitozantrone, talc or tetracycline) significantly reduced recurrence of effusion compared with pleurodesis using saline or tube drainage alone, with 10 RCTs (308 patients) reporting talc to be the most efficacous type of sclerosant (systematic review with search date 2002).[164] Comparing 2 agents used for chemical pleurodesis, an additional RCT (110 people) found that talc sclerosants also reduced the risk of recurrence of effusion compared with quinacrine.[165] Talc sclerosants did not increase mortality compared with other sclerosants but was associated with respiratory complications, fever, dyspnea and pain.[164] Thoracoscopy plus talc insufflation was shown by 2 RCTs to be as effective as thoracostomy plus talc slurry at preventing recurrence of effusion at 30 days.[166,167] In patients with low pH pleural effusion, where talc sclerosants are less effective, limited evidence from one RCT (87 women with breast cancer) found that thoracoscopic mechanical pleurodesis may be more effective, and reduce hospital stay and complication rates.[168] There was limited evidence from 1 RCT that bleomycin

pleurodesis may increase response to treatment at 30 days and delay progression compared with intrapleural interferon alfa-2-b.[169]

Fatigue

A recent systematic review defined fatigue as a tiredness that is not improved by typical measures that normally restore vigor, stressing the subjective, multidimensional and distressing nature of this phenomenon.[170] Approximately 40% of cancer patients experience fatigue at the time of diagnosis and it may intensify during or after chemotherapy treatment.[171] Its prevalence rises to higher than 75% in patients with advanced cancer.[170] Fatigue is also common among people with COPD and heart failure.

Fatigue assessment

Valid methods to assess fatigue are essential for its treatment. Fatigue, as with other symptoms, is best evaluated by self-assessment measures, not by the observations of a health professional. A systematic review identified and evaluated self-report tools that focused on assessment of adults with fatigue.[170] It found that despite efforts to produce fatigue instruments, no gold standard was available.

Fatigue management

There is good evidence for the effect of psychological and psychoeducational interventions on cancer-related fatigue, although applying the evidence to people with advanced disease is difficult.[171] There is evidence for a small benefit from methylphenidate, exercise and energy conservation and activity management. No reduction of fatigue resulted from administering progestational steroids, such as medroxyprogesterone and megestrol acetate, paroxetine, or multivitamins. There is insufficient data to recommend any specific complementary therapies for the treatment of cancer-related fatigue.

As a complex and multifaceted symptom, cancer-related fatigue has been associated with psychological (anxiety and depression) and physical factors (hemoglobin and cytokine levels, physical activity), sleep disturbances and symptom burden, but not tumor stage or treatment type.[172] In most patients, fatigue has multiple causes and will require an individualized treatment plan.[171]

Psychological and psychoeducational interventions

A systematic review (search date 2005) identified 24 RCTs using a broad range of psychological interventions (11 CBT, 3 educational programs, 3 supportive-expressive group therapy, and 3 supportive therapy, 4 RCTs were specifically in people with meta-static disease) and conducted a meta-analysis that showed a small improvement in cancer-related fatigue with psychological interventions (standardized mean difference: 0.10, 95% CI 0.02 to 0.18).[173] A second systematic review identified one RCT (235 women with metastatic breast cancer at the end of life), which found that group psychotherapy was beneficial for reducing fatigue.[171] An RCT of 113 patients undergoing chemotherapy for

breast and lung cancer showed that a tailored supportive intervention including teaching, counseling, and support reduced fatigue, pain, and total symptom burden. Similarly, a subsequent RCT of 103 people receiving chemotherapy compared an investigator-designed information pack combined with monthly home visits by support nurses versus usual care; the nurses assessed fatigue, provided psychological support, and coached participants in self-care.[174] The intervention significantly lowered fatigue and the impact of fatigue on valued pastimes.

Exercise interventions
A recent systematic review (search date 2007) found moderate-quality evidence of a small improvement in cancer-related fatigue with an exercise intervention (1664 people, mostly with breast cancer, SMD –0.23, 95% CI –0.33 to –0.13).[175] Results were not broken down by disease stage. We found insufficent evidence to assess the effects of Tai Chi or qigong on cancer-related fatigue. [176,177] Recent European guidelines found strong evidence that aerobic exercise reduced fatigue in cancer survivors and those undergoing cancer treatment.[178] However, they found little evidence for people with advanced disease and impaired performance.

Exercise conservation and energy management
A systematic review (search date not reported) identified 1 multisite RCT that showed a small but statistically significant effect on fatigue with semistructured exercise conservation and energy management intervention in people initiating treatment for cancer (P = 0.01), applying the result to people with advanced disease is difficult.[171]

Drug treatments
A systematic review (search date 2007) identified 2 RCTs (264 people) that showed methylphenidate (a CNS stimulant, 10 to 20 mg/day) having a small but significant positive effect on fatigue compared with placebo (P = 0.02).[179] An additional small RCT (68 people) found a small but nonsignificant trend toward reduction in fatigue with methylphenidate.[180] The review noted an increased risk of harm from methylphenidate compared with placebo, although the difference did not reach statistical significance.[179] Adverse reactions can include stroke and MI, elevated BP, seizures, visual symptoms, headache, insomnia, nausea, decreased appetite, anxiety and palpitations.[181]

The systematic review found no significant difference between progestational steroids such as medroxyprogesterone or megestrol acetate (4 heterogeneous RCTs, 587 people) or paroxetine (2 RCTs, 645 people) versus placebo for the treatment of cancer-related fatigue.[179]

Complementary therapies and nutritional supplements
A systematic review (search date 2006) identified 21 clinical trials, but none of sufficient quality to recommend any complementary therapy for cancer-related fatigue.[182] Tested interventions included acupuncture, aromatherapy, adenosine triphosphate infusions, healing touch, hypnosis, mistletoe extract, American and

Asian ginseng, levocarnitine, massage, mindfulness-based stress reduction, polarity therapy, relaxation, support group and Tibetan yoga. More research is needed to clarify whether any of these modalities can be useful in improving fatigue and how they might apply to people with advanced disease.

Hematopoietic growth factors in people with anemia
Although hematopoietic growth factors reduce fatigue in people with anemia recent trial evidence has confirmed shortened overall survival and/ or time to tumor progression and their recommended use is now restricted.[183,179]

Improving sleep disturbances
In the general population inadequate or unrefreshing sleep is generally associated with increased risk of medical and psychiatric illness, and reduced quality of life. It is likely that this holds for people with advanced disease. Sleep disorders are reported by 30% to 50% of cancer patients during all phases of cancer care, twice the level of the general population.[184] However, a systematic review (search date 2005) found no randomized evidence on pharamacologic treatments for sleep disturbances.[184] It found only 1 small RCT (42 people with advanced cancer). This RCT compared a 4-week course in aromatherapy massage and massage alone and no intervention. It found that both interventions significantly improved sleep scores compared with no intervention. We found 1 additional small RCT (57 breast cancer survivors with insomnia) comparing 8 weekly sessions of group CBT versus waiting list controls.[185] It found that CBT significantly improved sleep indices and reduced the frequency of medicated nights.

Distress, depression and mental health
Psychological distress, including grief, sadness, despair, fear, anxiety, loss and loneliness occur among most people at some time with advanced disease.[186] Distress is underrecognized and undertreated,[187] but with support many people can achieve equanimity and acceptance.[186] The clinician has an important role in assessing stressors and helping the patient to identify coping strategies.

Assessment and management
Symptoms present across a continumum and evaluation of psychological symptoms is required to identify those at high risk of psychiatric disorders. Clinicians have a key role in screening for mental illness and initiating first-line treatment. With serious mental illness a collaborative approach with mental health specialists for patients with personality disorders, major mental illness, and substance abuse problems is recommended. About 50% of patients with advanced cancer meet criteria for a psychiatric disorder, the most common being adjustment disorders (11% to 35%) and major depression (5% to 26%).[56] There is less good evidence in people with cardiac, pulmonary renal, or neurologic disease. Although anxiety has a high prevalence in this population, this is often not about death but about symptom management, isolation and

family needs.[188] Symptoms such as fatigue or chronic pain, although common in this population, can also present due to somatization of an underlying depression.

A systematic review of psychological distress in cancer patients found that clinicians needed training in skills for assessing and managing distress.[187] It recommended treating patients holistically and shared decision making with uninterrupted patient talk time. It also found that if clinicians were willing to use emotional words, this facilitated patient expression. Self-completed quality-of-life questionnaires, screening tools for distress, and patient question prompt cards can help with the diagnosis. Providing time for open, patient-led conversations, active listening and responding to patients' emotional cues are important. A tendency to overrely on symptoms such as depressed mood or crying should be avoided as these are not sensitive indicators, particularly in this population.

The keys to good management are effective communication and trust, control of symptoms, and attention to psychological issues. Symptoms need to be actively solicited because patients may view psychological distress as being appropriate to their situation, may consider that distress reflects a lack of coping skills, or simply believe that it is not appropriate to report such issues to their clinician. Clinicians themselves may adopt distancing techniques to avoid discussions that can be seen as an emotional challenging and time-consuming, although effective communication is beneficial for both patients and doctors.

Evidence on the effectiveness of treatments
We found low-quality evidence that behavioral techniques may reduce depression and improve functioning. We found little good-quality evidence on pharmacologic treatments. With complementary and alternative medicines the best evidence is for aromatherapy and massage (low-quality evidence of a reduction in anxiety), music therapy (low-quality evidence of improvement in quality of life), and reflexology (low-quality evidence of an improvement in anxiety and pain intensity). The Toolkit contains best practice recommendations (see Appendix A).

Pharmacologic interventions

Anxiety
Despite the high prevalence of anxiety, a systematic review on drug therapy for anxiety in palliative care (search date 2003) identified no good-quality RCTs on drug therapy in patients with advanced cancer, end-stage disease, or those receiving hospice or palliative care.[188]

Depression
A second systematic review (search date 2005) of treatments for depression in cancer patients identified 7 trials of pharmacologic agents and four of nonpharmacologic interventions.[189] Only 1 drug RCT was specifically in people with advanced cancer (163 people with at least occasional evidence of depressed

mood) and this found limited evidence of a difference between fluoxetine and placebo on depression. A subsequent RCT (189 people with advanced cancer but without major depression) found no effect on depression or quality of life with sertraline compared with placebo.[190] Four drug trials in people with cancer of different stages found no significant difference between different antidepressants. A small RCT found no significant difference between paroxetine and placebo in people with end-stage COPD.[191]

Nonpharmacologic interventions
Most studies measured multiple outcomes, including different psychological outcomes and physical functioning, thus disaggregating which interventions should be targeted at specific symptoms is difficult.

Cognitive and behavioral therapies
A systematic review (search date 2003) showed moderate-quality evidence of a small to moderate reduction in distress with behavioral therapy techniques in women with metastatic breast cancer (standardized mean difference of 0.43).[125] It found very low-quality evidence that individual therapy may be more effective than group therapy. A previous systematic review (search date 2002) in patients with advanced cancer (mainly breast cancer) reported from 7 trials that behavior therapy improved depression, physical functioning, and global quality of life.[192] Four trials of behavior therapy suggested that group support improved depression and physical functioning. One trial suggested that behavioral therapy with breathing techniques may improve depression.

Our literature search identified 2 subsequent RCTs. The first RCT (123 people with advanced cancer) found problem-solving techniques delivered by nurses reduced symptom severity at 10 and 20 weeks.[193] The second small trial reported that cognitive therapy significantly reduced depression.[194]

Mindfulness

We found mixed evidence on mindfulness approaches from 2 RCTs in people with a variety of cancer disagnosis.[195,196]

Complementary medicine

AROMATHERAPY AND MASSAGE
A systematic review in people with cancer but not exclusively with advanced disease (search date 2002) identified some evidence of a reduction in anxiety from massage.[129] It found conflicting evidence on additional benefit from aromatherapy and mixed evidence about depression from 3 trials. A second systematic review identified 2 RCTs of aromatherapy in palliative care.[197] The larger RCT (103 people) provided very low-quality evidence of an improvement in overall symptom control. The smaller RCT found no evidence of an effect on anxiety or depression from massage.

