

The Management of Cancer Pain

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Abstract

The experience of pain in cancer is widely accepted as a major threat to quality of life, and the relief of pain has emerged as a priority in oncology care. Pain is associated with both the disease as well as treatment, and management is essential from the onset of early disease through long-term survivorship or end-of-life care. Effective relief of pain is contingent upon a comprehensive assessment to identify physical, psychological, social, and spiritual aspects and as a foundation for multidisciplinary interventions. Fortunately, advances in pain treatment and in the field of palliative care have provided effective treatments encompassing pharmacological, cognitive-behavioral, and other approaches. The field of palliative care has emphasized that attention to symptoms such as pain is integral to quality cancer care. *CA Cancer J Clin* 2011;61:157–182. © 2011 American Cancer Society, Inc.

Introduction

Although cancer is recognized as encompassing multiple physical symptoms, as well as psychological and existential concerns, the symptom of pain is often cited as most critical. Unrelieved pain impacts all dimensions of quality of life (QOL) and profoundly influences the patient's ability to endure treatment, return to health as a cancer survivor, or achieve a peaceful death. The relief of pain is contingent upon competent, compassionate, evidence-based practice by oncology clinicians.^{1,2}

This review of the current optimal practice of pain management begins with a discussion of the prevalence of cancer pain, its global impact, and barriers to effective relief, and continues with a discussion of cancer pain syndromes, followed by the essential foundation of comprehensive pain assessment. Advances in understanding pain syndromes and assessment have contributed to major progress in addressing pain in oncology.

The treatment of cancer pain has also advanced over the past 2 decades, with a wide spectrum of pharmacologic and complementary therapies available. This article reviews the available treatment approaches with consideration of the distinct needs of individual patients as well as special populations, including the elderly, cancer survivors, patients with addictive disease, and those at the end of life.

Cancer Pain Prevalence

The prevalence of pain in cancer is estimated at 25% for those newly diagnosed, 33% for those undergoing active treatment, and greater than 75% for those with advanced disease.^{3,4} Chronic pain in cancer survivors who have completed treatment is estimated to be approximately 33%.² Factors for the development of chronic pain syndromes in cancer survivorship include chemotherapy (eg, painful peripheral neuropathy), radiation (eg, radiation-induced brachial plexopathy, chronic pelvic pain secondary to radiation), and surgery (eg, mastectomy pain, neuropathic intercostal nerve injury after thoracotomy).⁵ Pain prevalence is also high in specific cancer types, such as pancreatic (44%) and head and neck cancers (40%).^{6,7} With such a high prevalence, cancer pain should be anticipated and responded to early in its course rather than only in crisis once it is severe. Extensive literature

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has supported attention to pain as an institutional priority for oncology settings with established quality improvement efforts devoted to pain.^{8,9}

The Global Perspective

The World Health Organization (WHO) and international pain community have identified cancer pain as a global health concern.¹⁰ Pain prevalence is high in developing countries due to late diagnosis of disease and major impediments to opioid access. A recent population-based study that explored cancer pain prevalence in 11 European countries and Israel found that 56% of patients suffered moderate to severe pain at least monthly, and 69% reported pain-related difficulties with everyday activities.¹¹ The WHO estimates that over 80% of the world's population is inadequately treated for moderate to severe pain.¹⁰

Barriers to Cancer Pain Relief

The high prevalence of cancer pain and often unfortunate failure to relieve it has resulted in great attention to the barriers that persist. These barriers have been classified as patient, professional, and system obstacles. Targeted attention to each of these barriers can lead to major improvements in the delivery of care.

Despite the wealth of scientific evidence and efforts to synthesize and disseminate the evidence through clinician guidelines, suboptimal management of pain persists in clinical settings. The barriers to optimum pain relief were captured by the first national cancer pain clinical practice guidelines published by the Agency for Health Care Policy and Research (AHCPR) (now known as the Agency for Healthcare Research and Quality) in 1994, in which the framework of barriers to pain relief was first introduced.¹² The framework notes that patients play a key role in the undertreatment of pain.^{12,13} Key reasons for patients' reluctance to communicate pain include fear of side effects, fatalism about the possibility of achieving pain control, fear of distracting physicians from treating the cancer, and belief that pain is indicative of progressive disease.¹⁴⁻²⁰ Over the years, studies have demonstrated that it is possible to overcome these patient barriers.^{21,22} Model programs have supported the use of pain assessment tools, strategies to dispel misconceptions, and patient coaching to improve pain management. It has also been suggested that interventions require

attention to both pain knowledge and attitudes.^{21,23,24}

Significant professional barriers to adequate pain relief have also been described in the current literature. Adequate pain assessment and recognition of pain barriers are often lacking in clinical settings.²⁵⁻²⁷ Physicians and nurses are often lacking in knowledge of the principles of pain management; side effects; or key concepts such as addiction, tolerance, and dosing.²⁸⁻³¹ Legal and regulatory structures that interfere with the provision of optimal care, such as inadequate reimbursement for pain services, are common system-related barriers to optimal pain relief. System-related barriers can also occur internally within a clinical setting, and these include low referrals to supportive care services.¹² The Institute of Medicine and the National Cancer Policy Board have continued to document and emphasize the importance of system-related barriers in quality pain management.^{32,33} System-related barriers also include a lack of access to pain medications, particularly in minority neighborhoods or for those who are poor. Several studies have documented the inequalities that persist since those with financial burdens or minorities have less access to pain treatment.^{34,35} Cancer care settings address system barriers by establishing pain policies and creating pain or palliative care services to provide expert consultation.^{9,36}

A 5-year National Cancer Institute-supported study tested a patient, professional, and system-wide intervention to decrease barriers to achieving pain relief for patients with breast, colon, lung, and prostate cancer with moderate to severe pain. The study occurred across 3 phases. The primary goal of phase 1 was to assess usual care of pain (n=83). Patients provided demographic and disease data at baseline along with other outcome measures to assess overall QOL, barriers to pain management, and pain knowledge. A chart audit was conducted 1 month later. The sample included 45% ethnic minorities, and most subjects had stage III or IV disease. Patients believed that pain medicines are addictive, and that tolerance to the effects of pain medicine is high. The overall pain knowledge score was moderate to high, but knowledge deficits persisted for items related to addiction. Overall, the chart audit data reflected deficits in pain documentation and low supportive care referrals.^{36,37}

The primary goal of phase 2 was to implement and test the “Passport to Comfort” model to improve pain management (n=187). Patients were given education sessions administered by advanced practice nurses, with each session covering topics that included the assessment and management of pain. Outcome measures were collected at baseline, at 1 month, and at 3 months. A chart audit was conducted at the 1-month evaluation. Comparative analyses between phase 1 (usual care) and phase 2 (intervention) were conducted. The sample included 34% ethnic minorities, with 77% of patients receiving chemotherapy at the time of study accrual. Study results demonstrated significant and immediate improvements for the intervention group compared with the usual care group subscale (physiological concerns, fatalism, and belief in harmful effects) and total scores for barriers to pain management over time. Barriers were significantly higher in the usual care group compared with the intervention group over time. The overall knowledge score for the usual care group at baseline was lower (73%) compared with the intervention group (78%). Knowledge about pain increased significantly for the intervention group to 87% at 1 month and 88% at 3 months.³⁸

In addition to the 2 previous phases, the study was designed with the inclusion of a third phase to begin disseminating the “Passport to Comfort” model into routine ambulatory care. Phase 3 provided an opportunity to test the sustainability of the intervention. The intervention was focused on system-wide dissemination of the “Passport to Comfort” model, in which research personnel focused on integrating the intervention into ambulatory oncology care. As a result, significant system-related changes occurred across each level of patient, professional, and system barriers. Since the end of the study funding period, the systems-related changes have been sustained within ambulatory care settings, and clinicians continue to use the intervention and its educational materials to provide optimal pain and fatigue management.³⁹ This study illustrates the institutional effort needed to address patient, professional, and system barriers.

Cancer Pain Syndromes

Pain is often categorized as related to the disease versus as a result of treatment or due to unrelated

causes. This distinction has become more important as many cancer treatments are now associated with pain, such as the neuropathic pain associated with the use of taxanes. As the cancer population ages, it is also important to assess and treat chronic pain that may occur concurrently with cancer, such as chronic arthritis, back pain, or diabetic neuropathies. Another mechanism for categorizing cancer pain syndromes is by determining whether they are nociceptive (usually described as aching or throbbing pain) or neuropathic (described as burning, tingling, electrical sensations). As described in the pharmacology section below, understanding these categorizations of pain is essential to the selection of treatment approaches and optimal use of the myriad of analgesic approaches available.^{4,40}

Nociceptive pain occurs with the stimulus of nociceptors, resulting in injury to somatic and visceral structures. A pain history and assessment that identifies pain described as localized, sharp, throbbing, or pressure is somatic. Visceral pain is identified as aching, cramping, and diffuse, as may be seen in the presence of tumor in the peritoneum. Somatic pain is from bone, joint, muscle, skin, or connective tissue while visceral pain rests in visceral organs such as the gastrointestinal (GI) tract or pancreas.

Neuropathic pain has been the focus of attention in treatment advances and results from insult or injury to the central or peripheral nervous system. Patients often describe neuropathic pain as tingling, burning, stabbing, or shooting. Careful assessment to detect neuropathic pain by clinicians can alter the course of treatment as described below with adjuvant analgesics.

