Cancer-related pain management in clinical oncology

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Uncontrolled pain is one of the most feared and debilitating symptoms among cancer patients, and many suffer unnecessarily from suboptimal pain control. Cancer-related pain is often multidimensional and can affect all aspects of a patient's life. Hence, achieving adequate pain relief among cancer patients involves a proper assessment of psychosocial, spiritual, and physical pain issues, matched with an individualized treatment plan involving pharmacologic, nonpharmacologic, and procedural therapies when appropriate. Providing effective pain relief can help ease the overall burden of disease among oncology patients while helping them tolerate cancer-directed therapies and achieve the most optimal quality of life throughout all phases of the disease continuum. In this review, the authors will discuss the syndromes, assessment of, and treatment for cancer-related pain in the outpatient setting.

Clinical oncologists know that pain is prevalent among cancer patients and can present during any phase of illness. A meta-analysis described pain in 59% of patients in active treatment, 33% of survivors after treatment, and 64% of those with metastatic, advanced, or terminal disease.[1] Pain is not only one of the most common cancer-related symptoms but among the most feared.[2] Suboptimal pain management can lead to severe and unnecessary physical suffering, hindered relationships, and an overall decrease in patient quality of life.

Despite recognition of its importance, pain management for patients with cancer is not always adequate. In a prospective study published in 2012 that assessed more than 3,000 outpatients, 33% of cancer patients reporting pain were found to be receiving inadequate analgesia, and 23% of patients with severe pain and 27% of those with moderate pain were not receiving any analgesia.[3] A review of 26 relevant studies conducted in 2008 suggested that 43% of cancer patients had pain that was undertreated.[4]

Cancer-related pain is often multidimensional, involving nociceptive and neuropathic pain, and may affect many aspects of a person's life, including their psychosocial and spiritual health. Conversely, psychological, social, and spiritual factors can affect both the patient's pain experience and its clinical manifestation; thus, pain in cancer patients can have a complex presentation. Appropriately assessing pain, developing an analgesic regimen, minimizing medication adverse effects, and optimizing patient compliance are all key components to effective pain management. Increasingly, some form of screening for substance abuse disorders is also important. In this review, we discuss the syndromes, assessment of, and treatment for cancer-related pain in the outpatient setting.

Syndromes

Cancer pain syndromes are defined by particular pain characteristics and physical symptoms that are associated with the underlying disease process or its treatments. These pain syndromes can be acute or chronic and are categorized according to their etiology. Cancer pain is often multifactorial and may involve the malignancy itself, oncologic treatments, as well as psychosocial and spiritual distress. One study found that 60%-65% of cancer pain is related to direct tumor involvement, 20%-25% is related to cancer treatment, and 10%-15% is unrelated to the actual cancer.[5]

Malignancies can directly involve the bone, nerves, or viscera and can also produce an inflammatory response that can lead to worsening pain. Pain mechanisms can be categorized as neuropathic or nociceptive; nociceptive pain is often further categorized into somatic or visceral subtypes. Somatic pain results from injury to the skin, subcutaneous tissue, bone, muscle, blood vessels, and connective tissue; it is often described as localized, con-

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stant, aching, and dull. Visceral pain arises from damage to organs and the lining of body cavities, and can be described as poorly localized, cramping, and deep. Neuropathic pain arises from injury to nerve tissue, and is often described as burning, shooting, and electrical. Frequently neuropathic pain persists in the absence of ongoing neural tissue injury. Allodynia (pain response to a normally innocuous stimulus) and hyperalgesia (increased pain response to a normally painful stimulus) can also occur, and severe nerve damage can result in paresthesia, numbness, weakness, and muscle wasting.

Pain is one of the most common symptoms related to cancer therapy (Table 1). About 20% of chronic cancer pain problems are related to adverse consequences of chemotherapy, surgery, and radiation.[6] Among breast cancer survivors, 42% of patients have chronic pain.[7] Chemotherapy agents, including taxanes, vinca alkaloids, platinum-based compounds, epothilones, bortezomib, thalidomide, and lenalidomide, can lead to both acute and chronic neuropathic pain. The incidence of chemotherapy-induced peripheral neuropathy (CIPN) ranges from 30%-40% of patients receiving chemotherapy.[8] CIPN predominantly affects the peripheral nervous system and presents as a dose-dependent, sensory polyneuropathy that often begins acutely in the hands and feet.

Surgical interventions, such as thoracotomies or mastectomies, can also lead to pain syndromes. Chronic pain was noted in 20% of women after mastectomy or lumpectomy with axillary node dissection.[9] This is thought to be due to intercostobrachial nerve trauma. Similarly, patients who have undergone thoracotomies or port insertions for intravenous access may develop postthoracotomy syndrome, presenting as numbness, tenderness, and burning sensations over the surgical site, likely from injury to the intercostal nerves. Radiation therapy can lead to plexopathies, enteritis, and proctitis.