A large subsequent RCT (288 cancer patients with anxiety and/or depression, 43% with advanced disease) found a reduction in anxiety and a smaller

reduction in depression from aromatherapy message at 6 to 10 weeks.[198] Three small RCTs in palliative care found mixed outcomes with aromatherapy and massage.[199,200,201]

MUSIC THERAPY

Music therapists use methods including song writing, improvisation, singing, instrument playing and music therapy relaxation techniques in palliative care.[202] An RCT (80 people with advanced cancer) found improvement in hospice-related quality of life from music therapy.[202] A second review of music therapy indicated that it may reduce depression and improve well-being in people with cancer/terminal illness/HIV.[203] Similarly, an additional RCT (70 women with metastatic breast cancer) found short-term improvements in mood, although differences were not maintained.[204]

REFLEXOLOGY

One RCT (86 patients with metastatic cancer and their partners) found low-quality evidence that partner-delivered foot reflexology reduced pain intensity and anxiety postintervention.[205]

OTHER COMPLEMENTARY THERAPIES

We found insufficient evidence to assess the effectiveness of acupuncture, therapeutic touch, multisensory stimulation, breathing training, homeopathy, yoga or guided imagery.[197,206,207]

Service organisation

Three systematic reviews identified little good evidence on the effects of service management on mental health outcomes.[208,8,189] Breast cancer nurses were the best-studied service intervention, but all trials were conducted in women with early stage breast cancer and results would be difficult to apply to women with advanced disease.

Delirium

Delirium is a common illness/condition in ill elderly people, especially those with dementia.[209] It is also the most frequent complication of hospitalizations among the elderly. In the SUPPORT study, delirium affected 20% to 30% of people with cancer, COPD and end-stage liver disease.[8] Its prevalence increases to 26% to 44% in terminal cancer, and eventually to 83% in people during their final days.

Delirium is associated with a higher rate of mortality, both during and following hospitalization.[210] A prospective cohort study with patients who had experienced delirium during hospitalization found a 62% increased risk of mortality at 1 year compared with patients without delirium (adjusted survival: 274 days vs. 321 days).[211] In people with advanced cancer, delirium was associated with a significantly lower survival time (21 vs. 39 days). Delirium also increases length of hospital stay (on average by 7 days), and impaires cognitive and physical status for 6 and 12 months after hospital discharge, often delaying a return to the patients' prior site of residence.[209]

The pathophysiology of delirium is not well understood, but abnormal neuro-transmitter levels, particularly those of acetylcholine and dopamine may be involved.

Delirium and dementia are closely interconnected; the presence of dementia increases the risk of delirium. Other risk factors include older age, frailty, severe illness or multiple comorbidities, polypharmacy, and hospital admission due to infection or dehydration—all commonly encountered in palliative care. In an older patient with these risk factors, the addition of one of the following precipitants may contribute to the onset of delirium:

• Urinary tract infection/catheter

• Lower respiratory tract infection

• Electrolyte abnormality including dehydration,renal failure

• Constipation

• Surgery

• Addition of a new medication often anticholinergic or psychoactive (e.g., antihistamines, antispasmodics, tricyclic depressants, benzodiazepines, opioid analgesics, antiarrhythmics, diuretic, brochodilators, antiparkinsonian agents, bladder stabilizers)

• Environmental-intrahospital transfers, absence of reading glasses, use of physical or pharmacologic restraints

• Alcohol or drug withdrawal.

Delirium is not detected in 22% to 50% of cases or its symptoms may be attributed to a primary psychiatric disorder.[212] This is not surprising as delirium may present as hyperactive, hypoactive, or a mixed subtype and with different combinations of recent-onset variation of consciousness, diminished attention span, and impaired cognition. Hallucinations and abnormal sleep-wake cycles may also occur. In addition to symptom variability, factors related to failure to recognise delirium include pre-existing dementia, older age, and the presence of sensorial alterations (e.g., failing eyesight).[213] Delirium is a clinical diagnosis, which needs to be made in view of the history of the present illness as provided by family members, and requires monitoring and comparison with the baseline situation. The Confusion Assessment Method is a valid, sensitive, specific, reliable and easy to use instrument for the identification of delirium.[214] This tool can be completed in less than 5 minutes and consists of 9 criteria from the Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised (DSM-III-R). The diagnosis of delirium requires the presence of 2 criteria (acute onset and fluctuating course, and inattention) and of either disorganized thinking or altered level of consciousness. Delirium severity can be assessed using the Memorial Delirium Assessment Scale (MDAS).[215]

Prevention of delirium

The Yale delirium prevention model of care has been found to reduce the incidence (9.9% vs. 15%) and duration of delirium (105 vs. 161 days) significantly compared with usual care (852 people admitted for general medical care).[209,216] This intervention has been translated into routine practice as the hospital elder life program (HELP),[217] which is now used internationally, and has been shown to reduce the rates and costs of delirium in elderly hospitalized patients at risk of delirium.[214] Effective components of the HELP program include orienting communication, therapeutic activities, early mobilization and walking, nonpharmacologic approaches to sleep and anxiety, maintaining adequate nutrition and hydration, and use of adaptive equipment for vision and hearing.

General management

Delirium diagnosed on admission to a palliative care unit may be reversible in 1 in 2 patients and an even higher percentage of cases when triggered by drugs, dehydration or hypercalcemia.[213] A systematic review (search date 2006) stated immediate identification, reduction and potential withdrawal of precipitating agents (as listed above), and supportive care regarding hypoxia, hydration, nutrition and mobilization as general management principles of delirium in the elderly.[209] Good care of patients with delirium includes reassurance and a safe and comfortable environment for the patient as well as provision of information to the family about the fluctuating nature and clinical symptoms of delirium.

Existing medications

Drugs are the most common cause of delirium.[213] After documentation of previous and existing medications, reduction and possibly withdrawal of andticholinergic and psychoactive drugs should be considered. A proportion of people who receive opioid therapy develop neuroexcitatory toxicity, either secondary to a rapidly increasing dose, an accumulation of opioid metabolites caused by renal impairment, or individual sensitivity to opioids. It is hypothesised that in these patients opioid dose reduction and/or rotation (usually at an equianalgesic dose with a reduction of 20% to 30%) may alleviate delirium. The clinical practice of opioid rotation as a means of balancing pain control and opioid side effects in patients with cancer or chronic noncancer pain is widely accepted but its evidence is based on case reports and uncontrolled studies.[218] A systematic review found that opioid rotation resulted in clinical improvement in over 50% of patients with chronic pain and poor response to one opioid.[219] For conversion ratios, please see Table 1 on Opioid treatment in cancer pain.[220] However, the process of determining the optimal dose is not purely a mathematical calculation, but needs to be considered as part of an individualized and comprehensive evaluation of pain, adverse effect intensity, comorbidities and concomitant drugs.

Drug treatments

Drug treatments for delirium patients should be reserved for the following indications:[221]

- Patients who pose a danger to themselves or others

- Uncontrollable agitation despite nonpharmacologic interventions

- Anxiety in the presence of agitation or hallucinations

- Need to control agitation during a diagnostic or clinical intervention.

Antipsychotics
There is consensus based mainly on observational evidence and experience that haloperidol and other butyrophenones such as dropiderol are effective for the management of delirium in the palliative care setting. A systematic review (search date 2006) identified 3 RCTs in hospitalized patients, and demonstrated that haloperidol treatment was more effective at improving delirium scores at 7 days compared with placebo.[222] The review found no significant difference in the effect of haloperidol compared with the atypical antipsychotics risepridone or olanzapine. However, haloperidol improved delirium scores significantly later than olanzapine, and was associated with significantly higher rates of dry mouth and dystonia.

Most people with dementia are sensitive to adverse effects from antipsychotics, especially sedation and extrapyramidal symptoms.[223] In people with dementia, olanzapine and risperidone have been found to increase the risk of sudden death and nonfatal cerbrovascular events, and should be avoided.[224,225,226] Patients on antipsychotic medications should be regularly monitored for QT prolongation, although this recommendation may not apply in someone already very near the end of life.[221]

Other medications
Our literature searches found no clinically important results about the effects of profolol or barbiturates in people with delirium caused by a terminal illness. Similarly, we found no high-quality evidence on the effectiveness of phenothiazines (chlorpromazine, levomepromazine) compared with placebo, although these agents are used clinically for treatment of delirium at the end of life, usually second line to haloperidol. Although benzodiazepines, especially midazolam, are also used extensively for the treatment of delirium in terminally ill patients, we found no evidence from well-conducted trials that they are beneficial. A systematic review (search date 2003)[227] identified only 1 small RCT in 30 patients with terminal AIDS reporting that lorazepam actually worsened delirium and was associated with serious adverse effects, including oversedation, disinhibition and ataxia.[228]

Anorexia and cachexia
Loss of appetite (anorexia) occurs in 70% of patients with advanced cancer, and is often worsened by cytotoxic treatments that lead to dysphagia, nausea and mucositis.[229] Although cachexia (significant weight loss due to disease) often occurs with anorexia, it is not caused solely by reduced nutritional intake

but characterized by a catabolic state with increased resting energy expenditure, preferential loss of skeletal muscle as well as fat, increased proteolysis, and lipolysis, possibly caused by chronic systemic inflammation and circulating tumor-derived factors.[230,231]

Management

Effective treatments to improve appetite in terminally ill people with anorexia include the progestogen megestrol acetate and corticosteroids.

- *Progestogens:* Although systematic reviews have found high-quality evidence that progestins (megestrol acetate [MA] and medroxyprogesterone acetate) increase appetite and weight gain in cancer patients compared with placebo, they also increase the risk of adverse effects, particularly lower limb edema (11 RCTs, 1,767 people: RR 1.74).[229,232] A retrospective case-control analysis of 2,127 elderly nursing home residents with cachexia found no significant difference in median weight at 6 months between residents with and without MA, and demonstrated that the median survival of people receiving MA was significantly reduced compared with untreated residents (23.9 months vs. 31.2 months).[233]

- *Corticosteroids:* Six RCTs (647 patients) found that methylprednisolone, prednisolone or dexamethasone increased appetite in the short term compared with placebo, but that the benefit may decrease after several weeks.[229] The review reported no results on survival. Side effects of prolonged use include osteoporosis, proximal muscle weakness, immunosuppression, delirium and skeletal muscle atrophy.[230]

- *Enteral nutrition:* Orally consumed supplements (volitional nutritional support [VNS]) may increase survival in malnourished geriatric patients but neither VNS nor enteral nutrition via a tube can be recommended in people with cancer or other advanced chronic diseases.[234] No results for weight gain or increase in appetite were reported.

- *Parenteral nutrition:* We identified only 2 RCTs evaluating parenteral nutrition as part of a combination therapy in cancer patients.[235,236] The first RCT (152 people with advanced cancer) found that adding parenteral nutrition to enteral nutritional support signficantly increased mean BMI at 48 weeks (21.9 vs. 20.5) and cumulative survival compared with enteral nutrition alone.[235] The second RCT (309 cancer patients with cachexia followed up to 2 years) found that adding oral and home parenteral nutrition to the cyclooxygenase-1 (COX-1) selective inhibitor indomethacin plus erythropoietin improved energy balance but found no significant differences between groups in intention-to-treat analysis.[236] Although not observed in the 2 RCTs, parenteral nutrition carries an increased risk of line infection and associated sepsis.

- *Other interventions:* A systematic review concluded that there was no benefit from hydrazine sulfate, and that the evidence was inconclusive about the benefits of metoclopramide, cyproheptadine, pentoxyfylline, melatonin, fatty

acids and eicosapentaenoic acid, erythropoietin, androgenic steroids, ghrelin, interferon, NSAIDs, cannabinoids, or thalidomide.[229]

Dehydration

Reduced fluid intake is common in palliative care patients, caused by a variety of factors such as physical obstruction, anorexia/cachexia syndrome, generalised weakness, bowel obstruction, nausea, decreased level of consciousness and loss of desire to drink, although in some cases no specific cause may be identified. High-quality evidence on the management of dehydration is sparse and routine practice varies widely geographically and between care settings.[237] Once treatable differential diagnoses such as delirium or opioid toxicity have been been assessed, the chosen course of action needs to be decided, if possible, in discussion with the patient, both as part of advance directive discussions and when the condition occurs, and with family and staff involved. There is some observational evidence that terminally ill people may not experience suffering from terminal dehydration, provided that good mouth hygiene is maintained.[238,239] In a small prospective trial in a comfort care setting, 20/32 patients (62%) experienced either no thirst or thirst only initially during their terminal illness. In all cases, symptoms of thirst and dry mouth could be alleviated, usually with small amounts of fluids, and/or by the application of ice chips and lubrication to the lips.[238] In another small prospective study of 88 terminally ill cancer patients, perception of thirst was shown to be associated with hyperosmolality (300 mosmol/kg or more), poor general condition, stomatitis, oral breathing, and use of opioids.[240]

Medically assisted hydration, performed either intravenously, subcutanously (hypodermoclysis) or via gastrostomy, remains a much debated issue among palliative care physicians. A systematic review (search date 2008) identified only 5 studies including 2 RCTs (including 93 patients) on the effects of short-term hydration in terminal cancer, which were deemed insufficient to make recommendations as trials were either underpowered or of insufficient quality.[241] There was weak evidence that artificial hydration might improve sedation and myoclonus, but it had no beneficial affect on other outcomes and increased fluid retention (e.g., pleural effusion, peripheral edema and ascites) compared with no artificial hydration. We found no evidence on the use of artificial hydration in the wider palliative care population.