Pain Assessment

Clinical practice guidelines developed by the National Comprehensive Cancer Network (NCCN)⁴ and American Pain Society (APS)⁴⁰ emphasize the essential practice of comprehensive pain assessment. Initial and ongoing assessment of pain includes the evaluation of pain intensity using a numerical rating scale of 0 (indicating no) to 10 (indicating the worst pain imaginable). Other factors considered in pain assessment include discerning the quality of pain, onset, and duration and what actions may worsen or relieve the pain. Careful patient interviews should also probe the degree of patient distress from the pain as well as psychological or social factors. Distress can

TABLE 1. Comprehensive Pain Assessment

<p>Patient's self-report of pain is the standard of care. If the patient is unable to verbally report pain, an alternative method to obtain pain rating and response should be utilized.</p> <ul style="list-style-type: none"> • Pain experience <ul style="list-style-type: none"> ◦ Location, referral pattern, and radiation of pain(s) ◦ Intensity <ul style="list-style-type: none"> ▪ Last 24 h and current pain ▪ At rest and with movement ◦ Interference with activities <ul style="list-style-type: none"> ▪ General activity, mood, relationship with others, sleep, and appetite ◦ Timing: onset, duration, course, persistent, or intermittent ◦ Description or quality <ul style="list-style-type: none"> ▪ Aching, stabbing, throbbing, pressure; often associated with somatic pain in skin, muscle, and bone ▪ Gnawing, cramping, aching, sharp; often associated with visceral pain in organs or viscera ▪ Sharp, tingling, ringing, shooting; often associated with neuropathic pain caused by nerve damage ◦ Aggravating and alleviating factors ◦ Other current symptoms ◦ Current pain management plan, both pharmacologic and nonpharmacologic. If medications are used, determine: <ul style="list-style-type: none"> ▪ What medication(s), prescription, and/or over the counter? ▪ How much? ▪ How often? ▪ Current prescriber? ◦ Response to current therapy <ul style="list-style-type: none"> ▪ Pain relief ▪ Patient adherence to medication plan ▪ Medication side effects such as constipation, sedation, cognitive slowing, nausea, and others ◦ Prior pain therapies <ul style="list-style-type: none"> ▪ Reason for use, length of use, response, and reasons for discontinuing 	<ul style="list-style-type: none"> ◦ Special issues relating to pain <ul style="list-style-type: none"> ▪ Meaning and consequences of pain for patient and family ▪ Patient and family knowledge and beliefs surrounding pain and pain medications ▪ Cultural beliefs toward pain and pain expression ▪ Spiritual, religious considerations, and existential suffering ▪ Patient goals and expectations regarding pain management • Psychosocial <ul style="list-style-type: none"> ◦ Patient distress (see NCCN distress management guidelines) ◦ Family and other support ◦ Psychiatric history including current or prior history of substance abuse ◦ Risk factors for aberrant use or diversion of pain medication <ul style="list-style-type: none"> ▪ Patient, environmental, and social factors ◦ Risk factors for undertreatment of pain <ul style="list-style-type: none"> ▪ Pediatric, geriatric, minorities, female, communication barriers, history of substance abuse, neuropathic pain, and cultural factors • Medical history <ul style="list-style-type: none"> ◦ Oncologic treatment including current and prior chemotherapy, radiation therapy, and surgery ◦ Other significant illnesses and conditions ◦ Pre-existing chronic pain • Physical examination • Relevant laboratory and imaging studies to evaluate for disease progression • The endpoint of the assessment is to establish the "pain diagnosis" and individualized pain treatment plan based on mutually developed goals. The "pain diagnosis" includes the etiology and pathophysiology of pain: <ul style="list-style-type: none"> ◦ Etiology <ul style="list-style-type: none"> ▪ Cancer ▪ Cancer therapy (RT, chemotherapy, or surgery) or procedures ▪ Coincidental or noncancer ◦ Pathophysiology <ul style="list-style-type: none"> ▪ Nociceptive ▪ Neuropathic
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NCCN indicates National Comprehensive Cancer Network; RT, radiation therapy.

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also be measured using a 0-to-10 scale and this has been shown to be a valid measure.⁴¹

The experience of pain has been strongly associated with suffering. Thus, it is important to understand the unique patient experience, which may include religious beliefs and cultural influences, on the expression or treatment of pain.^{42,43} Table 1 provides a guide for a comprehensive pain assessment from the NCCN cancer pain guidelines.

There are many scales designed to assess pain intensity, more comprehensive instruments, and tools

specific to neuropathic pain and those developed to observe patient behaviors for those who are nonverbal or cognitively impaired.⁴⁴ Numerous resources exist to identify pain assessment tools for specific populations or for use in electronic medical records.⁴⁵ The issue of cultural assessment is paramount, with attention needed regarding the assessment of culturally based beliefs about pain, the availability of translators for non-English-speaking patients, and the collaboration with an interdisciplinary team.⁴⁶ Assessment of cancer pain begins with a patient rating of pain intensity but also often involves very complex

emotions, fears, family distress, misconceptions related to pain treatment, and expression of suffering.⁴⁷

Pharmacologic Treatments for Cancer Pain

Pharmacologic therapies are the foundation of cancer pain management. These therapies include non-opioids, opioids, and adjuvant analgesics, along with a variety of anticancer therapies. In addition to a discussion of these classes of agents, routes of delivery, principles of use, and safe handling procedures will be discussed.

Nonopioid Analgesics

Acetaminophen is analgesic and antipyretic but not anti-inflammatory. Previously considered to be coanalgesic with opioids, and to be first-line therapy in the elderly patient with musculoskeletal pains or pain associated with osteoarthritis, new attention has been focused on the relative limited efficacy and significant adverse effects of this agent, particularly hepatic and renal toxicity.^{48,49} This concern is compounded by the inclusion of acetaminophen in a variety of prescription opioid preparations (eg, hydrocodone or codeine) as well as in a wide selection of over-the-counter products. Of additional concern in those receiving cancer chemotherapy are case reports of interactions between anticancer agents and acetaminophen leading to hepatic toxicity.⁵⁰ Reduced doses of 2000 mg/day or the avoidance of acetaminophen is recommended in the face of renal insufficiency or liver failure, and particularly in individuals with a history of significant alcohol use.⁵¹

Nonsteroidal anti-inflammatory drugs (NSAIDs) produce analgesia by blocking the biosynthesis of prostaglandins, inflammatory mediators that initiate, cause, intensify, or maintain pain. These agents also appear to reduce pain through their influence on the peripheral or central nervous system independent of their anti-inflammatory mechanism of action, although this effect remains poorly understood. The nonselective NSAIDs, such as aspirin or ibuprofen, inhibit enzymes that convert arachidonic acid to prostaglandins and as a result, GI ulceration, renal dysfunction, and impaired platelet aggregation can occur.⁵² The cyclooxygenase-2 (COX-2) enzymatic pathway is induced by tissue injury or other inflammation-inducing conditions and there appears

to be reduced risk of GI bleeding when using a COX-2 selective agent; however, this advantage appears to diminish after 6 months of use.⁵³ Furthermore, taking 81 mg of aspirin for cardioprotection along with a COX-2 inhibitor (coxib) results in the GI ulcer risk effect of a traditional, nonselective NSAID.⁵⁴ In addition, there is a risk of cardiovascular events, such as myocardial infarction, and cerebrovascular complications, such as stroke, with prolonged coxib use (see Table 2 for a list of NSAIDs and dosing guidelines).⁵⁵⁻⁵⁷

As a class, the NSAIDs are useful in the treatment of pain conditions mediated by inflammation, including those caused by cancer, such as bone metastases. The NSAIDs do offer the potential advantage of causing minimal nausea, constipation, sedation, or adverse effects on mental functioning. Therefore, depending on the cause of pain, NSAIDs may be useful for the control of moderate to severe pain, usually as an adjunct to opioid analgesic therapy.⁵⁸ The addition of NSAIDs to opioids has the potential benefit of reducing the opioid dose when sedation, obtundation, confusion, dizziness, or other central nervous system effects of opioid analgesic therapy alone become burdensome. Decreased renal function and liver failure are relative contraindications for NSAID use. Platelet dysfunction or other potential bleeding disorders, common due to cancer or its treatment, contraindicate use of the nonselective NSAIDs due to their inhibitory effects on platelet aggregation, with resultant prolonged bleeding time. Proton pump inhibitors or misoprostol can be given to prevent GI bleeding.⁵⁹

Opioids

Opioids are critical to providing effective analgesia in cancer pain. A review of each opioid follows. There is great interindividual variability in response to a particular agent and clinicians would benefit from understanding the basic differences between these drugs. This will assist in drug selection and, later, opioid rotation. Of note, there is no evidence that a specific opioid agonist is superior to another as first-line therapy. The agent that works for a particular patient is the "right" drug. Another factor to consider when selecting an opioid is cost because high-cost agents can place undue burden on patients and families.

Transdermal buprenorphine has recently been approved for use in the United States; it has been

TABLE 2. Acetaminophen and Selected Nonsteroidal Anti-Inflammatory Drugs

DRUG	DOSE IF PATIENT WEIGHS 50 KG	DOSE IF PATIENT WEIGHS <50 KG
Acetaminophen ^{a,b}	4000 mg/24 h every 4-6 h	10-15 mg/kg every 4 h (oral)
		15-20 mg/kg every 4 h (rectal)
Aspirin ^{a,b}	4000 mg/24 h every 4-6 h	10-15 mg/kg every 4 h (oral)
		15-20 mg/kg every 4 h (rectal)
Ibuprofen ^{a,b}	2400 mg/24 h every 6-8 h	10 mg/kg every 6-8 h (oral)
Naproxen ^{a,b}	1000 mg/24 h every 8-12 h	5 mg/kg every 8 h (oral/rectal)
Choline magnesium trisalicylate ^{a,c}	2000-3000 mg/24 h every 8-12 h	25 mg/kg every 8 h (oral)
Indomethacin ^b	75-150 mg/24 h every 8-12 h	0.5-1 mg/kg every 8-12 h (oral/rectal)
Ketorolac ^d	30-60 mg im/iv initially, then 15-30 mg every 6 h bolus iv/im or continuous iv/sq infusion; short-term use only (3-5 d)	0.25-1 mg/kg every 6 h; short-term use only (3-5 d)
Celecoxib ^{c,e}	100-200 mg orally up to bid	No data available

im indicates intramuscularly; iv, intravenously; sq, subcutaneous; bid, twice daily.

^aCommercially available in a liquid form.

^bCommercially available in a suppository form.

^cMinimal platelet dysfunction.

^dPotent anti-inflammatory (short-term use only due to gastrointestinal side effects).

^eCyclooxygenase-2 selective nonsteroidal anti-inflammatory drug.

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used in the management of cancer pain in Europe and open-label and randomized controlled trials suggest this partial agonist is useful in relieving cancer pain.^{60,61} The available doses are 5, 10, and 20 $\mu\text{g}/\text{hour}$ and the patch is changed every 7 days. The 5- $\mu\text{g}/\text{hour}$ patch was approved for opioid-naïve patients. Studies of buprenorphine suggest there is a ceiling effect for analgesia, limiting the efficacy of this agent in palliative care.⁶² The maximum recommended dose is 20 $\mu\text{g}/\text{hour}$ because, at greater doses, QT prolongation has been observed. Most of the published experience with transdermal buprenorphine reflects its use in patients with relatively small opioid doses; therefore, clinicians should refrain from starting this agent in patients who are tolerant to strong opioids. In addition, little experience exists to recommend an optimal breakthrough opioid when using transdermal buprenorphine, because early studies were conducted in Europe, where sublingual buprenorphine is available for rescue dosing. Intravenous morphine has been found to be safe and effective, although this route is not practical for patients in the home setting.⁶³ More research is needed.⁶⁴ Buprenorphine is also available parenter-

ally in the United States and sublingually, alone or in combination with naloxone. These latter formulations are primarily used in the treatment of opioid addiction.