Nausea and vomiting

Nausea, vomiting and retching are all prevalent in palliative care patients. Emesis is a word used to represent all 3 components of the symptom complex.[76] A recent systematic review in patients with incurable cancer found that nausea occurred in 17% (6 studies, 2219 patients) and vomiting in 13% of patients (3 studies, 799 patients) in the last 1 or 2 weeks of life.[83] Another review comparing symptom prevalence in different advanced conditions, reported that nausea was present in 6% to 68% of patients with cancer (19 studies, 9,140 patients), 43% to 49% of patients with AIDS (2 studies, 689

patients), 17% to 48% of patients with heart disease (3 studies, 146 patients), and 30% to 43% of patients with renal disease (3 studies, 362 patients).[84]

Nausea and vomiting can cause dehydration, electrolyte disturbances and diminished quality of life for patients and their families, and can negatively affect a patient's ability to complete activities of daily living. Chemotherapy-induced nausea and vomiting (CINV) and other chemotherapy-related toxic effects may also lead to lengthier hospitalizations and elevated costs, and delay chemotherapy for up to 50% of affected patients.[242]

Assessment of nausea and vomiting

Nausea is a subjective symptom and assessed using a self-report tool (unless cognitive impairment is an issue), whereas vomiting, as an objective sign/event, can be assessed by its volume, frequency, and consistency. Retching is not usually measured independently.

A systematic review (search date 2004) evaluated the validity and suitability of available tools for assessment of nausea, vomiting and retching in palliative care patients.[76] It found a paucity of agreement regarding assessment tools for all 3.

For daily clinical assessment, simple visual analogue scales or numerical rating scales are recommended. Multidimensional tools (e.g., the revised Rhodes index of nausea, vomiting and retching) are reserved for antiemetic drug trials and provide specific data on frequency, duration, amount, distress and effect on functioning.

Treatment approach

There is a large gap in the evidence base regarding high-quality studies in the management of nausea and vomiting in chronic advance disease other than related to cancer treatments. In order to optimize treatment and minimize side effects, the current management of nausea targets specific receptors, which vary by underlying pathophysiology. The VOMIT acronym is helpful for remembering the causes of nausea, see Table 2.[243]

Table 2. VOMIT acronym for the major causes of nausea

Cause	Receptors involved	Drug classes	Drug examples
V – vestibular	Cholinergic Histaminic	Anticholinergic Antihistaminic	Scopolamine patch Promethazine, diphenhy-dramine

Cause	Receptors involved	Drug classes	Drug examples
O – obstructive (bowel obstruction caused by constipation)	Cholinergic Histaminic 5HT3	Drugs stimulating the myenteric plexus	Senna products
M – motile (dysmotility of upper gut)	Cholinergic Histaminic 5HT3	Prokinetics (stimulating 5HT4 receptors)	Prokinetics, metoclopramide
I – infectious/ inflammatory	Cholinergic Histaminic 5HT3 Neurokinin 1	Anticholinergic Antihistaminic 5HT3 antagonists Neurokinin 1 antagonists Anti-inflammatory agents	Scopolamine Promethazine, diphenhy-dramine Ondansetron, granisetron Aprepitant Corticosteroids

Constipation

The prevalence of constipation from opioid utilization for noncancer pain ranges from 15% to 90%.[244,245] Patients following WHO guidelines for cancer pain management have a constipation prevalence of 23%. In a large U.S. hospice study, 40% to 63% of patients had constipation.

Management

Bowel prophylaxis (e.g., with senna plus docusate) is recommended in all people starting opioid treatment.

Oral laxatives

● Senna, a stimulant laxative, has been shown in an RCT to be similarly effective as lactulose for reducing the frequency of hard stools in people prescribed opioids.[246] Another RCT indicated that senna may be as equally effective as the Ayurvedic herbal preparation Misrakasneham in people with advanced cancer.[247]

● Docusate, a stool softening agent, is prescribed in people taking opioids, but there is no good evidence to support its use.[248]

● There is evidence from a systematic review of RCTs that lactulose, an osmotic laxative, may reduce the number of hard stools compared with placebo in people taking opioids.[246] A systematic review (search date 2003) found that

lactulose and and polyethylene glycol 3350/electrolyte solution (PEG) may be equally effective.[249] However, a subsequent RCT comparing lactulose versus PEG showed that intestinal obstruction or Ogilvie syndrome occurred more frequently with lactulose than with PEG.[250]

● Macrogels (PEG), an osmotic agent, may improve stool consistency compared with placebo in people prescribed opioids.[249] There is moderate-quality evidence suggesting that macrogels may be as effective as lactulose at reducing the number of hard stools in people prescribed opioids.

● Our literature search found no clinically important results about the effects of bisacodyl, sodium picosulfate, isapaghula husk, methylcellulose or magnesium salts on constipation in people prescribed opioids.

Rectally applied medications

Our search identified one systematic review (search date 2007) and found no clinically important results about the effects of phosphate enemas on constipation in people prescribed opioids.[251] There were also no clinically important results about the effects of liquid paraffin, glycerol suppositories, sodium citrate micro-enemas, and arachis oil enemas on constipation in people prescribed opioids.

Opioid antagonists

Constipation arises when opioids are used therapeutically because the drug acts on peripheral opioid receptors in the GI tract, in addition to those in the nervous system where their analgesic benefits arise. Opioid antagonists can block GI opioid receptors and so potentially reverse the analgesic effect of opioids but the main drawback of their use is the difficulty of retaining the central beneficial effects while preventing constipation.[252]

A systematic review (search date 2007) identified 2 RCTs, which compared subcutaneous methylnaltrexone (MNTX) versus placebo in hospice or palliative care patients with advanced medical illness (mainly cancer, with life expectancy < 6 months, no bowel movement for over 48 hours or < 3 bowel movements in the preceding week.[253] Both RCTs showed that MNTX significantly increased the rate of bowel movements within 4 hours without interfering with central analgesia. Subcutaneous methylnaltrexone bromide has just gained FDA approval for the treatment of opioid-induced constipation in patients with advanced illness who are receiving palliative care.[254]

Another systematic review (search date 2005) identified one RCT of 168 people with opioid-induced bowel dysfunction, 148 of whom were taking opioids for chronic pain, primarily back pain.[252] The RCT compared dosages of alvimopan 0.5mg and 1.0mg taken once daily versus placebo for 21 days. Significantly more people taking alvimopan at either dosage had a bowel movement within 8 hours compared with placebo; alvimopan at the 1.0 mg dose significantly increased the frequency of bowel movements and overall patient satisfaction. Alvimopan is not approved in the U.S. for opioid-induced constipation.

Our literature search found no evidence of sufficient quality on the effectiveness of naloxone, an opioid antagonist which can be taken orally, after conversion from injectable form.

REFERENCES

1. Lorenz K, Lynn J, Morton SC, et al. End-of-life care and outcomes. Evidence Report/Technology Assessment No. 110. (Prepared by the Southern California Evidence-based Practice Center, under Contract No. 290-02-0003.) 2004. AHRQ Publication No. 05-E004–2. Rockville, MD: Agency for Healthcare Research and Quality.

2. Central Intelligence Agency: The World Factbook. Life expectancy in years by country. 2008 est. Available at: https://www.cia.gov/library/publications/the-world-factbook/fields/2102.html. Accessed on: May 10, 2008.

3. Boockvar KS, Meier DE. Palliative care for frail older adults: 'there are things I can't do anymore that I wish I could …' JAMA. 2006;296:2245–2253.

4. Meier DE. Palliative care in hospitals. *J Hosp Med.* 2006;1:21–28.

5. Bickel-Swenson D. End-of-life training in U.S. medical schools: a systematic literature review. *J of Palliative Med.* 2007;10:229–235.

6. Plonk WM, Arnold RM. Terminal care in the last weeks of life. *J Palliative Med.* 2005;8:1042–1054.

7. World Health Organisation. Cancer control: knowledge into action: WHO guide for effective programmes: module 5: Palliative care. 2007. Available at: http://www.who.int/cancer/media/FINAL-Palliative%20Care%20Module.pdf. Accessed on: May 10, 2008.

8. Lorenz KA, Lynn J, Dy SM, et al. Evidence for improving palliative care at the end of life: A systematic review. *Ann Intern Med.* 2008;148:147–159.

9. Dy S, Lynn J. Getting services right for those sick enough to die. *BMJ.* 2007;334;511–513.

10. Murray SA, Kendall M, Boyd K, et al. *BMJ.* 2005;330:1007–1011.

11. Glare P, Virik K, Jones M, et al. A systematic review of physicians' survival predictions in terminally ill cancer patients. *Br Med J.* 2003;327:195.

12. Stone PC, Lund S. Predicting prognosis in patients with advanced cancer. *Ann Oncol.* 2007;18:971–976.

13. Christakis NA, Lamont EB. Extent and determinants of error in doctors' prognoses in terminally ill patients: prospective cohort study. *Br Med J.* 2000;320:469–472.

14. Christakis NA, Escarce JJ. Survival of Medicare patients after enrollment in hospice programs. *N Engl J Med.* 1996;335:172–178.

15. Hagerty RG, Butow PN, Ellis PM, et al. Communicating prognosis in cancer care: a systematic review of the literature. *Ann Oncol.* 2005;16:1005–1053.

16. Barclay J, Blackhall L, Tulsky J. Communication strategies and cultural issues in the delivery of bad news. *J Palliative Med*. 2007;10:958–977.

17. Pirovano M., Maltoni M, Nanni O, et al. A new palliative prognostic score: a first step for the staging of terminally ill cancer patients. Italian Multicenter and Study Group on Palliative Care. *J Pain Symptom Manage*. 1999;17:231–239.

18. Coventry PA, Grande GE, Richards DA, et al. Prediction of appropriate timing of palliative care for older adults with non-malignant life-threatening disease: a systematic review. *Age and Aging*. 2005;34:218–227.

19. Hancock K, Clayton JM, Parker SM, et al. Discrepant perceptions about end-of-life communication: a systematic review. *J Pain Symptom Manage.* 2007;34:190–200.

20. The SUPPORT Principal Investigators. A controlled trial to improve care for seriously ill hospitalized patients. The study to understand prognoses and preferences for outcomes and risks of treatments (SUPPORT). *JAMA.* 1995;274:1591–1598. Erratum in: JAMA. 1996;275:1232.

21. Goodlin SJ, Hauptman PJ, Arnold R, et al. Consensus statement: Palliative and supportive care in advanced heart failure. *J Card Fail.* 2004;10:200–209.

22. Parker SM, Clayton JM, Hancock K, et al. A systematic review of prognostic/end-of-life communication with adults in the advanced stages of a life-limiting illness: patient/caregiver preferences for the content, style, and timing of information. *J Pain Symptom Manage.* 2007;34:81–93.

23. Lorenz K, Rosenfeld K, Wenger N. Quality indicators for palliative and end-of-life care in vulnerable elders. *JAGS.* 2007;55:S318-S326.

24. Knops KM, Srinivasan M, Meyers FJ. Patient desires: A model for assessment of patient preferences for care of severe or terminal illness. *Palliat Support Care.* 2005;3:289–299.

25. Williams A. Perspectives on spirituality at the end of life: a meta-summary. *Palliat Support Care.* 2006;4;407–417.

26. Legalhelpmate. What is Patient Self Determination Act? Available at: http://www.legalhelpmate.com/health-care-directive-patient-act.aspx. Accessed on: May 10, 2008.

27. Shalowitz DL, Garrett-Mayer E, Wendler D. The accuracy of surrogate decision makers: a systematic review. *Arch Intern Med.* 2006;166:493–497.

28. Thomas REW. A literature review of randomized controlled trials of the organization of care at the end of life. *Can J Aging.* 2006;25:271–293.

29. Johnson KS, Elbert-Avila KI, Tulsky JA. The influence of spiritual beliefs and practices on the treatment preferences of African-Americans: a review of the literature. *J Am Geriatr Soc.* 2005;53:711–719.

30. Tang ST. When death is imminent: where terminally ill patients with cancer prefer to die and why. *Cancer Nurs.* 2003;26:245–251.

31. Hays JC, Galanos AN, Palmer TA, et al. Preference for place of death in a continuing care retirement community. *Gerontologist.* 2001;41:123–128.

32. Gruneir A, Mor V. Where people die: a multilevel approach to understanding influences on site of death in America. *Med Care Res Rev.* 2007;64:351–378.