Codeine is a relatively weak opioid that can be given alone, although it is more frequently administered in combination with acetaminophen. It is available in oral tablets, alone or in combination with acetaminophen or other products, and as a syrup, often with promethazine. Codeine is metabolized by glucuronidation primarily to codeine-6-glucuronide, and to a much lesser degree to norcodeine, morphine, morphine-3-glucuronide (M-3-G), morphine-6-glucuronide, and normorphine.⁶⁵ Codeine is a prodrug and must undergo this metabolism to be converted to its active agents. This process is largely through the action of the enzyme CYP 2D6. The polymorphism seen

in this enzyme between various ethnic groups, and between individuals, leads to a significant percentage of patients obtaining reduced analgesia. Approximately 3% of Asians and African Americans and 10% of Caucasians are poor metabolizers. These individuals would obtain reduced analgesic effects.⁶⁶ In addition, some individuals are ultrarapid metabolizers, leading to the possibility of increased serum levels and adverse effects.⁶⁷ The death of an infant whose mother was given codeine while breastfeeding illustrates these safety concerns; genotyping of the mother for the CYP 2D6 enzyme revealed her to be an ultrarapid metabolizer.⁶⁸

Fentanyl is a highly lipid soluble opioid (partition coefficient 820) that can be administered parenterally, spinally, transdermally, transmucosally, buccally, and intranasally.^{69,70} It can also be given by nebulizer for the management of dyspnea. Dosing units are usually in micrograms due to the potency of this opioid, and serious safety issues arise when these units are confused with milligrams, particularly during intravenous delivery. Although no significant differences in serum levels were seen when intravenous fentanyl was given to lean and obese patients, questions have arisen

regarding the efficacy of fentanyl, particularly when delivered transdermally, in cachectic cancer patients.⁷¹ A comparative study of normal versus low-weight cancer patients (16 kg/m²) receiving transdermal fentanyl revealed lower plasma levels in the cachectic patients at 48 and 72 hours.⁷²

Hydrocodone is approximately equipotent with oral morphine. It is found only in combination oral products, including acetaminophen or ibuprofen. Liquid cough formulations of hydrocodone contain homatropine. These additives limit the use of hydrocodone in oncology care when higher doses of opioid are required. Hydrocodone is metabolized through demethylation to hydromorphone.⁷³ Laboratory evidence suggests that CYP 2D6 polymorphism may alter the analgesic response to hydrocodone.⁷⁴

Hydromorphone has similar properties when compared with morphine and is available in oral tablets, liquids, suppositories, and parenteral formulations.⁷⁵ A long-acting formulation has been available internationally for many years and is now available in the United States.⁷⁶ It is highly soluble and approximately 5 to 10 times more potent than morphine, and as a result, hydromorphone is used frequently when small volumes are needed for intravenous or subcutaneous infusions. Hydromorphone undergoes glucuronidation and the primary metabolite is hydromorphone-3-glucuronide (H-3-G).⁷⁷ Recent experience suggests that this metabolite may lead to opioid neurotoxicity, including myoclonus, hyperalgesia, and seizures.⁷⁸⁻⁸⁰ Evidence from the laboratory suggests this metabolite may be more neurotoxic than the morphine metabolite M-3-G.⁸¹ This neurotoxicity appears to be of particular risk with high doses, prolonged use, or in individuals with renal dysfunction. The metabolites of hydromorphone are more readily dialyzable, making it a safer drug for those patients with renal failure who are undergoing dialysis.⁸²

Methadone has several characteristics that make it useful in the management of severe cancer pain.⁸³ Methadone is a mu and delta opioid receptor agonist, and is an antagonist to the N-methyl d-aspartic acid (NMDA) receptor, with affinity similar to ketamine. This is believed to be of particular benefit in the relief of neuropathic pain, although a Cochrane review of existing studies found similar analgesic effects when compared with morphine.^{84,85} In addition, Bruera et al conducted a randomized controlled

trial in cancer patients and found no significant clinical difference when compared with morphine.⁸⁶ Methadone also blocks reuptake of serotonin and norepinephrine, another potentially favorable attribute in its use to treat neuropathic pain. The prolonged plasma half-life of methadone (ranging from 15 to 60 hours or more) allows for a dosing schedule of every 8 hours.⁸³ Another advantage of methadone use is the variety of available routes that can be used, including oral, rectal, subcutaneous, intravenous, and epidural.⁸⁷ Nasal and sublingual administration has been reported to be effective, but preparations are not currently commercially available. The ratio from oral to parenteral methadone is 2:1 and from oral to rectal is 1:1. Subcutaneous methadone infusions can be used when intravenous access is not available, although this may produce local irritation. Using a more diluted solution or changing the needle more frequently can mitigate this. In addition, methadone has been found to provide analgesia in patients who have failed to respond to high doses of other opioids.⁸⁸ Finally, methadone is much less expensive than comparable doses of commercially available continuous-release opioid formulations, making it a useful option for patients without sufficient financial resources for more costly drugs.

Several of these attributes also complicate the use of methadone. Although the long half-life is an advantage, it also increases the potential for drug accumulation before achieving steady-state blood levels, putting patients at risk for oversedation and respiratory depression. This might occur after 2 to 5 days of treatment with methadone and therefore close monitoring of these potentially adverse or even life-threatening effects is required.^{89,90} In addition, the appropriate dosing ratio between methadone and morphine or other opioids, as well as the safest and most effective time course for conversion from another opioid to methadone, is not known.^{91,92} Early studies suggested the ratio might be 1:1, and this appears to be true for individuals without recent prior exposure to opioids; however, new clinical experience suggests the dose ratio increases as the previous dose of oral opioid equivalents increases.⁹⁰ In fact, several experts now discourage attempts at calculating an equianalgesic conversion, but rather, starting the opioid-tolerant patient at a dose of 10 mg every 8 hours and allowing sufficient breakthrough medication. Due to the long half-life, dose escalation should not

occur any more frequently than 3 to 5 days. An additional complicating factor in the use of methadone is limited experience in reverse rotation from methadone to another opioid.⁹² Despite these concerns, a recent study in outpatient cancer patients suggested that initiation and rotation to methadone occurred without serious adverse effects.⁹³

There is great variability in the kinetics of methadone between individuals, and causes for this variability include protein binding, CYP 3A4 activity, urinary pH, and other factors.⁹⁴ Methadone binds avidly to α_1 glycoprotein, which is increased in advanced cancer, leading to decreasing amounts of unbound methadone and initially delaying the onset of effect. As a result, the interindividual variability of the pharmacokinetics of methadone may be more pronounced in patients with cancer.⁹⁴

Methadone is metabolized primarily by CYP 3A4, but also by CYP 2D6 and CYP 1A2.^{95,96} As a result, drugs that induce CYP enzymes accelerate the metabolism of methadone, resulting in reduced serum levels of the drug. This may be demonstrated clinically by shortened analgesic periods or reduced overall pain relief.⁹⁷ Drugs that inhibit CYP enzymes slow methadone metabolism, potentially leading to sedation and respiratory depression. Of particular concern in oncology care are interactions with ketoconazole, omeprazole, and selective serotonin reuptake inhibitor (SSRI) antidepressants such as fluoxetine, paroxetine, and sertraline.

Studies suggest higher doses of methadone may lead to QT wave changes (also called torsade de pointe), although it is not clear whether this is due to the methadone or to preservatives in the parenteral formulation.^{98,99} A more recent study of 100 patients taking methadone found that one-third had prolonged QT wave intervals on electrocardiogram, occurring more frequently in males, yet there did not appear to be a risk of serious prolongation.^{100,101} However, another recent study conducted in cancer patients suggests QT interval changes exist commonly at baseline and are not changed with the addition of methadone.¹⁰²

Patients currently receiving methadone as part of a maintenance program for addictive disease will have developed cross-tolerance to the opioids, and as a result, will require higher doses than opioid-naïve patients.^{103,104} Prescribing methadone for addictive disease requires a special license in the United States and thus, when prescribing methadone to manage

pain, the prescription should include the phrase “for pain.”

Although morphine was previously considered the “gold standard,” we now recognize that due to the wide variability in response, the most appropriate agent is the opioid that works for a particular patient. Morphine is available in a wide range of formulations and routes, including oral, parenteral, and rectal delivery.¹⁰⁵ The active metabolite of morphine, M-3-G, may contribute to myoclonus, seizures, and hyperalgesia (increasing pain), particularly when clearance is impaired due to renal impairment, although this has been reported to occur with hydromorphone, methadone, and fentanyl as well.^{77,106,107}

Oxycodone is a synthetic opioid available in immediate-release, long-acting, and liquid formulations.^{108,109} It is also available in combination with acetaminophen, although this can limit dose escalation in the person with cancer. It is not yet available as a parenteral formulation in the United States. Bioavailability is greater with oxycodone when compared with oral morphine.¹¹⁰ The equianalgesic ratio is approximately 20 to 30:30 when compared with oral morphine. Metabolites of oxycodone include noroxycodone and oxymorphone. In addition to binding to the mu receptor, oxycodone binds to the kappa opioid receptor, although the clinical utility of this is unclear. Side effects appear to be similar to those experienced with morphine; however, one study comparing these long-acting formulations in persons with advanced cancer found that oxycodone produced less nausea and vomiting.¹¹¹ Drug interactions can occur between oxycodone and agents affecting the P450 3A4 enzyme.