33. Center for gerontology and health care research. Policy relevant data on care at the end of life. 2004. Available at http://www.chcr.brown.edu/dying/usastatistics.htm. Accessed on: May 10, 2008.

34. Gomes B, Higginson IJ. Factors influencing death at home in terminally ill patients with cancer: systematic review. *BMJ.* 2006;332:515–521.

35. Pritchard RS, Fisher ES, Teno JM, et al. Influence of patient preferences and local health system characteristics on the place of death. SUPPORT Investigators. Study to Understand Prognoses and Preferences for Risks and Outcomes of Treatment. *J Am Geriatr Soc.* 1998;46:1242–1250.

36. Hudson PL, Kristjanson LJ, Ashby M, et al. Desire for hastened death in patients with advanced disease and the evidence base of clinical guidelines: a systematic review. *Palliative Med.* 2006; 20: 693–701.

37. Burridge L, Winch S, Clavarino A. Reluctance to care: a systematic review and development of a conceptual framework. *Cancer Nurs.* 2007;30:E9-E19.

38. Cannuscio CC, Jones C, Kawachi I, et al. Reverberations of family illness: a longitudinal assessment of informal caregiving and mental health status in the Nurses' Health Study. *Am J Public Health.* 2002;92:1305–1311.

39. Schulz R, Beach SR. Caregiving as a risk factor for mortality: The caregiver health effects study. JAMA. 1999;282:2215–2219.

40. Harding R, Higginson IJ. What is the best way to help caregivers in cancer and palliative care? A systematic literature review of interventions and their effectiveness. J Palliative Med 2003;17:63–74.

41. Hebert RS, Arnold RM, Schulz R. Improving well-being in caregivers of terminally ill patients. Making the case for patient suffering as a focus for intervention research. *J Pain Symptom Manage.* 2007; 34: 539–546.

42. Jayawardena K, Liao S. Elder abuse at end of life. *J Palliative Med.* 2006;9:127–136.

43. McPherson CJ, Wilson KG, Murray MA. Feeling like a burden to others: a systematic review focusing on the end of life. *Palliative Med.* 2007;21:115–128.

44. Yabroff KR, Mandelblatt JS, Ingham J. The quality of medical care at the

end-of-life in the USA: existing barriers and examples of process and outcome measures. *Palliative Med.* 2004;18:202–216.

45. Chibnall, JT, Bennett ML, Videen SD, et al. Identifying barriers to psycho-social spiritual care at the end of life: a physician group study. *Am J Hosp Palliat Care.* 2004;21:419–426.

46. Jacobsen R, Sjøgren P, Møldrup C, et al. Physician-related barriers to cancer pain management with opioid analgesics: a systematic review. *J Opioid Manage.* 2007;3:207–214.

47. Emanuel L, Bennett, K, Richardson, VE. The dying role. *J Palliative Med.* 2007;10:159–168.

48. Reid CM, Gooberman-Hill R, Hanks GW. Opioid analgesics for cancer pain: symptom control for the living or comfort for the dying. A qualitative study to investigate the factors influencing the decision to accept morphine for pain caused by cancer. *Ann Oncol.* 2008;19:44–48.

49. Berry PH. The pain of residents with terminal cancer in USA nursing homes: family members' perspectives. *Int J Palliative Nurs.* 2007;13:20–27.

50. McCarthy EP, Burns RB, Davis RB, et al. Barriers to hospice care among older patients dying with lung and colorectal cancer. *J Clin Oncol.* 2003;21:728–735.

51. Lorenz KA, Ettner SL, Rosenfeld KE, et al. Accommodating ethnic diversity: a study of California hospice programs. *Med Care.* 2004;42:871–874.

52. Rodriguez KL, Barnato AE, Arnold RM. Perceptions and utilization of palliative care services in acute care hospitals. *J Palliative Med.* 2007;10:99–110.

53. Yohannes AM. Palliative care provision for patients with chronic obstructive pulmonary disease. *Health Qual Life Outcomes.* 2007;5:17.

54. Knauft E, Nielsen EL, Engelberg RA, et al. Barriers and facilitators to end-of-life care communication for patients with COPD. *Chest.* 2005;127:2188–2196.

55. Sachs GA, Shega JW, Cox-Hayley D. Barriers to excellent end-of-life care for patients with dementia. *J Gen Intern Med.* 2004;19:1057–1063.

56. Miovic M, Block S. Psychiatric disorders in advanced cancer. *Cancer.* 2007;110:1665–1676.

57. Alvarez MP. Systematic review of educational interventions in palliative care for primary care physicians. *Palliative Med.* 2006;20:673–683.

58. Gorman TE, Ahern SP, Wiseman J, et al. Residents' end-of-life decision making with adult hospitalized patients: a review of the literature. *Acad Med.* 2005;80:622–633.

59. Frank C, Whiting N. "Get the code status:" Teaching housestaff about end-of-life communication with older patients. *Geriatrics Today: J Can Geriatr Soc.* 2004;7:6–9.

60. Fellowes D, Wilkinson S, Moore P. Communication skills training for health care professionals working with cancer patients, their families and/or careers. *Cochrane Database of Syst Rev.* 2004;2:CD003751.

61. Clayton JM, Butow PN, Tattersall MH, et al. Randomized controlled trial of a prompt list to help advanced cancer patients and their caregivers to ask questions about prognosis and end-of-life care. *J Clin Oncol.* 2007;25:715–723.

62. Jezewski MA, Meeker MA, Sessanna L, et al. The effectiveness of interventions to increase advance directive completion rates. *J Aging Health.* 2007;19:519–536.

63. Ramsaroop SD, Reid MC, Adelman RD. Completing an advance directive in the primary care setting: what do we need for success? *J Am Geriatr Soc.* 2007;55:277–283.

64. Elbogen EB, Swanson JW, Appelbaum PS, et al. Competence to complete psychiatric advance directives: effects of facilitated decision making. *Law & Hum Behav.* 2007;31:275–289.

65. Sudore RLL. An advance directive redesigned to meet the literacy level of most adults: A randomized trial. *Patient Educ Couns.* 2007;69:165–195.

66. Nicolasora N, Pannala R, Mountantonakis S, et al. If asked, hospitalized patients will choose whether to receive life-sustaining therapies. *J Hosp Med.* 2006;1:161–167.

67. Hammes BJ, Briggs LA. Initiating, facilitating, and honoring conversations about future medical care. In: Doka KJ, Jennings B, Corr CA, eds. Ethical dilemmas at the end of life. Washington, DC: Hospice Foundation of America; 2005:125–138.

68. Schmidt TA, Hickman SE, Tolle SW, et al. The Physician Orders for Life-Sustaining Treatment (POLST) program: Oregon emergency medical technicians' practical experiences and attitudes. *J Am Geriatr Soc.* 2004;52:1430–1434.

69. Lemiengre J, de Casterlé BD, Van Craen K, et al. Institutional ethics policies on medical end-of-life decisions; a literature review. *Health Policy.* 2007;83:131–143.

70. Morss S. Enteral and parenteral nutrition in terminally ill cancer patients: a review of the literature. Am J Hosp Palliat Med. 2006;23:369–377.

71. Zimmermann D, Riechelmann R, Krzyzanowska M, et al. Effectiveness of specialized palliative care: a systematic review. *JAMA.* 2008;299:1698–1709.

72. Brandsen CK. Social work and end-of-life care: reviewing the past and moving forward. *J Soc Work End Life Palliat Care.* 2005;1:45–70.

73. Casarett DJ, Quill TE. "I'm not ready for hospice": strategies for timely and effective hospice discussions. *Ann Intern Med.* 2007;146:443–449.

74. Wilson DM, Justice C, Thomas R, et al. End-of-life care volunteers: a systematic review of the literature. *Health Serv Manage Res.* 2005;18:244–257.

75. Au D, Udris E, Fihn S, et al. Differences in health care utilization at the end of life among patients with chronic obstructive pulmonary disease and patients with lung cancer. *Arch Intern Med.* 2006;166:326–331.

76. Saxby C, Ackroyd R, Callin S, et al. How should we measure emesis in palliative care? *Palliative Med.* 2007;21:369–383.

77. Nekolaichuk C, Watanabe S, Beaumont C. The Edmonton Symptom Assessment System: a 15-year retrospective review of validation studies (1991–2006). *Palliat Med.* 2008;22:111–122.

78. Tranmer JE, Heyland D, Dudgeon D, et al. Measuring the symptom experience of seriously ill cancer and noncancer hospitalized patients near the end of life with the memorial symptom assessment scale. *J Pain Symptom Manage.* 2003;25:420–429.

79. TIME: Toolkit of instruments to measure end-of-life care. About the Toolkit. 2004. Available at: http://www.chcr.brown.edu/pcoc/toolkit.htm. Accessed on: May 10, 2008.

80. Mularski RA, Dy SM, Shugarman LR, et al. A systematic review of measures of end-of-life care and its outcomes. *Health Services Res.* 2007;42:1848–1870.

81. City of Hope Pain and Palliative Care Resource Center. 2008. Available at: http://www.cityofhope.org/prc/. Accessed on: May 10, 2008.

82. Lorenz KA, Lynn J. Cancer care quality measures: symptoms and end of life care. *Evidence Report/Technology Assessment.* 2006;137:1–77.

83. Teunissen SCCM, Wesker W, Kruitwagen C, et al. Symptom prevalence in patients with incurable cancer: a systematic review. *J Pain Symptom Manage.* 2007;34:94–104.

84. Solano JP, Gomes B, Higginson IJ. A comparison of symptom prevalence in far advanced cancer, AIDS, heart failure, chronic obstructive pulmonary disease, and renal disease. *J Pain Symptom Manage.* 2006;31:58–69.

85. Holen JC, Polit C, Hjermstad MJ, et al. Pain assessment tools: is the content appropriate for use in palliative care? *J Pain Symptom Manage.* 2006;32:567–580.

86. TIME: Toolkit of instruments to measure end-of-life care. Pain and physical symptoms. 2004. Available at: http://www.chcr.brown.edu/pcoc/Physical.htm. Accessed on: May 10, 2008.

87. Pautex S, Herrmann F, Le Lous P, et al. Feasibility and reliability of four pain self-assessment scales and correlation with an observational rating scale in hospitalized elderly demented patients. *J Gerontol A Biol Sci Med Sci.* 2005;60A:524–529.

88. City of Hope. Pain and symptom management: Pain assessment tools. 2008. Available at http://www.cityofhope.org/prc/pain_assessment.asp. Accessed on: May 10, 2008.

89. Pace MC, Passavanti MB, Grella E. Buprenorphine in long-term control of chronic pain in cancer patients. *Front Biosci.* 2007;12:1291–1299.

90. Quigley C. The role of opioids in cancer pain. *BMJ.* 2005;331:825–829.

91. Fine PG. The evolving and important role of anesthesiology in palliative care. *Anesth Analg.* 2005;100:183–188.

92. Marinangeli F, Ciccozzi A, Leonardis M. Use of strong opioids in advanced cancer pain: a randomised trial. *J Pain Symptom Manage.* 2004;27:409–416.

93. Wiffen PJ, McQuay HJ. Oral morphine for cancer pain. *Cochrane Database Syst Rev.* 2007;4:CD003868.

94. Quigley C. Opioids in people with cancer-related pain. *BMJ Clinical Evidence* 2008 (in press).

95. Davis MP, Weissman DE, Arnold RM. Opioid dose titration for severe cancer pain: A systematic evidence-based review. *J Palliative Med.* 2004;7:462–468.

96. Zeppetella G, Ribeiro MDC. Opioids for the management of breakthrough pain in cancer patients. *Cochrane Database Syst Rev.* 2006;1:CD004311.

97. Slatkin NE, Xie F, Messina J, et al. Fentanyl buccal tablet for relief of breakthrough pain in opioid-tolerant patients with cancer-related chronic pain. *J Support Oncol.* 2007;5:327–334.

98. FDA. FDA warns of potential serious side effects with breakthrough cancer pain drug. 2007. Available at http://www.fda.gov/bbs/topics/NEWS/2007/NEW01711.html. Accessed on: May 10, 2008.

99. Anderson SL, Shreve ST. Continuous subcutaneous infusion of opiates at end-of-life. *Ann Pharmacother.* 2004;38:1015–1023.

100. Ballantyne JC, Carwood CM. Comparative efficacy of epidural, subarachnoid, and intracerebroventricular opioids in patients with pain due to cancer. *Cochrane Database Syst Rev.* 2005;2:CD005178.

101. Grosset AB, Roberts MS, Woodson ME, et al. Comparative efficacy of oral extended-release hydromorphone and immediate-release hydromorphone

in patients with persistent moderate to severe pain: two randomized controlled trials. *J Pain Symptom Manage.* 2005;29:584–594.

102. Reid CMM. Oxycodone for cancer-related pain: Meta-analysis of randomized controlled trials. *Arch Intern Med.* 2006;166:837–843.

103. Nicholson AB. Methadone for cancer pain. *Cochrane Database Syst Rev.* 2007;4:CD003971.

104. McNicol E, Strassels SA, Goudas L, et al. NSAIDS or paracetamol, alone or combined with opioids, for cancer pain. *Cochrane Database Syst Rev.* 2005;2:CD005180.

105. Gøtzsche P. NSAIDs. *BMJ Clinical Evidence.* 2007. Available at: http://clinicalevidence.bmj.com/ceweb/conditions/msd/1108/1108.jsp. Accessed on: May 10, 2008.

106. Mercadante S, Fulfaro F, Casuccio A. A randomised controlled study on the use of anti-inflammatory drugs in patients with cancer pain on morphine therapy: effects on dose-escalation and a pharmacoeconomic analysis. *Eur J Cancer.* 2002;38:1358–1363.

107. Axelsson B, Borup S. Is there an additive analgesic effect of paracetamol at step 3? A double-blind randomized controlled study. *Palliative Med.* 2003;17:724–725.

108. Rodriguez RF, Castillo JM, Del Pilar Castillo M. Codeine/acetaminophen and hydrocodone/acetaminophen combination tablets for the management of chronic cancer pain in adults: a 23-day, prospective, double-blind, randomized, parallel-group study. *Clin Therapeutics.* 2007;29:581–587.

109. Gooch K, Culleton BF, Manns BJ, et al. NSAID use and progression of chronic kidney disease. *Am J Med* 2007;120:280.e1–7.

110. Mercadante SL, Berchovich M, Casuccio A. A prospective randomized study of corticosteroids as adjuvant drugs to opioids in advanced cancer patients. *Am J Hosp Palliat Care.* 2007;24:13–19.

111. Bell RF, Eccleston C, Kalso E. Ketamine as an adjuvant to opioids for cancer pain. J Pain Symptom Manage. 2003;26:867–875.

112. Yan BM, Myers RP. Neurolytic celiac plexus block for pain control in unresectable pancreatic cancer. *Am J Gastroenterol.* 2007;102:430–438.

113. Süleyman Ozyalçin N, Talu GK, Camlica H, et al. Efficacy of coeliac plexus and splanchnic nerve blockades in body and tail located pancreatic cancer pain. *Eur J Pain.* 2004;8:539–545.

114. Saarto T, Wiffen PJ. Antidepressants for neuropathic pain. *Cochrane Database Syst Rev.* 2007;4:CD005454.

115. Finnerup NB, Otto M, Jensen TS, et al. An evidence-based algorithm for the treatment of neuropathic pain. Med Gen Med. 2007; 9: 36.

116. Wiffen PJ, Rees J. Lamotrigine for acute and chronic pain. *Cochrane Database Syst Rev.* 2007;2:CD006044.

117. Keskinbora K, Pekel AF, Aydinli I. Gabapentin and an opioid combination versus opioid alone for the management of neuropathic cancer pain: a randomized open trial. *J Pain Symptom Manage.* 2007;34:183–189.

118. Eisenberg E, McNicol E, Carr DB. Opioids for neuropathic pain. *Cochrane Database Syst Rev.* 2006;3:CD006146.

119. Hans G. Buprenorphine: a review of its role in neuropathic pain. *J Opioid Manage.* 2007;3:195–206.

120. Challapalli V, Tremont-Lukats IW, McNicol ED. Systemic administration of local anesthetic agents to relieve neuropathic pain. *Cochrane Database Syst Rev.* 2005;4:CD003345.

121. Mailis-Gagnon A, Furlan AD, Sandoval JA, et al. Spinal cord stimulation for chronic pain. *Cochrane Database Syst Rev.* 2004:3:CD003783.

122. Devine EC, Westlake SK. The effects of psychoeducational care provided to adults with cancer: meta-analysis of 116 studies. *Oncol Nurs Forum.* 1995;22:1369–1381.

123. Dalton JA, Keefe FJ, Carlson J, et al. Tailoring cognitive-behavioral treatment for cancer pain. *Pain Management Nursing.* 2004;5:3–18.

124. Given C, Given B, Rahbar M, et al. Effect of a cognitive behavioral intervention on reducing symptom severity during chemotherapy. *J Clin Oncol.* 2004;22:507–516. Available at: http://jco.ascopubs.org/cgi/content/full/22/3/507?ck=nck. Accessed on: May 10, 2008.

125. Tatrow K, Montgomery GH. Cognitive behavioral therapy techniques for distress and pain in breast cancer patients: a meta-analysis. *J Behavioral Med.* 2006;29:17–27.

126. McDonald MV, Pezzin LE, Feldman PH, et al. Can just in time, evidence-based "reminders" improve pain management among home health care nurses and their patients? *J Pain Symptom Manage.* 2005;29:474–488.

127. Dy GK, Bekele L, Hanson LJ, et al. Complementary and alternative medicine use by patients enrolled onto phase I clinical trials. *J Clin Oncol.* 2004;22:4810–4815. Erratum in: *J Clin Oncol.* 2005;23:248.

128. Hlubocky FJ, Ratain MJ, Wen M, et al. Complementary and alternative medicine among advanced cancer patients enrolled on phase I trials: a study of prognosis, quality of life, and preferences for decision making. *J Clin Oncol.* 2007;25:548–554.

129. Fellowes D, Barnes K, Wilkinson S. Aromatherapy and massage for symptom relief in patients with cancer. *Cochrane Database Syst Rev.* 2004;3:CD002287.

130. Bardia A, Barton DL, Prokop LJ, et al. Efficacy of complementary and alternative medicine therapies in relieving cancer pain: a systematic review. *J Clin Oncol.* 2006;24:5457–5464.

131. Stephenson NL, Swanson M, Dalton J, et al. Partner-delivered reflexology: effects on cancer pain and anxiety. *Oncol Nurs Forum*. 2007;34:127–132. Available at: http://ons.metapress.com/content/k477114620185x62/fulltext. html. Accessed on: May 10, 2008.

132. Tsai PS, Chen PL, Lai YL, et al. Effects of electromyography biofeedback-assisted relaxation on pain in patients with advanced cancer in a palliative care unit. *Cancer Nurs.* 2007;30:347–353.

133. Xu L, Lao LX, Ge A, et al. Chinese herbal medicine for cancer pain. *Integrative Cancer Ther.* 2007;6:208–234.

134. Finlay I, Mason M, Shelley M. Radioisotopes for the palliation of metastatic bone cancer: a systematic review. *Lancet Oncol.* 2005;6:392–400.

135. Serafini AN. Therapy of metastatic bone pain. *J Nuclear Med.* 2001;42:895–906.

136. Mystakidou K, Katsouda E, Kouloulias V, et al. Comparison of transdermal fentanyl with codeine/paracetamol, in combination with radiotherapy, for the management of metastatic bone pain. *J Opioid Manage.* 2005;1:204–210.

137. Chow E, Harris K, Fan G, et al. Palliative radiotherapy trials for bone metastases: a systematic review. *J Clin Oncol.* 2007;25:1423–1436.

138. Bauman G, Charette M, Reid R, et al. Radiopharmaceuticals for the palliation of of painful metastasis: a systematic review. *Radiotherapy Oncol.* 2005;75:258–270.

139. Wong R, Wiffen PJ. Bisphosphonates for the relief of pain secondary to bone metastases. *Cochrane Database of Syst Rev.* 2002;2:CD002068.

140. Diel IJ, BodyJJ, Lichinitser MR, et al. Improved quality of life after long-term cancer treatment with the biphosphonate ibandronate in patients with metastatic bone disease due to breast cancer. *Eur J Cancer.* 2004;40;1704–1712.

141. Yuen KK, Shelley M, Sze WM, et al. Biphosphonates for advanced prostate cancer. *Cochrane Database Syst Rev. 2*006;4:CD006250.

142. Liapi E, Geschwind JF. Transcatheter and ablative therapeutic approaches for solid malignancies. *J Clin Oncol.* 2007;25:978–986.

143. Goetz MP, Callstrom MR, Charboneau JW, et al. Percutaneous image-guided radiofrequency ablation of painful metastases involving bone: a multicenter study. *J Clin Oncol.* 2004;22:300–306.

144. Wood RND. Encyclopedia of cancer: calcitonin. Available at: http://findarticles.com/p/articles/mi_gGEC/is_0010/ai_2699001073. Accessed on: May 10, 2008.

145. Martinez-Zapata MJ, Roque M, Alonso Coello P, et al. Calcitonin for metastatic bone pain. *Cochrane Database Syst Rev.* 2006;3:CD003223.

146. Kalso E, Edwards JE, Moore RA, et al. Opioids in chronic non-cancer pain: a systematic review of efficacy and safety. *Pain.* 2004;112:372–380.

147. Booth S, Wade R, Johnson M, et al. The use of oxygen in the palliation of breathlessness. A report of the expert working group of the Scientific Committee of the Association of Palliative Medicine; Expert Working Group of the Scientific Committee of the Association of Palliative *Medicine Respir Med.* 2004;98:66–77.

148. Roberts DK, Thorne SE, Pearson C. The experience of dyspnea in late-stage cancer. Patients and nurses' perspectives. *Cancer Nurs.* 1993;16:310–320.

149. Dorman S, Byrne A, Edwards A. Which measurement scales should we use to measure breathlessness in palliative care? A systematic review. *Palliat Med.* 2007;21:177–191.

150. Bausewein C, Farquhar M, Booth S, et al. Measurement of breathlessness in advanced disease: a systematic review. *Resp Med.* 2007;101:399–410.

151. Bruera E, Sweeney C, Willey J, et al. A randomized controlled trial of supplemental oxygen versus air in cancer patients with dyspnea. *Palliat Med.* 2003;17:659–663.

152. Gallagher R, Roberts DA. Systematic review of oxygen and airflow effect on relief of dyspnea at rest in patients with advanced disease of any cause. *J Pain Palliat Care Pharmacother.* 2004;18:3–15.

153. Booth S, Moosavi SH, Higginson IJ. The etiology and management of intractable breathlessness in patients with advanced cancer: a systematic review of pharmacological therapy. *Nat Clin Pract Oncol.* 2008;5:90–100.

154. Jennings AL, Davies AN, Higgins JP, et al. A systematic review of the use of opioids in the management of dyspnoea. *Thorax.* 2002;57:939–944.

155. Abernethy AP, Currow DC, Frith P, et al. Randomised double blind controlled crossover trial of sustained release morphine for the management of refractory dyspnoea. *BMJ.* 2003;327:523–528.

156. Navigante AH, Cerchietti LCA, Castro MA, et al. Midazolam as adjunct therapy to morphine in the alleviation of severe dyspnea perception in patients with advanced cancer. *J Pain Symptom Manage.* 2006;31:38–47.

157. Salman GF, Mosier MC, Beasley BW, et al. Rehabilitation for patients with chronic obstructive pulmonary disease: meta-analysis of randomized controlled trials. *J Gen Intern Med.* 2003;18:213–221.

158. Pan CX, Morrison RS, Ness J, et al. Complementary and alternative medicine in the management of pain, dyspnea, and nausea and vomiting near the end of life. A systematic review. *J Pain Symptom Manage.* 2000;20:374–387.

159. Lewith GT, Prescott P, Davis CL. Can a standardised acupuncture technique palliate disabling breathlessness: a single-blind, placebo controlled crossover study. *Chest.* 2004;125:1783–1790.

160. Vickers AJF. Acupuncture for dyspnea in advanced cancer: a randomized, placebo-controlled pilot trial [ISRCTN89462491]. *BMC Palliative Care.* 2005;4:5.

161. Lester JF, Macbeth FR, Toy E, et al. Palliative radiotherapy regimens for non small cell lung cancer. *Cochrane Database Syst Rev.* 2006;4:CD002143.

162. Lutz S, Chow E, Hartsell A, et al. A review of hypofractionated palliative radiotherapy. *Cancer.* 2007;109:1462–1470.

163. Ung YC, Yu E, Falkson C, et al. The role of radiation therapy in malignant pleural mesothelioma: A systematic review. *Radiotherapy Oncol.* 2006;80:13–18.

164. Shaw P, Agarwal R. Pleurodesis for malignant pleural effusions. *Cochrane Database Syst Rev.* 2004;1:CD002916.

165. Ukale V, Agrenius V, Hillerdal G, et al. Pleurodesis in recurrent pleural effusions: a randomized comparison of a classical and a currently popular drug. *Lung Cancer.* 2004;43:323–328.

166. Goodman A, Davies CW. Efficacy of short-term versus long-term chest tube drainage following talc slurry pleurodesis in patients with malignant pleural effusions: a randomised trial. *Lung Cancer.* 2006;54:51–55.