Oxymorphone is a semisynthetic opioid that has been available parenterally and as a suppository for more than 50 years; more recently, immediate- and extended-release (12-hour) oral formulations have been developed.¹¹²⁻¹¹⁴ Oxymorphone is believed to be twice as potent as morphine¹¹⁵ and it does not appear to induce or inhibit the CYP 2D6 or CYP 3A4 enzyme pathways.¹¹⁶ The prevalence of adverse effects does not appear to differ from other opioids.¹¹⁷

Tapentadol is a new opioid that binds to the mu opioid receptor activation and inhibits norepinephrine reuptake.¹¹⁸ To date, no studies have been published in cancer pain. In other clinical trials, there appear to be fewer GI adverse effects when compared with oxycodone.^{118,119}

Tramadol is a synthetic oral opioid that binds to the mu opioid receptor and blocks reuptake of serotonin and norepinephrine.¹²⁰ This additional effect is believed to provide benefit in the relief of neuropathic pain. However, as a result of this monoamine action, naloxone will not completely reverse respiratory depression, should it occur. In addition, tramadol use should be avoided in patients receiving SSRIs or tricyclic antidepressants. Analgesia is affected by CYP 2D6, increasing the potential for drug-drug interactions. Tramadol is thought to be approximately one-tenth as potent as morphine in cancer patients.¹²⁰ Individuals receiving higher doses of tramadol or who have a history of seizures may be at increased risk for seizures. Currently available in immediate-release and extended-release formulations, the ceiling dose of tramadol is generally considered to be 400 mg/day. In a double-blind study of cancer patients, tramadol produced more adverse effects, including vomiting, dizziness, and weakness, when compared with hydrocodone and codeine.¹²¹

Other Opioids

Meperidine and propoxyphene are not recommended in cancer pain management due to the neurotoxic effects of their metabolites, normeperidine and norpropoxyphene, respectively.¹²² Levorphanol is an analog of morphine that binds to mu, kappa, and delta opioid receptors, is an antagonist at NMDA receptors, and is a monoamine reuptake inhibitor. It is not widely used, largely due to its limited availability. Mixed agonist-antagonist opioid analgesics, including butorphanol, nalbuphine, and pentazocine, are not recommended in cancer pain management due to their ceiling effect for analgesia; they are more likely to cause psychotomimetic effects, and they can precipitate the abstinence syndrome if given to a patient who is physically dependent on a pure opioid agonist.

Opioid-Related Adverse Effects

A significant factor in nonadherence to an analgesic regimen is opioid-related adverse effects, particularly constipation and sedation. Tolerance does not develop to constipation and therefore it must be prevented and, if unsuccessful, treated aggressively. Most recommend a bowel regimen that includes a laxative and stool softener, such as

senna and docusate, although a recent study suggested that senna alone was just as effective.¹²³ Bulking agents, such as psyllium, are ineffective and may even exacerbate the problem unless the patient can drink significant amounts of fluids. Once constipation develops, stimulant laxatives, such as magnesium-based products or bisacodyl (available in tablets or suppositories) should be used as early as possible to prevent painful defecation. Methylnaltrexone, an opioid antagonist that works on receptors in the GI system and is given subcutaneously, can be used as a rescue when constipation is clearly related to opioid therapy.^{124,125}

Sedation is often attributed to opioid therapy, although many other drugs used in cancer care can contribute to this adverse effect, including benzodiazepines, antiemetics, and other agents. Tolerance to opioid-induced sedation may develop within a few days of regular use; however, in some cases this may persist and opioid rotation may be warranted. An alternate treatment can include the addition of psychostimulants, such as methylphenidate at a dose of 5 to 10 mg once or twice daily. One study found that the timing of methylphenidate, including evening intake, did not disrupt sleep.¹²⁶

Nausea and vomiting and pruritus are more common in opioid-naïve individuals. Around-the-clock antiemetic therapy instituted at the beginning of opioid therapy in those patients who report nausea and vomiting with past intake often prevents this adverse effect. The antiemetic can be weaned in most cases after 2 to 3 days. For complicated nausea and vomiting, combinations of antiemetics working on different receptors (eg, phenothiazines, antihistamines, and/or steroids) may be warranted. If ineffective, opioid rotation may be necessary.

Pruritus is also more likely to occur early in the course of treatment in the opioid-naïve patient. Antihistamines may be at least partly beneficial. Opioid rotation to a more synthetic agent, such as fentanyl or oxymorphone, has been reported to be helpful.

Other adverse effects, including respiratory depression, are greatly feared and lead to clinician underprescribing and reluctance by patients to take the medication, despite the rarity of this event in persons with cancer. Despite this fear, studies have revealed no correlation between opioid dose, timing of opioid administration, and time of death.¹²⁷⁻¹²⁹

TABLE 3. Adjuvant Analgesics

DRUG CLASS	DAILY ADULT STARTING DOSE, RANGE	ROUTES OF ADMINISTRATION	ADVERSE EFFECTS	INDICATIONS
Antidepressants	Nortriptyline, 10-25 mg every h	Orally	Anticholinergic effects	Neuropathic pain
	Desipramine, 10-25 mg every d	Orally		
	Venlafaxine, 37.5 mg bid	Orally	Nausea, dizziness	
	Duloxetine, 30 mg every d		Nausea	
Antiepilepsy drugs	Gabapentin, 100 mg tid	Orally	Dizziness	Neuropathic pain
	Pregabalin, 50 mg tid	Orally	Dizziness	
	Clonazepam, 0.5-1 mg every hs, bid or tid	Orally	Sedation	
Corticosteroids	Dexamethasone, 2-20 mg every d	Orally/iv/sq	"Steroid psychosis"	Neuropathic pain, cerebral edema, spinal cord compression, bone pain, visceral pain
			Dyspepsia	
Lidocaine	Lidocaine patch 5% every d	Topical	Rare skin erythema	Neuropathic pain
	Lidocaine infusion (see text for dosing)	iv/sq	Perioral numbness, cardiac changes	Intractable neuropathic pain
<i>N</i> -methyl-D-aspartic acid antagonists	Ketamine (see text for dosing)	Orally/iv	Hallucinations	Unrelieved neuropathic pain; need to reduce opioid dose
Bisphosphonates	Pamidronate, 60-90 mg every 2-4 wk	iv	Pain flare, osteonecrosis	Osteolytic bone pain
	Zoledronic acid, 4 mg every 3-4 wk			

bid indicates twice daily; tid, 3 times a day; iv, intravenous; sq, subcutaneous; hs, once at night.

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Adjuvant Analgesics

Tricyclic antidepressants provide analgesia through inhibition of the reuptake of norepinephrine and serotonin. A recent review of analgesic studies conducted in neuropathic pain conditions, primarily diabetic neuropathy and other noncancer conditions, determined that there is evidence for these agents in providing a clinically relevant effect.¹³⁰ Despite the absence of positive controlled clinical trials in cancer pain, the tricyclic antidepressants are generally believed to provide relief from neuropathic pain.¹³¹ One consensus panel listed this pharmacologic category as one of several first-line therapies for neuropathic pain.¹³² Side effects can be dose-limiting. Cardiac arrhythmias, conduction abnormalities, narrow-angle glaucoma, and clinically significant prostatic hyperplasia are relative contraindications to the tricyclic antidepressants. Their sleep-enhancing and mood-elevating effects may be of benefit. Table 3 lists antidepressants and other adjuvant analgesics.

Newer serotonin-norepinephrine reuptake inhibitor agents have been shown to be effective in relieving neuropathic pain, including venlafaxine and duloxetine.^{133,134} These have the added advantage of treating hot flashes, a common and disturbing

symptom, particularly in breast cancer patients undergoing hormonal therapy. However, an important drug-drug interaction has been identified between tamoxifen and strong CYP 2D6 inhibitors, including duloxetine. Concomitant use reduces the bioavailability of tamoxifen, potentially limiting survival.¹³⁵ There remains little support for the analgesic effect of SSRIs.¹³⁰

The most commonly employed antiepilepsy drugs for the treatment of cancer pain are gabapentin and pregabalin.¹³⁶ These agents act at the α - δ subunit of the voltage-gated calcium channel. Both have undergone extensive testing in many noncancer neuropathy syndromes.¹³⁷ A recent review concluded that these drugs have a clinically meaningful effect.¹³⁰ The most common adverse effects reported by patients are dizziness; some patients also develop fluid retention. Other anticonvulsants have been reported to be successful in treating neuropathies, including lamotrigine, levetiracetam, tiagabine, topiramate, and lacosamide, yet the data in support of these agents are not conclusive.¹³⁰ As with most adjuvant analgesics, these agents will be used in combination with opioid therapy, particularly when pain is moderate to severe. A review of cancer trials found that adjuvant analgesics added to opioids provide

additional relief, usually within 4 to 8 days, with the strongest evidence for gabapentin.¹³⁸ Another report described the successful use of gabapentin to reduce mucositis pain in patients receiving concomitant radiotherapy and chemotherapy.¹³⁹

Corticosteroids have long been used to relieve neuropathic pain syndromes, including plexopathies, and pain associated with stretching of the liver capsule due to metastases.¹⁴⁰ Corticosteroids have also been effective for treating bone pain due to their anti-inflammatory effects as well as relieving malignant intestinal obstruction. Unfortunately, very little research exists regarding the efficacy of these agents in cancer pain. Dexamethasone produces the least amount of mineralocorticoid effect and is available in a variety of delivery forms, including oral, intravenous, subcutaneous, and epidural. The standard dose is 4 to 24 mg/day and can be administered once daily due to the long half-life of this drug.³ Doses as high as 100 mg may be given with severe pain crises. Intravenous bolus doses should be pushed slowly, to prevent uncomfortable perineal burning and itching. Long-term use can lead to myopathy and osteonecrosis.¹⁴¹

Local anesthetics act by inhibiting the movement of ions across the neural membrane.¹⁴² They are useful in preventing procedural pain and in relieving neuropathic pain. Local anesthetics can be given topically, intravenously, subcutaneously, or spinally.¹⁴³ Both gel and patch versions of lidocaine have been shown to reduce the pain of postherpetic neuropathy and cancer-related pain.^{143,144} Intravenous or subcutaneous lidocaine at 1 to 5 mg/kg administered over 1 hour, followed by a continuous infusion of 1 to 2 mg/kg/hour, has been reported to reduce intractable neuropathic pain in patients in inpatient palliative care and home hospice settings.¹⁴² Epidural or intrathecal lidocaine or bupivacaine delivered with an opioid can reduce neuropathic pain.¹⁴⁵

Antagonists to NMDA are believed to block the binding of glutamate and other excitatory amino acids in the spinal cord. The most commonly used agent, ketamine, is given by a variety of routes: oral, intravenous, subcutaneous, intranasal, sublingual, epidural, intrathecal, and topical. The usual oral dose of ketamine is 10 to 15 mg every 6 hours. Parenteral dosing is typically 0.04 mg/kg/hour with titration to a maximum of 0.3 mg/kg/hour. Onset of analgesia is 15 to 30 minutes, with the duration of effect ranging between 15 minutes to 2 hours.