167. Dresler CM, Olak J, Herndon JE, et al. Phase III intergroup study of talc poudrage vs talc slurry sclerosis for malignant pleural effusion. *Chest.* 2005;127:909–915.

168. Crnjac A, Sok M, Kamenik M. Impact of pleural effusion pH on the efficacy of thoracoscopic mechanical pleurodesis in patients with breast carcinoma. *Eur J Cardiothoracic Surg.* 2004;26:432–436.

169. Sartori S, Tassinari D, Ceccotti P, et al. Prospective randomized trial of intrapleural bleomycin versus interferon alfa-2b via ultrasound-guided small-bore chest tube in the palliative treatment of malignant pleural effusions. *J Clin Oncol.* 2004;22:1228–1233.

170. Mota DDCF, Pimenta CAM. Self-report instruments for fatigue assessment: a systematic review. *Res Theory Nurs Pract.* 2006;20:49–78.

171. Mitchell SA, Berger AM. Cancer-related fatigue: the evidence base for assessment and management. *Cancer J.* 2006;12:374–387.

172. Prue G, Rankin J, Allen J, et al. Cancer-related fatigue: a critical appraisal. *Eur J Cancer.* 2006;42:846–863.

173. Jacobsen PB, Donovan KA, Vadaparampil ST, et al. Systematic review and meta-analysis of psychological and activity-based interventions for cancer-related fatigue. *Health Psychol.* 2007;26:660–667.

174. Ream E, Richarson A, Dann C. Supportive intervention for fatigue in patients undergoing chemotherapy: a randomized controlled trial. *J Pain Symptom Manage.* 2006;31:148–161.

175. Cramp F, Daniel J. Exercise for the management of cancer-related fatigue in adults. *Cochrane Database Syst Rev.* 2008:2:CD006145.

176. Lee MS, Pittler MH, Ernst E. Is Tai Chi an effective adjunct in cancer care? A systematic review of controlled clinical trials. *Supportive Care in Cancer.* 2007:15:597–601.

177. Lee MS, Chen KW, Sancier KM, et al. Quigong for cancer treatment: a systematic review of controlled clinical trials. *Acta Oncologica.* 2007;46:717–722.

178. Radbruch L, Strasser F, Elsner F, et al. and the Research Steering Committee of the European Association for Palliative Care (EAPC). Fatigue in palliative care patients—an EAPC approach. *Palliat Med.* 2008;22:13–32.

179. Minton O, Stone P, Richardson A, et al. Drug therapy for the management of cancer related fatigue. Cochrane Database Syst Rev. 2008;1:CD006704.

180. Butler JM Jr, Case LD, Atkins J, et al. A phase III double-blind, placebo-controlled prospective randomized clinical trial of d-threo-methylphenidate HCL in brain tumor patients receiving radiation therapy. *Int J Radiat Oncol Biol Phys.* 2007;69:1496–1501.

181. FDA. Ritalin LA. 2007. Available at: http://www.fda.gov/medwatch/safety/2007/Apr_PI/RitalinLA_PI.pdf. Accessed on: May 10, 2008.

182. Sood A, Barton DL, Bauer BA, et al. A critical review of complementary therapies for cancer-related fatigue. *Integr Cancer Ther.* 2007;6:8–13.

183. FDA. Additional trials showing increased mortality and/or tumor progression with EPOGEN®/PROCRIT® and Aranesp®. 2008. Available at: http://www.fda.gov/medwatch/safety/2008/epo_DHCP_03102008.pdf. Accessed on: May 10, 2008.

184. Berger AM, Sankaranarayanan J, Watanabe-Galloway S, et al. Current methodological approaches to the study of sleep disturbances and quality of life in adults with cancer: a systematic review. *Psycho-Oncology.* 2007;16:401–420.

185. Savard J, Simard S, Ivers H. et al. Randomized study on the efficacy of

cognitive-behavioral therapy for insomnia secondary to breast cancer, part I: sleep and psychological effects. *J Clin Oncol.* 2005;23:6083–6096.

186. Block SD, Block SD. Psychological issues in end-of-life care. *J Palliative Med.* 2006;9:751–772.

187. Ryan H, Schofield P, Cockburn J, et al. How to recognize and manage psychological distress in cancer patients. *Eur J Cancer Care.* 2005;14:7–15.

188. Jackson KC, Lipman AG. Drug therapy for anxiety in palliative care. *Cochrane Database Syst Rev.* 2004;1:CD004596.

189. Rodin G, Lloyd N, Katz M, et al. The treatment of depression in cancer patients: a systematic review. *Supportive Care in Cancer.* 2007;15:123–136.

190. Stockler MR, O'Connell R, Nowak AK, et al. Effect of sertraline on symptoms and survival in patients with advanced cancer, but without major depression: a placebo-controlled double-blind randomised trial. *Lancet Oncol.* 2007;8:603–612.

191. Lacasse Y, Beaudoin L, Rousseau L, et al. Randomized trial of paroxetine in end-stage COPD. *Arch Chest Dis.* 2004;61:140–147.

192. Uitterhoeve RJ, Vernooy M, Litjens M, et al. Psychosocial interventions for patients with advanced cancer – A systematic review of the literature. *Br J Cancer.* 2004;91:1050–1062.

193. Sherwood P, Given BA, Given CW, et al. A cognitive behavioral intervention for symptom management in patients with advanced cancer. *Oncol Nurs Forum.* 2005;32:1190–1198.

194. Savard J, Simard S, Giguere I, et al. Randomized clinical trial on cognitive therapy for depression in women with metastatic breast cancer: psychological and immunological effects. *Palliative Supportive Care.* 2006;4:219–237.

195. Smith JE, Richardson J, Hoffman C, et al. Mindfulness-Based Stress Reduction as supportive therapy in cancer care: systematic review. *J Adv Nurs.* 2005;52:315–327.

196. Monti DA, Peterson C, Kunkel EJ, et al. A randomized, controlled trial of mindfulness-based art therapy (MBAT) for women with cancer. *Psycho-Oncology.* 2006;15:363–373.

197. Thomas R, Wilson D. Randomized controlled trials of non-medical and non-surgical therapies for palliative care: a literature review. *Alt Med Rev.* 2005;10:204–215.

198. Wilkinson SM, Love SB, Westcombe AM, et al. Effectiveness of aromatherapy massage in the management of anxiety and depression in patients with cancer: a multicenter randomized controlled trial. *J Clin Oncol.* 2007;25:532–539.

199. Wilcock A, Manderson C, Weller R, et al. Does aromatherapy massage benefit patients with cancer attending a specialist palliative care day centre? *Palliat Med.* 2004;18:287–290.

200. Williams AL, Selwyn PA, Liberti L, et al. A randomized controlled trial of meditation and massage effects on quality of life in people with late-stage disease: a pilot study. *J Palliative Med.* 2005;8:939–952.

201. Soden K, Vincent K, Craske S, et al. A randomized controlled trial of aromatherapy massage in a hospice setting. *Palliat Med.* 2004;18:87–92.

202. Hilliard RE. Music therapy in hospice and palliative care: a review of the empirical data. *Evid Based Complement Alternat Med.* 2005;2:173–178.

203. Dileo C. Effects of music and music therapy on medical patients: A meta-analysis of the research and implications for the future. *J Soc Integrative Oncol.* 2006;4:67–70.

204. Hanser SB, Bauer Wu S, Kubicek L, et al. Effects of a music therapy intervention on quality of life and distress in women with metastatic breast cancer. *J Soc Integrative Oncol.* 2006;4:116–124.

205. Stephenson NL, Swanson M, Dalton J, et al. Partner-delivered reflexology: effects on cancer pain and anxiety. *Oncol Nurs Forum.* 2007;34:127–132.

206. Milazzo S, Russell N, Ernst E. Efficacy of homeopathic therapy in cancer treatment. *Eur J Cancer.* 2006;42:282–289.

207. Roffe L, Schmidt K, Ernst E. A systematic review of guided imagery as an adjuvant cancer therapy. *Psychooncology.* 2005;14:607–617.

208. Cruickshank S, Kennedy C, Lockhart K, et al. Specialist breast care nurses for supportive care of women with breast cancer. *Cochrane Database Syst Rev.* 2008;1: CD005634.

209. Young J, Inouye SK. Delirium in older people. *BMJ.* 2007;334:842–846.

210. Leslie DL, Zhang Y, Holford TR, et al. Premature death associated with delirium at 1-year follow-up. *Arch Intern Med.* 2005;165:1657–1662.

211. Caraceni A, Nanni O, Maltoni M, et al. Impact of delirium on the short term prognosis of advanced cancer patients. *Cancer.* 2000;89:1145–1149.

212. Bruera E, Miller L, McCallion J, et al. Cognitive failure in patients with terminal cancer: a prospective study. *J Pain Symptom Manage.* 1992;7:192–195.

213. Centeno C, Sanz Á, Bruera E. Delirium in advanced cancer patients. Palliat Med. 2004;18:184–194.

214. Inouye SK, van Dyck CH, Alessi CA, et al. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. *Ann Intern Med.* 1990;113:941–948.

215. Breitbart W, Rosenfeld B, Roth A, et al. The Memorial Delirium Assessment Scale. *JPSM.* 1997;13:128–137.

216. Inouye SK. A multicomponent intervention to prevent delirium in hospitalized older patients. *N Engl J Med.* 1999;340;669–676.

217. Inouye SK, Bogardus ST, Baker DI, et al. The hospital elder life program: a model of care to prevent cognitive and functional decline in hospitalized older patients. *J Am Geriatr Soc.* 2000:48:1697–1706.

218. Quigley C. Opioid switching to improve pain relief and drug tolerability. *Cochrane Database Syst Rev.* 2004:3:CD004847.

219. Mercadante S, Bruera E. Opioid switching: a systematic and critical review. *Cancer Treat Rev.* 2006;32:304–315.

220. Indelicato RA, Portenoy RK. Opioid rotation in the management of refractory cancer pain. *J Clin Oncol.* 2002;20:348–352.

221. Michaud L, Büla C, Berney A, et al. Delirium: Guidelines for general hospitals. *J Psychosomatic Res.* 2007;62:371–383.

222. Lonergan E, Britton AM, Luxenberg J, et al. Antipsychotics for delirium. *Cochrane Database Syst Rev.* 2007;2:CD005594.

223. Warner J, Butler R, Wuntakal B. Dementia. *BMJ Clinical Evidence.* 2006. Available at: http://clinicalevidence.bmj.com/ceweb/conditions/meh/1001/1001.jsp. Accessed on: May 10, 2008.

224. Wooltorton E. Risperidone(Risperdal):Increased rate of cerebrovascular events in dementia trials. *CMAJ.* 2002;167:1269–1270.

225. Wooltorton E. Olanzapine (Zyprexa): Increased incidence of cerebrovascular events in clinical trials. *CMAJ.* 2004;170:1395.

226. FDA. Atypical antipsychotic drugs information. 2006. Available at: http://www.fda.gov/cder/drug/infopage/antipsychotics/default.htm. Accessed on: May 10, 2008.

227. Jackson KC, Lipman AG. Drug therapy for delirium in terminally ill patients. *Cochrane Database Syst Rev.* 2004;2:CD004770.

228. Breitbart W, Rocco M, Platt MM, et al. A double-blind of haloperidol, chlorpromazine, and lorazepam in the treatment of delirium in hospitalized AIDS patients. *Am J Psychiatry.* 1996;153:231–237.

229. Yavuzsen T, Davis MP, Walsh D, et al. Systematic review of the treatment of cancer-associated anorexia and weight loss. *J Clin Oncol.* 2005;23:8500–8511.

230. Couch M, Lai V, Cannon T, et al. Cancer cachexia syndrome in head and neck cancer patients: part I. Diagnosis, impact on quality of life and survival, and treatment. *Head Neck.* 2007;29:401–411.

231. Moses AW, Slater C, Preston T, et al. Reduced total energy expenditure and physical activity in cachectic patients with pancreatic cancer can be modulated by an energy and protein dense oral supplement enriched with n-3 fatty acids. *Br J Cancer.* 2004;90:996–1002.

232. Berenstein EG, Ortiz Z. Megestrol acetate for treatment of anorexia-cachexia syndrome. *Cochrane Database Syst Rev.* 2005;2:CD004310.

233. Bodenner D, Spencer T, Riggs AT, et al. A retrospective study of the association between megestrol acetate administration and mortality among nursing home residents with clinically significant weight loss. *Am J Geriatr Pharmacother.* 2007;5:137–146.

234. Koretz RL, Avenell A, Lipman TO, et al. Does enteral nutrition affect clinical outcome? A systematic review of the randomized trials. *Am J Gastroenterol.* 2007;102:412–429.