A general recommendation is to reduce the opioid dose by approximately 25% to 50% when starting ketamine to avoid sedation. Although a Cochrane review found insufficient trials to determine its safety and efficacy in relieving cancer pain, case reports and small studies suggest that intravenous or oral ketamine can be used in adults and children with cancer for the relief of intractable neuropathic pain or to reduce opioid doses.¹⁴⁶ Routine use is often limited by cognitive changes and other adverse effects. In addition, an oral formulation is not commercially available in the United States. The parenteral solution can be used for oral delivery but the bitter taste must be masked by adding juice or cola.

In a small (n=10) study of cancer patients who reported pain that was unrelieved with morphine, a slow bolus of ketamine (0.25 mg/kg or 0.50 mg/kg) was evaluated using a randomized, double-blind, crossover, double-dose design. Ketamine significantly reduced the pain intensity in almost all the patients at both doses, with greater effect seen in those treated with higher doses. Adverse effects, including hallucinations and unpleasant cognitive sensations, responded to diazepam at a dose of 1 mg intravenously.¹⁴⁷ Another small study included young children and adolescents who were receiving high doses of opioids yet continued to experience uncontrolled cancer pain. The effect of adding a low-dose ketamine infusion was evaluated, with 8 of 11 patients demonstrating improvement in pain with a reduction in opioid dose.¹⁴⁸

Bisphosphonates inhibit osteoclast-mediated bone resorption and alleviate pain related to metastatic bone disease and multiple myeloma.^{43,149} Pamidronate disodium has been shown to reduce the pain, hypercalcemia, and skeletal morbidity associated with breast cancer and multiple myeloma.^{150,151} Dosing is generally repeated every 4 weeks and the analgesic effects occur in 2 to 4 weeks. Despite these experiences, a combined analysis of 2 randomized, controlled trials of pamidronate in men experiencing pain due to prostate cancer failed to demonstrate any pain relief or prevention of fractures.¹⁵² Zoledronic acid has also been shown to relieve pain due to metastatic bone disease, with at least one study suggesting superiority when compared with pamidronate.^{153,154} Ibandronate, another bisphosphonate, is taken either orally or intravenously and has been shown in a small trial to reduce pain in women with metastatic breast

cancer.¹⁵⁵ A newer compound, denosumab, is a monoclonal antibody that inhibits receptor activator of nuclear factor kappa-B (RANK) ligand to reduce bone loss. It has been approved for use in postmenopausal women at risk for osteoporosis¹⁵⁶ and more recently in the prevention of skeletal events in patients with bone metastases from solid tumors.¹⁵⁷ Older agents, including clodronate and sodium etidronate, appear to provide little or no analgesia.¹⁵⁸ A troubling adverse effect of bisphosphonates is the development of osteonecrosis of the jaw. This is more common when the drug is delivered intravenously, in those with cancer, and in patients who have had recent tooth extraction or dental surgery.¹⁵⁹

Calcitonin is available in subcutaneous or nasal formulations. Usual doses are 100 to 200 IU/day administered subcutaneously or nasally. However, although a Cochrane review found no evidence to support the use of calcitonin for bone pain, some experts suggest a trial when other options have failed.¹⁶⁰

Topical capsaicin, believed to relieve pain by inhibiting the release of substance P, has been shown to be useful in relieving pain associated with post-mastectomy syndrome, postherpetic neuralgia, and postsurgical neuropathic pain in cancer.¹⁶¹ Discontinuation is common, however, due to an increase in pain and burning. A high-concentration (8%) topical capsaicin patch applied for 1 hour has been shown to be effective in the relief of postherpetic neuropathy and human immunodeficiency virus-associated painful neuropathy.^{162,163} This may one day be of benefit in patients with cancer pain.

There is much interest in and controversy surrounding the use of cannabinoids for the relief of cancer pain. The cannabinoid receptors (CB1 and CB2) have been characterized, increasing our understanding of their role in pain. This has also allowed for the development of more selective agents that might provide analgesia without the central nervous system depressant effects seen with tetrahydrocannabinol. Evidence exists for the efficacy of some of these new selective compounds in animal models of noncancer and cancer pain, as well as in patients with neuropathy due to multiple sclerosis.^{164,165} However, review of the existing literature evaluating the role of cannabinoids currently approved for human use suggests that these agents are moderately effective with comparable adverse effects.¹⁶⁶ Concerns regarding the long-term safety and regulatory implications remain.¹⁶⁷

Anticancer Therapies

Palliative chemotherapy is the use of antitumor therapy to relieve symptoms associated with malignancy, and one example includes the reduction of dyspnea in those with lung cancer. Radiotherapy, given as single or multiple fractions, can be very effective in reducing pain associated with bone metastases or other lesions.¹⁶⁸ When considering these and other antitumor approaches, patient goals, performance status, sensitivity of the tumor, and potential toxicities must be considered. Communication with patients and their families clearly outlining the goals of these therapies is essential.¹⁶⁹

Routes of Administration

Numerous routes of drug administration are available, which is of particular benefit in oncology. In a study of cancer patients at 4 weeks, 1 week, and 24 hours before death, the oral route of opioid administration was continued in 62%, 43%, and 20% of patients, respectively.¹⁷⁰ When oral delivery is no longer feasible, many alternative routes exist. Sublingual, buccal, rectal, transdermal, subcutaneous, intramuscular, intravenous, pulmonary, nasal, spinal, and peripheral (topical) have all been described. Lipid solubility and the size of the molecule influence the transport of the opioid across biological membranes, affecting the pharmacokinetics of an agent. However, because a drug can be administered by a particular route does not imply that it will be effective. For example, topical morphine is not bioavailable, despite anecdotal reports of its effectiveness.¹⁷¹

Numerous options are available when patients are unable to swallow tablets or pills, including liquids or opening 24-hour, long-acting morphine capsules and placing the “sprinkles” in applesauce or other soft food. Oral morphine and oxycodone solutions can be swallowed or small volumes of a concentrated solution (eg, 20 mg/mL) can be placed sublingually or buccally in patients whose voluntary swallowing capabilities are limited.^{172,173} Liquid hydromorphone is also commercially available but not in a more concentrated solution. Most of the analgesic effect of liquid opioids administered in this manner is due to the drug trickling down the throat and the resultant absorption through the GI tract. Topical morphine mouthwash has been studied to treat chemotherapy-induced oral mucositis with positive results.¹⁷⁴

Enteral feeding tubes can be used to deliver medications when patients can no longer swallow. The size of the tube should be considered when placing long-acting morphine “sprinkles” to avoid obstruction. Commercially prepared suppositories, compounded suppositories, or microenemas can be used to deliver the drug into the rectum or stoma. Sustained-release morphine tablets have been used rectally, with resultant delayed time to peak plasma level and approximately 90% of the bioavailability when compared with oral administration.¹⁷⁵ Rectal methadone has bioavailability approximately equal to that of oral methadone.⁸⁷ Thrombocytopenia, neutropenia, or painful lesions may preclude the use of these routes. Clinicians should think about the burden on caregivers when considering these routes as it can be difficult for family members to administer the drug when the patient is obtunded or unable to assist in turning.

Several formulations of fentanyl are now available, including oral transmucosal fentanyl (comprised of fentanyl on an applicator that patients rub against the oral mucosa to provide rapid absorption of the drug), fentanyl buccal soluble film, and buccal tablets.¹⁷⁶⁻¹⁷⁹ The around-the-clock dose of the long-acting opioid does not predict the effective dose of these fentanyl formulations, and therefore dosing must be done carefully. Pain relief can usually be expected to be more rapid when compared with immediate-release morphine.

Currently, no pure agonist opioid is commercially available by the nasal route. Early studies of fentanyl, hydromorphone, and morphine suggest this may be an effective alternative.^{78,180,181}

Parenteral administration includes subcutaneous and intravenous delivery; intramuscular opioid delivery is inappropriate in oncology due to the pain associated with this route and the variability in systemic uptake of the drug. The intravenous route provides rapid drug delivery but requires vascular access, which can be cumbersome and places the patient at increased risk of infection. Subcutaneous boluses have a slower onset and lower peak effect when compared with intravenous boluses, although at continuous infusion produce similar levels of analgesia.¹⁸² Boluses can be given using an indwelling subcutaneous needle with preloaded syringes, eliminating the need for costly infusion pumps.¹⁸³ Subcutaneous infusions may include up to 10 mL/hour (although most patients absorb 2-3 mL/hour with the least difficulty).¹⁸⁴

Intraspinal routes, including epidural or intrathecal delivery, may allow the administration of drugs, such as opioids, local anesthetics, and/or an α_2 adrenergic agonist (such as clonidine), that can be helpful in the face of unrelieved cancer pain or intolerance of systemic opioid administration.¹⁸⁵ A randomized controlled trial demonstrated benefit for cancer patients experiencing pain.¹⁸⁶ Access to experts who can deliver this care, cost, complexity of the equipment used to deliver these medications, and potential caregiver burden must all be considered.¹⁸⁷

Topical morphine has poor bioavailability and should not be used in the management of cancer-related pain. Controversy exists regarding whether topical morphine or other opioids might be useful in providing pain relief when applied to open areas, such as pressure ulcers. Several case reports and open-label trials indicate this might be an effective route, yet a randomized controlled trial of topical morphine used to treat painful skin ulcers found no benefit when compared with placebo.¹⁸⁸ An analysis of the bioavailability of morphine when delivered to open ulcers found little systemic uptake, a possible explanation for the lack of efficacy.¹⁸⁹

Transdermal fentanyl has been used extensively and a wide range of dosing options (12.5-, 25-, 50-, 75-, and 100- μ g/hour patches) makes this route particularly useful when patients have dysphagia.^{190,191} It has been found to be comparable to oral sustained-release morphine in efficacy and tolerability.⁸⁸ There is some suggestion that transdermal fentanyl may produce less constipation when compared with long-acting morphine. A small subset of patients will develop skin irritation due to the adhesive in any patch. Spraying an aqueous steroid inhaler intended to treat asthma onto the area of application and allowing it to dry before applying the patch will often prevent skin reactions. A small but significant percentage of patients will experience decreased analgesic effects within only 48 hours of applying a new patch; this is managed by increasing the number of times the patch is changed to every 48 hours. As discussed earlier, cachexia results in reduced serum levels of fentanyl. Since dosing is done empirically, this does not preclude the use of a fentanyl patch in cachectic patients, yet dosing may need to be escalated. Early experience with transdermal buprenorphine is promising.¹⁹²

Principles of Cancer Pain Management

Basic guidelines will optimize the pharmacologic management of cancer patients with pain. These include anticipating, preventing, and treating side effects and adverse drug effects. Be aware of potential drug-drug and drug-disease interactions when devising the treatment plan. Analgesics should be titrated based on the patient's goals, their pain intensity, and the severity of undesirable or adverse drug effects. Their ability to function and sleep, their emotional state, and patients'/caregivers' reports of the impact of pain on the patient's QOL should also be considered when modifying the treatment plan. During this period of titration, monitor the patient's status frequently.

When including opioids in the treatment plan, changing from one opioid to another or one route to another is often necessary when adverse effects cannot be managed or when dose escalation fails to produce analgesia, and therefore facility with opioid rotation is an absolute necessity.¹⁹³ Use morphine equivalents as a “common denominator” for all dose conversions to avoid errors. Use equianalgesic tables, realizing these are approximations (see Table 4 for a standard equianalgesic table). Because incomplete cross-tolerance occurs, reduce the dose of the newly prescribed opioid, usually by 25%. For most patients, sustained-release formulations and around-the-clock dosing should be used for continuous pain syndromes.⁵¹ Immediate-release formulations should be made available for breakthrough pain. Cost and convenience (and issues influencing adherence) are highly practical and important matters that should be taken into account with every prescription. The NCCN produces practice guidelines for cancer pain management in adults that serve as an excellent resource for clinicians.⁴ Figures 1 and 2 provide guidelines for initiating short-acting opioids in opioid-naïve and opioid-tolerant patients. When faced with complex pain syndromes and the application of standard guidelines has been ineffective, obtain consultation from pain management experts.

Safe Handling

Diversion of medically appropriate analgesic agents, including opioids, is a serious public health problem. Furthermore, entry of these medications into the water supply is a significant environmental concern.

TABLE 4. Approximate Equianalgesic Doses of Most Commonly Used Opioid Analgesics

DRUG	PARENTERAL ROUTE	ENTERAL ROUTE
Morphine	10 mg	30 mg
Codeine	130 mg	200 mg (not recommended)
Fentanyl	50-100 µg	oral transmucosal and buccal available
Hydrocodone	Not available	30 mg
Hydromorphone	1.5 mg	7.5 mg
Levorphanol ^a	2 mg	4 mg
Methadone ^a		
Oxycodone	Not available	20 mg
Oxymorphone	1 mg	10 mg
Tramadol	Not available	50-100 mg

^aThese drugs have long half-lives and therefore accumulation can occur; close monitoring during the first few days of therapy is very important. See text for methadone conversion information.

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Patients and their caregivers should be advised to store medications in a secure, locked location, out of sight of children or other visitors. All family members should be advised to monitor their prescriptions. When expired or no longer needed, medications can be brought to designated safe disposal sites (eg, some pharmacies and police departments are offering these services, often in collaboration with the Environmental Protection Agency). If these options are not available, placing pills in kitty litter with liquid or adding to wet coffee grounds ensures they will degrade, will not directly enter the water supply, and will not be diverted, intentionally or unintentionally (see several websites for more information: <http://www.painfoundation.org/painsafe/safety-tools-resources/> and <http://notinmyhouse.drugfree.org/steps.aspx#monitor>).^{194,195}

Interventional Therapies

Interventional therapies, including nerve blocks, vertebroplasty, kyphoplasty, and other techniques, can be useful in the relief of cancer pain.^{3,196-199} Few of these procedures have undergone controlled clinical studies. One exception is the celiac plexus block, which has been shown to be superior to morphine in patients with pain due to unresectable pancreatic cancer.²⁰⁰ Vertebroplasty includes the injection of polymethylmethacrylate into the vertebral body, restoring mechanical stability while reducing pain

INITIATING SHORT-ACTING OPIOIDS IN OPIOID NAÏVE PATIENTS^a Monitor for acute and chronic adverse effects.

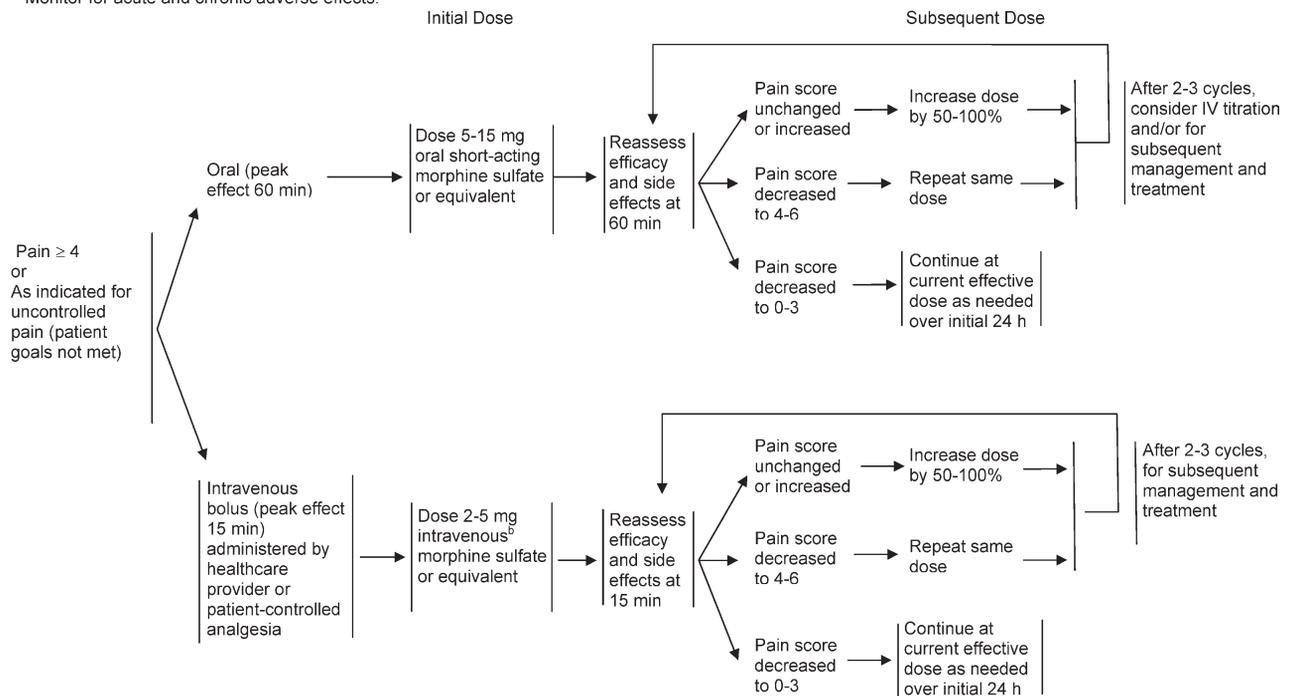


FIGURE 1. Initiating Short-Acting Opioids in Opioid-Naïve Patients. IV indicates intravenous. ^aOpioid naïve includes patients who are not chronically receiving opioid analgesic on a daily basis. ^bSubcutaneous can be substituted for IV; however, the subcutaneous route delays the onset of effect by up to 30 minutes. Reproduced with permission from the **National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines™) for Adult Cancer Pain V.1.2010**. © 2010 National Comprehensive Cancer Network, Inc. All rights reserved. The NCCN Guidelines™ and illustrations herein may not be reproduced in any form for any purpose without the express written permission of the NCCN. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES™, and all other NCCN Content are trademarks owned by the National Comprehensive Cancer Network, Inc.

and neurological symptoms.²⁰¹ Kyphoplasty is a related procedure in which a balloon is first placed within the vertebral body to serve as a compartment area for the injectate. These techniques have been most widely studied in pain due to multiple myeloma. Prospective evaluation of percutaneous radiofrequency ablation of bone metastases suggests improved pain control.²⁰² Spinal cord stimulation has been suggested to be useful for painful chemotherapy-induced peripheral neuropathies.²⁰³ Botulinum toxin injections into areas of muscle spasticity, tightness, and pain can result in relief. Although used extensively in migraine treatment and chronic pain conditions, this has been used more recently to relieve pain in people with cancer who experience radiation fibrosis, such as cervical dystonia, trigeminal nerve pain, and headache.²⁰⁴

Choosing one of these techniques is dependent upon the availability of experts in this area who understand the special needs of cancer patients. Oncologists should closely collaborate with anesthesiologists, interventional radiologists, neurosurgeons, and others within their clinical setting to clarify appropriate

patient selection. Imaging prior to the consult is warranted to guide interventional therapists, along with recent hematology profiles to ensure adequate platelet numbers to preclude bleeding complications. The patient's overall condition and ability to undergo the procedure should be taken into consideration.

Physical Techniques

Physical measures, such as physical activity, physical and occupational therapy, orthotics, and assistive devices can serve as adjuncts to analgesics in the management of cancer pain.^{205,206}

Optimally, physicians with training in physical medicine and rehabilitation can provide guidance to oncologists regarding the most advantageous technique for an individual patient. The patient's and caregivers' abilities to participate must be considered when selecting one of these therapies, including their fatigue level, interest, cognition, and other factors. Lymphedema is a common phenomenon in cancer and an excellent example of the benefit of collaboration with physical medicine and rehabilitation specialists.²⁰⁷ Physical activity, manual decompression, and