235. Shang E, Weiss C, Post S, et al. The influence of early supplementation of parenteral nutrition on quality of life and body composition in patients with advanced cancer. *J Parenteral Enteral Nutr.* 2006; 30:222–230.

236. Lundholm K, Daneryd P, Bosaeus I, et al. Palliative nutritional intervention in addition to cyclooxygenase and erythropoietin treatment for patients with malignant disease: effects on survival, metabolism, and function. *Cancer.* 2004;100:1967–1977.

237. Lanuke K, Fainsinger RL. Hydration management in palliative care settings: a survey of experts. *J Palliat Care* 2003;19:278–279.

238. McCann RM, Hall WJ, Groth-Juncker A. Comfort care for terminally ill patients. The appropriate use of nutrition and hydration. *JAMA.* 1994;272:1263–1266.

239. van der Riet P, Good P, Higgins I, et al. Palliative care professionals' perceptions of nutrition and hydration at the end of life. *Int J Palliat Nurs.* 2008;14:145–151.

240. Morita T, Tei Y, Tsunoda J, et al. Determinants of the sensation of thirst in terminally ill cancer patients. *Support Care Cancer.* 2001;9:177–186.

241. Good P, Cavenagh J, Mather M, et al. Medically assisted hydration for palliative care patients. *Cochrane Database Syst Rev.* 2008:2:CD006273.

242. Grunberg SM. Antiemetic activity of corticosteroids in patients receiving cancer chemotherapy: dosing, efficacy, and tolerability analysis. *Ann Oncol.* 2007;18:233–240.

243. Hallenbeck J. Fast fact and concepts #5: causes of nausea and vomiting. 2005. Available at: http://www.eperc.mcw.edu/fastFact/ff_005.htm. Accessed on: May 10, 2008.

244. Clemens KE, Klaschik E. Managing nausea, emesis, and constipation in palliative care. *Dtsch Arztebl.* 2007;104:A269-A278.

245. Pancha SJ, Muller-Schwefe J, Wurzelmann JI. Opioid-induced bowel dysfunction: prevalence, pathophysiology and burden. *J Clin Pract.* 2007;61:1181–1187.

246. Miles CL, Fellowes D, Goodman ML, et al. Laxatives for the management of constipation in palliative care patients. *Cochrane Database Syst Rev.* 2006:4:CD003448.

247. Ramesh P, Suresh Kumar K, Rajagopal M, et al. Managing morphine-induced constipation: a controlled comparison of the ayurvedic formulation and senna. *J Pain Symptom Manage.* 1998;16:240–244.

248. Hurdon V, Viola R, Schroder C. How useful is ducosate in patients at risk for constipation? A systematic review of the evidence in the chronically ill. *J Pain Symptom Manage.* 2000;19:130–136.

249. Ohlen K. The effect of polyethylene glycol in chronic constipation is not sufficiently evaluated. A systematic literature review. *Lakartidningen.* 2004;101:2568–2572.

250. Van Der Spoel JIO, Zandstra DFV. Laxation of critically ill patients with lactulose or polyethylene glycol: A two-center randomized, double-blind, placebo-controlled trial. *Crit Care Med.* 2007;35:2726–2731.

251. Mendoza J, Legido J, Rubio S, et al. Systematic review: The adverse effects of sodium phosphate enema. Aliment Pharmacol Ther*.. 2007:26:9–20.

252. Becker G, Galandi F, Blum HE. Peripherally acting opioid antagonists in the treatment of opiate-related constipation: a systematic review. *J Pain Symptom Manage.* 2007;34:547–565.

253. Yuan CS. Methylnaltrexone mechanisms of action and effects on opioid bowel dysfunction and other opioid adverse effects. *Ann Pharmacother.* 2007;41:984–993.

254. FDA. FDA approves Relistor for opioid-induced constipation. 2008. Available at: http://www.fda.gov/bbs/topics/NEWS/2008/NEW01826.html. Accessed on: May 15, 2008.

255. Morrison RS, Meier DE. Palliative care. *N Engl J Med.* 2004;350:2582–2590.

256. Arnold R, Back T. Discussing prognosis. *J Clin Oncol.* 2006;24:4209–4213. Available at: http://www.jco.ascopubs.org/cgi/content/full/24/25/4209. Accessed on: May 10, 2008.

257. Bruera E, Palmer JL, Pace E, et al. A randomized, controlled trial of physician postures when breaking bad news to cancer patients. *Palliat Med.* 2007;21:501–505.

258. Strasser F, Palmer JL, Willey J, et al. Impact of physician sitting versus standing during inpatient oncology consultations: patients' preference and

perception of compassion and duration. A randomized controlled trial. J Pain Symptom Manage. 2005;29:489–497.

259. Schofield P, Carey M, Love A, et al. 'Would you like to talk about your future treatment options'? Discussing the transition from curative cancer treatment to palliative care. *Palliat Med.* 2006;20:397–406.

APPENDIX A: METHODOLOGY

In this paper, we present the results of a systematic review (SR) on the effectiveness of palliative care interventions among adults. For the searches and literature appraisal, we adapted the search and appraisal methodology of *BMJ Clinical Evidence* reviews as described at http://www.clinicalevidence.com/ceweb/about/search_process.jsp. We included the best evidence available, focusing on SRs and randomized controlled trials (RCTs) for the effectiveness of interventions. We focused on studies conducted in a end-of-life context (indicated by for example, life expectancy less than 6 months, advanced cancer or terminal chronic disease). We extracted information from trials on the type and quality of evidence, study population, interventions, and reported results for our outcomes of interest (mainly quality-of-life or symptom-based clinical outcomes, not mortality/survival).

Our searches and the initial critical appraisal were conducted by an information specialist, and the second-round appraisal was performed by members of our editorial team. We eclipsed superseded SRs and studies identified by included SRs. The evidence syntheses on communication and symptom management were based on detailed evidence summaries provided by specifically trained editorial staff. The quality ratings of the evidence were based on the work of the GRADE working group, adapted from the method used for reviews on *BMJ Clinical Evidence* as described at http://clinicalevidence.bmj.com/ceweb/about/about-grade.jsp.

Challenges of conducting research in end-of-life care

There are particular challenges to conducting primary research in palliative care. These include difficulties in recruitment and retention in trials and a lack of funding for research in this area. We also found that some systematic reviews gave insufficient information on evidence synthesis for their methods to be reproducible. Despite this the evidence base is improving and we hope this report contributes to an understanding of the current state of research.

Our approach

Between December 2007 and February 2008, we searched the following databases to identify studies relevant to palliative/end-of-life care for this systematic review: MEDLINE and EMBASE; The Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Clinical Trials; the Database of Abstracts of Reviews of Effects (DARE), and the Health Technology Assessment (HTA) database. PsycINFO was also searched for citations on delirium. Results were limited to citations of SRs or RCTs published in English, German or Hungarian, with SR publication/RCT database entry dates from 2004. We chose a search date of 2004 as a cut-off point as we were building on the excellent work of the high-quality review on end-of-life care and outcomes prepared for the Agency for Healthcare Research and Quality.[1] We did not apply date or language restrictions for searches on opioids and cancer pain, constipation in people prescribed opioids, and delirium. For interventions

for constipation in people prescribed opioids, and for nausea and vomiting, we also carried out a search for prospective or retrospective cohort studies.

Search limitations

Date, language and search source restrictions as stated above limit the comprehensiveness of our search strategies.

One of the challenges of systematically searching for literature related to palliative/end-of-life care is the breadth of the field, which encompasses a variety of issues, specialties, conditions, symptoms, and interventions. Many of the search concepts of interest occur in the title/abstract/index terms of studies not related to palliative/end-of life care. In addition, literature on advanced stages of illness does not consistently use palliative/end-of-life related index terms, or include palliative/end-of-life related text words in the title or abstract. As our initial searches focused on studies where index terms and/or textwords indicated that content was or could be relevant to palliative/end-of-life care, we also carried out supplemental searches and extensive expert interviews.

As a result of these search limitations, we may not have identified all relevant citations.

APPENDIX B: TOOLKITS

Diane E. Meier, MD

David E. Weissman, MD FACP

1. Toolkit: Nine-step guide to optimizing palliative care in office practice

Goal: To assure high-quality palliative care in the outpatient environment

Palliative care focuses on the relief of suffering and support for best possible quality of life for patients with serious chronic illness and their families. It is offered simultaneously with all other appropriate life-prolonging or curative therapies. Palliative care, therefore, is not the same as hospice. Hospice is one form of intensive palliative care, supported by Medicare (and other insurers) and usually delivered at home, for patients with a prognosis of less than 6 months who have decided to give up curative or life-prolonging treatments.

The office setting is the optimal place to help patients maximize physical and psychological comfort, and explore values that can direct future medical care choices. All physicians should *provide primary palliative care*, and *identify resources for specialty-level palliative care* for more challenging problems. The following nine-step approach is aimed at the primary care provider (PCP) and outlines some key issues for primary palliative care.

Step 1: Identify chronic disease patients with palliative care needs

- ✔ Distressing pain or other physical/psychological symptoms

- ✔ Frequent hospitalizations or emergency room visits

- ✔ Weight loss

- ✔ Functional decline

- ✔ Spiritual or existential distress

- ✔ Exhausted/stressed family caregivers

Step 2: Assess and treat physical, psychological, and spiritual symptoms using standard tools

Many excellent tools exist that can be incorporated into standard clinic chart notes. See Resources (NPCRC) and individual sections within 4. Toolkit and Part 2. Evidence review: Symptom assessment and management.[255]

Step 3: Assess social/family system and identify at-risk caregivers

Care of the seriously ill patient places huge demands on the family and community. The PCP can best help by understanding the impact of the disease on the patient's family. See Resources (NPCRC).

Step 4: Help complete an advance care planning document

The most important task is to help the patient appoint a health care proxy or surrogate decision maker whom they trust and who can help make medical decisions for them in case of future loss of capacity.

A helpful practice is to have blank copies of state-sanctioned documents in the examination room to give to patients, along with enough support (e.g., trained office staff or patient education material) to help a patient complete the form. See Resources (POLST and Caring Connections).

Step 5: Coordinate medical opinions from consultants

Patients need their PCP to help them understand the often conflicting information about treatment choices and prognosis.

Step 6: Suggest and lead a patient-family meeting to discuss goals of care

See 2. Toolkit and section on Communication.

Step 7: When possible, provide prognostic information using ranges

See section on Prognostic accuracy and Arnold et al.[256]

Step 8: Make a timely referral for specialized palliative care and/or hospice services

PCPs should familiarize themselves with regional palliative care resources and the Medicare Hospice eligibility criteria. See Resources (NIPCR and MHB).

Step 9: Support families throughout the dying experience and during bereavement

A fear of many patients and family members is abandonment by their physician. Even though your patient may be receiving disease specific treatment from 1 or more subspecialists, maintaining routine contact and providing information and support will mitigate this fear for most patients and families.

2. Toolkit: Ten-step guide to conducting a meeting to establish goals of care

Goal: To assist seriously ill patients and their families with setting priorities for care

Establishing goals of care is a critical palliative care skill for the inpatient or outpatient setting. A successful meeting is more likely if key steps are completed, in the correct order. A 10-step process is outlined below.

Step 1: Pre-meeting planning

- **Review**   medical history, available treatment options, risks/benefits of treatments and prognostic information
- **Coordinate**   opinions among consultants
- **Ensure**   sufficient time is allocated for the meeting
- **Decide**   what is medically appropriate: what tests/procedures/interventions do you believe will improve or worsen function, longevity and quality of life?
- **Review**   Advance Directives documents
- **Determine**   who you wish to have present from the medical team and invite the family to bring whomever they wish to the meeting
- **Designate**   one person to serve as meeting leader
- **Assess**   decision-making capacity: a patient must be able to:
  - ✔ <u>Understand</u> information about diagnosis and treatment
  - ✔ <u>Evaluate</u> deliberate, weigh alternatives, compare risks and benefits
  - ✔ <u>Communicate</u> a choice verbally, in writing, or with a nod or gesture

Step 2: Environment

Find a quiet, private room. Two RCTs support giving bad news from a seated posture.[257,258]

Step 3: Introductions

Ask participants to introduce themselves and their relationship to the patient.

Step 4: Determine what the patient/family already knows

Suggested question: 'What is your understanding of your condition?'

Step 5: Medical review
Provide a short synopsis of the medical situation and how it fits within the larger illness trajectory (for chronic disease patients).

Step 6: Allow silence
Respond to questions and emotional reactions.

When the medical review has indicated that no further treatments are likely to reverse the disease process, there are 2 common reactions:

1. Acceptance: Patients and families who accept that death is approaching will typically ask, or be thinking, the following questions:

● How much time? What will happen? What do we do now?