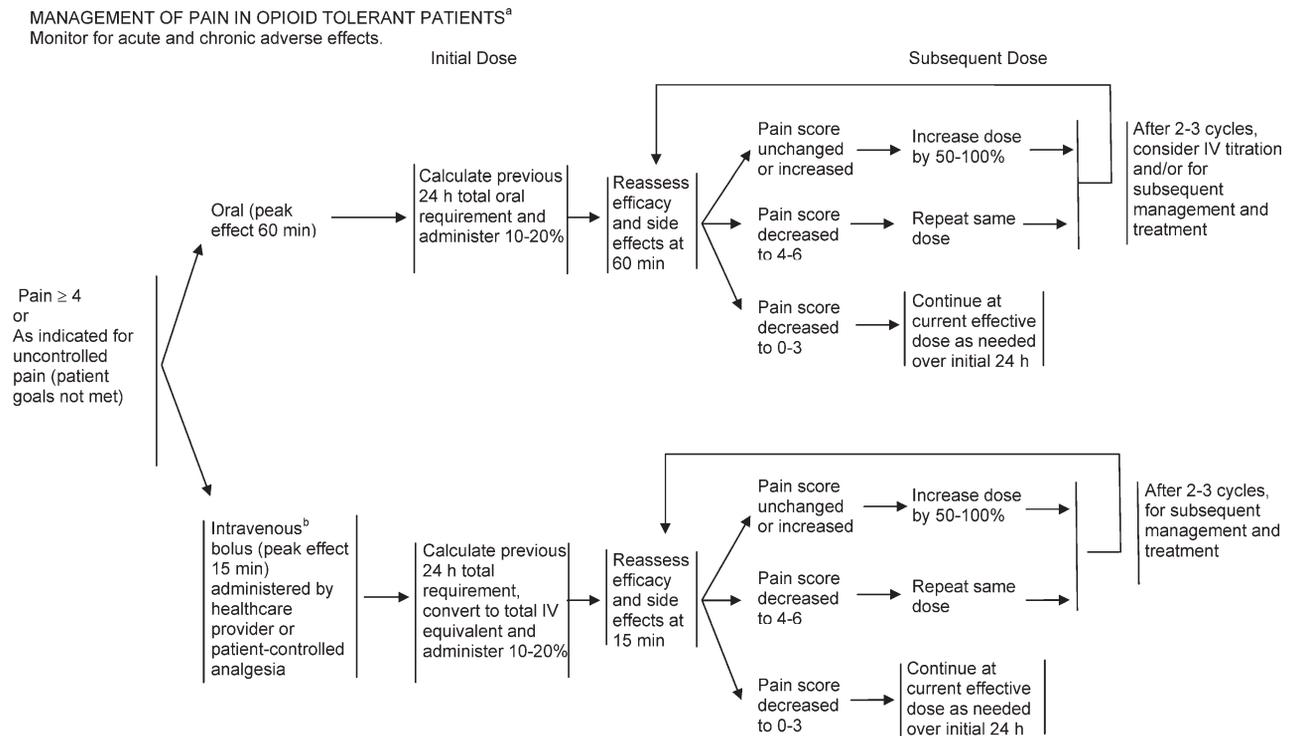


FIGURE 2. Management of Pain in Opioid-Tolerant Patients. IV indicates intravenous. ^aOpioid tolerant includes patients who are chronically receiving opioid analgesic on a daily basis. ^bSubcutaneous can be substituted for intravenous; however, the subcutaneous route delays the onset of effect by up to 30 minutes. Reproduced with permission from the **National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines™) for Adult Cancer Pain V.1.2010**. © 2010 National Comprehensive Cancer Network, Inc. All rights reserved. The NCCN Guidelines™ and illustrations herein may not be reproduced in any form for any purpose without the express written permission of the NCCN. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES™, and all other NCCN Content are trademarks owned by the National Comprehensive Cancer Network, Inc.

other physiotherapy techniques can reduce burden and pain.²⁰⁸ More research is needed regarding the role of these physical measures in producing pain relief.

Cognitive-Behavioral and Physical Medicine Interventions

Pain has been described above as an all-consuming experience including physical, psychosocial, and spiritual dimensions. Therefore, the treatment of cancer pain inherently requires combined therapies inclusive of cognitive-behavioral interventions. Thorough pain assessment can identify concurrent psychological symptoms such as depression or anxiety as well as the psychosocial sequelae of pain including fear, insomnia, or agitation. An excellent guide to the assessment of these factors is the NCCN psychological distress guidelines.⁴¹

The field of psychosocial oncology has advanced over the past 2 decades, with a strong body of evidence supporting the efficacy of cognitive-behavioral interventions. Social workers and psychologists are skilled in the assessment of psychological needs and selection of coping strategies. Patients and families

should be assured that emotional responses are expected in cancer and that integration of psychosocial interventions can support their ability to deal with treatment or symptoms such as pain.

Psychosocial interventions are aimed at enhancing a sense of control over the pain or underlying disease. Breathing exercises, relaxation, imagery, hypnosis, and other behavioral therapies can be very useful. Physical modalities such as massage, use of heat or cold, acupuncture, acupressure, and other physical methods can be provided in consultation with physical or occupational therapy. These treatments can greatly enhance patients' sense of control as well as greatly reduce the family caregivers' sense of helplessness when they are engaged in pain relief.⁴¹

The integration of cognitive-behavioral or physical medicine interventions should also be based on assessment of cultural considerations. Many patients hold cultural beliefs about such treatments, and home remedies, rituals, prayer, and other spiritual practices may be most helpful in relieving or coping with pain. Integrative oncology is the synthesis of mainstream cancer care and complementary therapies

that are evidence-based.²⁰⁹ Psychosocial interventions for cancer pain may include the following categories: cancer pain education, hypnosis and imagery-based methods, and coping skills training.²¹⁰ Educational programs are one of the most common interventions to address cancer pain barriers, and current studies provide high-quality evidence that pain education is feasible, cost-effective, and practical in oncology settings.^{7,210} Hypnosis and imagery appear to be beneficial for acute procedural pain and have been found to benefit women prior to breast biopsy.²¹¹ The effect of hypnosis/imagery on chronic cancer pain is less evident, and more studies are needed to explore the value of this technique. Finally, coping skills training may be beneficial for patients and family caregivers dealing with chronic cancer pain, although the dose and components of a coping skills training regimen remain uncertain.²¹⁰ Other integrative and behavioral approaches that may be beneficial for the management of cancer pain include massage therapy and acupuncture.²⁰⁹

There is growing interest in attention to spiritual needs in cancer care and the existential concerns often associated with pain.²¹² Pain has been associated with suffering and may be interpreted as a necessary part of illness or an act of redemption. Our increasingly culturally diverse population means that patients have diverse religious and spiritual beliefs and practices. Involvement of chaplains and other spiritual care providers is essential. Spiritual needs should be routinely assessed and oncology settings should incorporate spiritual care as a component of comprehensive pain assessment and treatment.⁴²

Special Populations

Elderly

Over 60% of patients diagnosed with cancer are over age 65 years and this percentage is expected to increase significantly over the next decade. The aging of the population and our enhanced ability to treat and support older patients with cancer has created an imperative to merge the best practices of oncology and geriatrics for the optimum treatment of this vulnerable population.^{213,214}

Substantial literature has been devoted to the topic of pain in the elderly, with numerous clinical practice guidelines and algorithms constructed for this group. There is strong consensus that pain

assessment in elderly patients should include the evaluation of concurrent chronic illness, which may include pain. Assessment should also determine the elderly patient's ability to report pain and any age-specific barriers to pain relief. For example, elderly patients may resist taking analgesics for fear of sedation or decreased function or to avoid side effects such as constipation.^{48,215}

Numerous studies have documented that elderly patients are often undertreated for pain, with patterns of low doses of analgesics or the use of only nonopioids. Guidelines from the APS, NCCN, and the American Geriatric Society recommend application of the same pharmacologic approaches as for younger adults with the direction to "start low and go slow" as the general rule of opioid titration and to compensate for possible concerns such as diminished drug metabolism and careful titration to effect.^{4,40,48}

There is also a substantial increase in those patients who are aged 85 years and older, the oldest old, in oncology. Geriatric oncologists emphasize the importance of individual assessment rather than treatment determined only by age. For those elderly patients confined to long-term care and with substantial cognitive impairment, there are several behavioral assessment scales designed to assess pain in the cognitively impaired or nonverbal elderly individual.^{45,214} These scales direct the clinician to assess for behaviors that might indicate pain such as vocalizations, frowning, withdrawal, rocking motion, or other signs of agitation.

Cancer Survivors

As survival rates improve, oncologists can expect to see an increase in the numbers of patients presenting with persistent pain syndromes. Tumor-related pain syndromes have long been recognized; now long-term, treatment-related pain etiologies are being described (Table 5).^{7,216,217} Although these pain syndromes are often characterized by the type of treatment employed, it is crucial to recall that most patients receive multiple modalities and the pain syndromes may reflect a combined effect of treatments (eg, radiation effects with combined fluorouracil effects). Surgery has long been documented to lead to persistent pain, including phantom sensations after limb amputation and chronic syndromes such as the post-thoracotomy or postmastectomy syndrome. Postradiation syndromes can occur from 6 months to 20 years after receiving treatment.

TABLE 5. Chronic Pain Syndromes Related to Cancer Treatment

Surgical pain syndromes	
• Postamputation phantom pain	• Postmastectomy pain
• Post-thoracotomy pain	
Radiation-related pain syndromes	
• Chest pain/tightness	• Osteoradionecrosis
• Cystitis	• Pelvic fractures
• Enteritis	• Peripheral nerve entrapment
• Fistula formation	• Plexopathies
• Myelopathy	• Proctitis
• Osteoporosis	• Secondary malignancies
Stem cell transplantation-mediated chronic graft-versus-host disease	
• Scleroderma-like skin changes	• Dyspareunia, vaginal pain
• Eye pain and dryness	• Paresthesias
• Oral pain and reduced jaw motion	• Arthralgias, myalgias
• Dysuria	
Chemotherapy-related pain syndromes	
• Chemotherapy-induced peripheral neuropathy	• Osteonecrosis from corticosteroids
Hormonal therapy-related pain syndromes	
• Osteoporotic compression fractures	• Arthralgias

Although not systematically studied, late effects have been reported to include fistula formation, plexopathy, and bone fractures.²¹⁸⁻²²⁰ Long-term corticosteroid use can result in osteonecrosis.

Chemotherapy can lead to painful peripheral neuropathies and these are increasing as more neurotoxic agents are introduced into clinical practice. The incidence of chemotherapy-induced peripheral neuropathy (CIPN) is variable (30%–40%) and is largely dependent on several factors, including patient age, dose intensity, cumulative dose, duration of therapy, use of regimens containing multiple neurotoxic chemotherapy agents, and any pre-existing conditions that are associated with peripheral neuropathy, such as diabetes and alcohol abuse.²²¹ CIPNs are bilateral, usually in a “stocking and glove” distribution.²²²⁻²²⁵ To date, both prevention and treatment studies have suffered from trial design flaws, including small sample sizes, heterogeneous samples, and lack of a control group.²²¹ When symptoms are severe or irreversible, CIPN can lead to serious clinical and QOL consequences for patients. Understanding the relationship between CIPN and

QOL in cancer is important. To thoroughly understand how CIPN affects patients’ QOL, there is a need to capture the overall experience of living with CIPN from the patient’s perspective. A recent qualitative study described CIPN symptom experience and the effect of symptoms on everyday life.²²⁶ Patients described CIPN as “background noise” that can be overshadowed by other treatment- and disease-related issues, but CIPN’s unpleasantness can interfere with daily activities and socialization.²²⁶ The awareness of CIPN was often inaccurate and surprising because most patients did not recall being educated or advised to anticipate the symptoms. When monitoring CIPN, clinicians primarily focused on how the symptoms affected motor functionality (dexterity, gait) but rarely asked about CIPN’s effect on daily living.²²⁶ CIPN caused disruptions with daily living, leisure, work, and family roles.²²⁶ Patients who reported a pain component to their CIPN often experienced functional difficulties, fatigue, sleep disturbance, and mood disturbances.²²⁶ Patients also described the use of multiple processes in learning to live with CIPN.²²⁶ Similar results have been described in another qualitative study conducted by Closs et al²²⁷ as well as Sun et al,²²⁸ who explored the impact of CIPN on QOL in a cohort (n=53) of patients with colorectal cancer. Findings suggest that significant differences in QOL were found after treatment initiation with an oxaliplatin-based regimen.²²⁸

Hormonal therapies, particularly the aromatase inhibitors used in the treatment of breast cancer, have been known to produce arthralgias.²²⁹⁻²³³ Systematic studies of women receiving these therapies revealed that 47% experienced joint pain, and 67% of the women with pain rated it as moderate to severe.²³⁴ In some cases, this leads to lack of adherence or cessation of treatment.²³⁵ Treatment is empiric, including acetaminophen, NSAIDs, opioids, glucosamine/chondroitin, omega-3 fish oil, probiotics, and physical activity, although none of these have undergone systematic investigation.²³⁶ A recent study revealed the efficacy of twice-weekly acupuncture administered over 6 weeks.²³⁷

Graft-versus-host disease (GVHD) is a serious adverse effect of stem cell transplantation and several chronic pain syndromes are being seen, particularly in those patients receiving allogeneic donor cells.^{238,239} Scleroderma-like skin fibrosis, leading to

severe pain and limited range of motion, can result, along with damage to mucous membranes.²⁴⁰ These patients also report painful peripheral neuropathies. The primary treatment of chronic GVHD incorporates immunosuppression with prednisone, plus cyclosporine or tacrolimus, often for 5 years or more.^{239,241} Unfortunately, little is known about the supportive care of patients with chronic GVHD, particularly strategies that might be effective in relieving pain.

As those with cancer live longer, more painful syndromes will likely be appreciated. Greater understanding through research is warranted.

Cancer Pain Management in People With Addictive Disease

As individuals live longer, and as the prevalence of substance abuse increases in the general population in the United States, oncologists and oncology professionals are more likely to care for patients with concomitant cancer pain and addictive disease. It is estimated that 7.1 million Americans are dependent on or have abused an illicit drug during 2009 and 8% of people aged 12 years and older have used an illicit substance within the past month.^{242,243}

Those with addictive disease are not a uniform group of individuals, creating complexities in the clinic as the type of care needed differs. For example, some people have a past history of addiction, yet have undergone recovery and continue to participate in a 12-step program. These patients may be extremely reluctant to take appropriate pain medications, particularly opioids, as they fear compromising their sobriety. Other patients may be currently abusing alcohol, opioids, and/or other substances.²⁴⁴⁻²⁴⁶ The challenge in the clinic is understanding who is at greatest risk for addictive disease and differentiating behaviors indicative of addiction from other factors, as well as knowing how to safely manage pain in patients with cancer who are at high risk for addiction.

The first step is to clearly understand the terminology surrounding addiction, including physical dependence and tolerance (Table 6). Second, the clinician must be aware of risk factors for addiction, which include a family history of substance abuse, personal drug or alcohol abuse, mental health problems, sexual abuse (particularly if this occurred as a preteen), multiple motor vehicle accidents, legal

TABLE 6. Definition of Addiction and Related Terms (From AAPM, APS, and ASAM [2001])

Addiction: A primary, chronic, neurobiological disease with genetic, psychosocial, and environmental factors influencing its development and manifestations. Includes the following behaviors: impaired control over drug use, compulsive use, continued use despite harm, and craving.
Physical dependence: A state of adaptation that is manifested by a drug class-specific withdrawal syndrome that can be produced by rapid cessation, decreasing blood level of the drug, and/or administration of an antagonist.
Tolerance: A state of adaptation in which exposure to a drug induces changes that result in diminution of one or more of the drug's effects over time.

AAPM indicates American Academy of Pain Medicine; APS, American Pain Society; ASAM, American Society of Addiction Medicine.

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problems, and cigarette smoking. At times it is difficult to determine why a patient may not be following a treatment plan and the assumption may be that they are exhibiting behaviors suggestive of addictive disease. However, other factors may explain altered drug-taking behavior (Table 7).^{245,246}

Using this information, clinicians can stratify their care based upon whether the patient is at low, medium, or high risk for addiction.²⁴⁷ For those patients with low risk, usual care is indicated. For those with medium risk, more vigilance is warranted. For those at high risk, agreements or contracts and random urine toxicology may be indicated, along with prescriptions for reduced duration (eg, 1-2-week supply vs 1-month supply). Sanctions for those found to have no opioids (suggestive of selling their medications) or finding other substances (implying interactions with family or friends using these agents) are enforced. Clinicians are encouraged to review Cone and Caplan²⁴⁸ for more information regarding the interpretation of urine toxicology findings.

When caring for those with medium or high risk, whether in the clinic or inpatient setting, a team approach involving oncologists, nurses, pharmacists, social workers, psychiatrists, psychologists, and other professionals is crucial, with regular case conferences to ensure consistent communication and expectations. Consultation with addiction specialists, if available, is vital. Goals should be realistic; the patient recently diagnosed with cancer or metastatic disease may be open to change or they may be overwhelmed or may not have the insight or other resources to consider life changes. Because some

TABLE 7. Differential Diagnosis of Aberrant Drug-Taking Behavior

▶ Addiction
▶ Pseudoaddiction (inadequate analgesia)
▶ Other psychiatric disorders
○ Chemical coping
○ Mood disorders (anxiety, depression)
○ Encephalopathy
○ Borderline personality disorder
▶ Inability to follow a treatment plan (low literacy)
▶ Criminal intent (selling or sharing drugs)

Adapted from Passik S, Kirsh KL, Portenoy RK. Pain and addictive disease. In: Von Roenn JH, Paice JA, Preodor ME, eds. *Current Diagnosis and Treatment of Pain*. New York, NY: Lange Medical Books; 2006:79.

individuals use substances to self-medicate mental illness, depression and comorbid psychiatric problems should be addressed. Whenever possible, treat the underlying cause of the pain (eg, radiotherapy for bone metastases). Introduce nondrug methods of pain control, including physical measures such as heat, cold, physical therapy, and the use of orthotic devices, as well as cognitive-behavioral approaches.²⁴⁹

When devising a pharmacologic treatment plan, a few strategies may be helpful when caring for those individuals at medium or high risk for addiction. Maximize the use of nonopioids (eg, NSAIDs and acetaminophen) and adjuvant analgesics (eg, antidepressants, antiepilepsy drugs). Select long-acting opioids whenever possible and minimize short-acting doses if possible. Avoid the parenteral route when administering opioids unless the patient is unable to receive oral medications; in that case, use continuous infusions rather than bolus administration. When patients have been using opioids recreationally, consider tolerance when devising a pharmacologic regimen as these patients generally require higher doses of opioids. Finally, clear documentation is necessary, including the 4 “As”: analgesia, activity, adverse effects, and aberrant behaviors (eg, finishing a month’s supply too soon, lost medications, etc).^{245,246}

Pain at the End of Life

Despite advances in cancer treatment, over 570,000 individuals die each year from cancer and greater than 70% are expected to have pain as a symptom at

the end of life. Hospice care has been the gold standard of end-of-life care, with aggressive attention to pain relief so that patients can have quality and meaning in the last phase of life.^{4,250}

Expert pain management in the terminal phase applies the principles cited above in relation to both pain assessment and pain management. Ongoing comprehensive pain assessment is necessary to detect changes in pain such as the development of painful bone metastasis, resolution of treatable causes such as infections, or worsened nociceptive or visceral pain due to tumor growth.⁴

Careful refinement of pain management regimens are often required at the end of life including changes in the route of analgesics if patients can no longer take oral medications, the need to alternate opioids, or the addition of agents such as steroids for a pain crisis (as in pathological fracture). Oncologists should seek expert consultation from pain services or palliative care teams for these complex pain concerns. There is also very strong consensus that earlier referral to hospice care is essential to allow time for a carefully planned pain regimen to ensure comfort at the end of life. Pain is often accompanied by other symptoms at the end of life such as dyspnea, agitation, delirium, and anxiety and there is a need to carefully assess each symptom and coordinate interventions.²⁵⁰ Fortunately, a wide array of analgesics, varied routes of administration, and skilled

TABLE 8. Key Web Sites With Pain Information/Resources

American Academy of Hospice and Palliative Medicine http://www.aahpm.org
American Cancer Society http://www.cancer.org or http://www.cancer.org/Healthy/InformationforHealthCareProfessionals/pain-management-pocket-tool
American Pain Society http://www.ampainsoc.org
American Society for Pain Management Nursing http://www.aspmn.org
City of Hope Pain & Palliative Care Resource Center http://prc.coh.org
Hospice and Palliative Nurses Association http://www.hpna.org
The University of Texas MD Anderson Cancer Center http://www.mdanderson.org/patient-and-cancer-information/cancer-information/cancer-topics/dealing-with-cancer-treatment/pain-management/index.html

psychosocial spiritual support have been well established as the standard of care.

Conclusions

The urgent need to address the problem of cancer pain emerged in oncology in the 1970s, largely influenced by the introduction of hospice care. Hospice providers demonstrated that pain could be relieved and that failure to do so meant greatly diminished QOL. Over the past 30 years, the relief of cancer pain has become a

priority in oncology, with significant advances being made yet also with continued barriers to quality care and relief of pain. Many resources exist to assist clinicians with the treatment of cancer pain (Table 8).

The continued challenge for optimum pain relief rests on the identified barriers, including professional, patient, and system concerns. For the over 1.5 million people diagnosed each year with cancer, the over 12 million cancer survivors, and the over 570,000 individuals who will die each year, pain relief remains the most critical need. ■

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