2. Nonacceptance: When patients or families are not ready to accept that death is coming, common questions include:

● How can you be sure? He was fine last week. We want a second opinion.

Step 7: Discuss prognosis and care options
Guidelines on discussing prognosis include:

■ Always ask if such a discussion is desired before providing data

■ Provide data using a range (e.g., a few weeks to a few months)

■ Reviews recommend when giving bad news to include positive language and present information on different outcomes[259,15]

■ Stop and allow silence after the information is provided, to address any emotional reaction.

Options usually break down into:

● Continuing or expanding life-prolonging treatments with a goal of improved function, lengthened life, and/or improved quality, OR

● Discontinue life-prolonging treatments with a goal solely on comfort/quality.

When patients can speak for themselves

■ Ask the patient what treatment he/she is considering and why

■ Ask the patient what type of support he/she would like from family members and health care team.

When patients cannot speak for themselves

■ Ask each family member, or surrogate decision-maker, what they believe the patient would choose if he/she were able to speak on his/her own behalf.

Making a recommendation

When patients/families struggle to make a decision, or you believe there is 1 preferred medical decision based on the facts and the patient's wishes, **make a clear recommendation**.

Step 8: Managing conflict
Conflicts concerning the goals of care between family members, or between the family/patient and the physician, are common:

- **Grief/Time:** Family members have not had sufficient time to psychologically adjust to imagining their life without the dying person

- **Information:** Incorrect, misleading, or conflicting information has been provided to the family by other health care providers or other sources

- **Anger/Guilt:** Long-lasting intrafamily issues may disrupt or preclude logical decision-making

- **Trust:** If a patient or family does not have trust in the medical team, it is impossible to work together to develop a treatment plan

- **Culture:** Differences in culture, religion, socioeconomic status and so on may all impede decision-making

Key points for managing conflict

■ Use good active listening skills: Strive to maintain a civil discourse

■ Provide an empathic statement: '*I can't imagine how hard this must be!*'

■ Correct factual misunderstanding

■ Keep the discussion focused on the patient's well-being

■ Recognize that time may be necessary and schedule a follow-up meeting

■ Establish a time-limited trial of continued life-sustaining treatments: Establish clear goals and a time line (e.g., improved cognition within the next 3 days)

■ Recognize that other resources may help the family: psychologist, spiritual counselor, palliative care team, ethics consultation

■ State directly that you (and the health care team) will not abandon the patient and family.

Step 9: Translate goals into a care plan
If a decision has been made to limit further life-sustaining treatments, it is time to refocus the goals of care. Even for patients with a poor prognosis hope is possible if they can focus on achievable goals.[16]

■ Suggested question: '*Knowing that time is short, what is important and what do you want or need to do in the time you have left?*'

■ Review the current medical tests/ medications and decide which ones are helping to meet the patient's goals, which are providing no benefit.

Step 10: Document and Discuss

■ Summarize the main points and reassess the patient's understanding

■ Provide concise written documentation of the meeting

■ Provide contact details for further information

■ Discuss the meeting with health care providers who were unable to attend.

3. Toolkit: Care coordination for early, middle and late stages of serious chronic illness

Adapted from Morrison RS, Meier DE. Palliative care. *N Engl J Med.* 2004;350:2582–2590.[255]

	Early stage (e.g., time of diagnosis)	Middle stage (e.g., progressive disease and increasing functional decline)	Late stage (e.g., death is imminent)
Goals of care	■ Discuss diagnosis, prognosis, and likely course of illness ■ Discuss/offer disease-modifying therapies ■ Discuss patient-centered goals, hopes, and expectations of medical treatments	■ Review understanding of diagnoses/ prognosis ■ Review efficacy and benefit/burden ratio of disease modifying treatment ■ Reassess goals of care and expectations; prepare patient/family for shift in goals ■ Encourage completion of important tasks, relationships, financial affairs	■ Assess understanding of diagnosis, disease course, prognosis ■ Review appropriateness of disease-modifying treatments ■ Review goals of care and recommend appropriate shifts ■ Explicitly plan for a peaceful death ■ Encourage completion of important tasks, relationships, financial affairs

	Early stage (e.g., time of diagnosis)	Middle stage (e.g., progressive disease and increasing functional decline)	Late stage (e.g., death is imminent)
Programmatic support	■ Visiting nurse and home care services ■ Case management services if available	■ Visiting nurse and home care services ■ Consider hospital/home care; palliative care programs; hospice; ■ Subacute rehabilitation; case management services; PACE	■ Hospital/home care based palliative care program; hospice ■ Case management services ■ PACE ■ Nursing home placement with hospice/palliative care if care needs are overwhelming to family
Financial planning	■ Advise financial/estate planning, long-term care, insurance options ■ Consider asset transfer if need for Medicaid ■ Refer to an elder lawyer	■ Assure financial planning for medical, home care, prescription, long-term care, and family support needs ■ Consider hospice referral; Medicaid eligibility	■ Ask about financial resources/needs ■ Inform patient/family of possibility of Medicaid eligibility if resources inadequate ■ Explicitly recommend and review advantages of hospice

	Early stage (e.g., time of diagnosis)	Middle stage (e.g., progressive disease and increasing functional decline)	Late stage (e.g., death is imminent)
Family support	■ Offer support groups ■ Ask about practical needs (transportation, prescription drug coverage, respite care, personal care) ■ Listen	■ Encourage support/counseling for family caregivers ■ Screen family caregivers for practical resource needs, stress, depression, adequacy of medical care, identify respite and practical support resources, recommend help from family/friends, raise possibility of hospice and its benefits ■ Listen	■ Encourage out-of-town family to visit ■ Refer to disease-specific support groups/counseling for family. Inquire about caregiver health, well-being, practical needs ■ Offer respite care ■ After death, send bereavement card and call after 1 to 2 weeks ■ Screen for high-risk bereavement ■ Maintain occasional contact after patient's death ■ Listen

4. Toolkit: Pain and other symptoms

Adapted from Morrison RS, Meier DE. Palliative care. *N Engl J Med*. 2004;350:2582–2590.[255]

Anorexia/Cachexia

■ Assessment: Dx disease process versus consequence of untreated nausea, constipation, pain? Is patient troubled by the symptom?

■ Treatment: **Megestrol acetate** or **dexamethasone**

Anxiety

■ <u>Assessment</u>: Common symptom, including restlessness, agitation, insomnia, hyperventilation, tachycardia, excessive worry

■ <u>Treatment</u>: **Supportive counselling**. **Benzodiazepines** (avoid long-acting agents in elderly)

Constipation

■ <u>Assessment</u>: Common symptom, has major adverse effects (perforation, bowel obstruction, nausea, anorexia, pain)

■ **Disimpact** prior to initiating oral therapy

■ <u>Treatment</u>: **Stool softener** (ineffective alone) **plus stimulant laxative**, titrate to effect. Add **osmotic laxatives**, **enemas** if necessary.

Depression

■ <u>Assessment</u>: Ask "*Are you depressed?*"—sensitive and specific question for dx

■ Symptoms: helplessness, hopelessness, anhedonia, loss of self-esteem, worthlessness, guilt, dysphoria, and suicidal ideation

■ Suicidal ideation represents extreme distress and should be routinely assessed

■ <u>Treatment</u>: **Cognitive/behavioral counselling**. **Psychostimulants** unless tachycardia or acute coronary ischemia. **Selective serotonin reuptake inhibitors** may take 3 to 4 weeks to take effect. Tricyclic antidepressants are relatively contraindicated due to their side effects.

Delirium

■ <u>Assessment</u>: Acute change in level of consciousness, with agitation and/or lethargy, inattention, disorientation, fluctuation, and reversibility. Often remembered and causes significant distress to patient and family

■ <u>Treatment</u>: Treat symptom while seeking reversible contributors. Reduce excess stimulation, provide reorientation, reassurance, assure presence of family if possible. Effective medications include **haloperidol**, **risperidone**, **olanzapine**. **Chlorpromazine** can be used for agitated or terminal delirium. Benzodiazepines exacerbate delirium and should be avoided.

Dyspnea

■ Treat reversible causes

■ <u>Treatment</u>: **Oxygen** is effective with or without hypoxia via stimulation of the V2 branch of the trigeminal nerve. Fans are helpful. **Opioids** reduce breathlessness in RCTs without reductions in respiratory rate or oxygen saturation. Effective doses are lower than those used to treat pain.
Anxiolytics: Low-dose benzodiazepines. **Behavioral:** Reassurance, relaxation, distraction, breathing techniques, and massage therapy.

Nausea

■ <u>Assessment:</u> Multiple mechanisms (chemoreceptor trigger zone stimulation, gastric stimulation, delayed gastric emptying/squashed stomach, bowel obstruction, intracranial processes, and vestibular vertigo) and neurotransmitter contributors

■ <u>Treatment:</u> Successful treatment is based on specific cause

Vestibular: Cholinergic, histaminic receptors. Rx: Anticholinergic (scopolamine), antihistaminic (diphenhydramine, promethazine)

Obstruction of bowel caused by constipation: Cholinergic, histaminic, 5HT3 receptors. Rx: Disimpact, myenteric plexus stimulants such as senna

Dysmotility of upper gut: Cholinergic, histaminic, 5HT3 receptors. Rx: Prokinetics, metoclopramide

Infection, inflammation: Cholinergic, histaminic, 5HT3, neurokinin 1 receptors. Rx: Anticholinergic (scopolamine), antihistaminic (diphenhydramine), 5HT3 antagonists (ondansetron, granisetron), anti-inflammatory (corticosteroids).

Toxins stimulating the CTZ in the brain such as opioids: Dopamine 2, 5HT3 receptors. Rx: Antidopaminergic (haloperidol, metoclopramide), 5HT3 antagonist (ondansetron).[243]

Pain

■ <u>Assessment:</u> Assess daily using numeric rating scale (0 to 10 or 0 to 3)

■ <u>Treatment:</u> Dose analgesics standing, interval based on half-life

■ PRN doses for pain not controlled by the standing regimen, dosing interval based on time to onset

■ All patients on opioids should be started on a bowel regimen

■ The WHO Analgesic Ladder should be used for most pain syndromes

Mild pain: Acetaminophen or a NSAID (opioids probably safer in older adults)

Moderate pain: Opioid combination product (acetaminphen + codeine, acetaminophen + oxycodone, acetaminophen + hydrocodone) and dose based upon opioid half-life (3 to 4 hours) not acetaminophen half-life (6 to 8 hours). No more than 4 g acetaminophen total per 24-hour period

Severe pain: Standing opioids (hydromorphone, morphine, oxycodone) and titrate to relief or intolerable side effects. Long-acting opioids (sustained release morphine/oxycodone, transdermal fentanyl) should be started after pain is well-controlled. Methadone should only be prescribed by clinicians experienced in its use.

Rescue doses: Short acting opioids at 10% of the 24-hour total opioid dose at 1 hour (oral) or 30 minute (parenteral) intervals; PRN

Adjuvant agents: Corticosteroids, anticonvulsants, tricyclic antidepressants, bisphosphonates should be employed for specific pain syndromes when applicable.

Resources

National Consensus Project
http://www.nationalconsensusproject.org

A national framework and preferred practices for palliative and hospice care quality
http://216.122.138.39/publications/reports/palliative.asp

Facts on dying: Policy relevant data on care at the end of life
http://www.chcr.brown.edu/dying/usastatistics.htm

Medicare Hospice Benefits (MHB)
http://www.medicare.gov/publications/pubs/pdf/02154.pdf

The Family Goal Setting Conference Pocket Card http://www.mcw.edu/palliativecare/pocketcards.htm

Caring Connections: End-of-life resources and state-specific living will or healthcare power of attorney
http://www.caringinfo.org

Physician Orders for Life-Sustaining Treatment (POLST) program
http://www.ohsu.edu/polst/professionals.shtml

Hospital Elder Life Program (HELP)
http://hospitalelderlifeprogram.org

National Palliative Care Research Center (NPCRC): Resources, Measurement and Evaluation tools
http://www.npcrc.org/resources/resources_list.htm?cat_id=1246

National Information on Palliative Care Resources (NIPCR)
www.Getpalliativecare.com

U.S. Pain Policy Resources
http://www.painpolicy.wisc.edu/states.htm

TIME: Toolkit of Instruments to Measure End-of-life Care
http://www.chcr.brown.edu/pcoc/toolkit.htm

City of Hope: Pain & Palliative Care Resource Center Website
http://www.cityofhope.org/prc/

End-of-Life/Palliative Education Resource Center
http://www.eperc.mcw.edu

Center to Advance Palliative Care
http://www.capc.org

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