Psychosocial distress exists among cancer patients and has a reciprocal relationship with physical pain. Studies of terminally ill cancer patients found that one-fourth experienced adjustment disorders and/or major depression,[10] and terminally ill cancer patients who were depressed were 4 times more likely to have a high desire for hastened death than were nondepressed patients.[11] Cancer pain has also been identified as one of the largest contributors to emotional distress among cancer patients.[12] Conversely, psychosocial stress can exacerbate physical pain, as was elucidated by a meta-analysis of randomized controlled studies on adult cancer patients during 1966-2010 that found positive effects of psychosocial interventions on pain severity.[13]

Similarly, spiritual interventions can be important for some patients. Spirituality can be defined as the way in which people seek and express meaning and purpose in life, and involves an individual's interconnectedness with oneself, others, and that which one considers significant and sacred.[14] Hence, it is no surprise that spiritual distress exists among cancer patients as their illness can affect their values, hopes, fears, and relationships. As their disease progresses, cancer patients may find themselves wrestling with existential questions related to the purpose and meaning of life, death, sickness, and suffering. Research on end-stage cancer patients demonstrated a significant correlation between the will to live and existential, psychological, social, and physical sources of distress.[15]

Oncologic pain emergencies may also arise. In particular, malignant epidural spinal cord compression is a medical emergency that affects about 5%-10% of adult solid tumor patients.[16] It can lead to permanent neurologic impairment and paraplegia if it is not diagnosed early and treated

TABLE 1 Pain syndromes associated with oncologic therapeutic interventions[87]

Intervention	Pain syndrome
Chemotherapy	Mucositis, corticosteroid-induced perineal discomfort, peripheral neuropathy, chemotherapy-related headache, taxol-induced arthralgia and myalgia, 5-flurouracil-induced angina chest pain, palmar-plantar erythrodysesthesia syndrome, chemotherapy-induced digital ischemia, avascular necrosis of femoral or humeral head, plexopathies, Raynaud's phenomenon
Hormonal therapy	Leutenizing hormone-releasing factor tumor flare in prostate cancer, hormone-induced pain flare in breast cancer, aromatase inhibitor-induced arthralgias
Radiotherapy	Oropharyngeal mucositis, radiation enteritis, proctocolitis and cystitis, plexopathies, radiation myelopathy, radiopharmaceutical-induced bone flare, lymphedema pain, burning perineum syndrome, post-prostate brachytherapy pelvic pain, osteoradionecrosis
Post-surgical	Breast surgery pain syndromes, postradical neck dissection pain, postthoracotomy pain, postthoracotomy/mastectomy frozen shoulder, postamputation phantom pain syndrome, stump pain, postsurgical pelvic floor myalgia
Chemotherapy infusion techniques	Intravenous infusion pain, intraperitoneal chemotherapy pain
Analgesic techniques	Local anesthetic infiltration pain, opioid injection pain, opioid headache, spinal opioid hyperalgesia syndrome, epidural injection pain

appropriately. The diagnosis of malignant spinal cord compression can be missed because it does not typically present as a unique pain syndrome and may not have abnormal neurologic findings on history or physical exam.[17] Early identification is vital because neurologic symptoms may be irreversible by the time symptoms arise, whereas patients who are treated while still ambulatory have a 90% chance of remaining ambulatory.[18]

In addition to clinical awareness, knowing when to obtain imaging studies and which imaging study to order are essential. A cancer patient with back pain and abnormal plain films of the spine has a 70% chance of having an epidural metastasis; however, as many as 5% of cancer patients with a normal bone scan will have metastatic bony disease on MRI.[19] In cancer patients, the symptom of back pain should alert clinicians to evaluate for bone metastasis and consider obtaining appropriate imaging studies.

Assessment

The pain assessment is a vital component of cancer pain management. A study that surveyed physicians found that 76% of physicians identified poor pain assessment as the single most important barrier to adequate pain management.[20] An effective cancer pain assessment identifies underlying pain syndromes and mechanisms to develop the most effective treatment plan for pain control. An effective pain assessment is predicated on a trusting physician-patient relationship and includes a detailed medical and pain history, physical exam, psychosocial and spiritual evaluation, and screen for substance abuse.

Obtaining a detailed pain history involves identifying pain characteristics, such as pain intensity, quality, location, radiation, and alleviating and aggravating factors. It is important to note temporal features (ie, acute, subacute, chronic), whether the pain is constant or episodic, and to establish a chronologic timeline of symptom presentation in the context of the underlying disease trajectory because cancer pain can be caused by either the malignancy itself or its treatments. Review of diagnostic studies can also be useful in identifying particular syndromes, and an appropriate physical exam can help identify underlying pain mechanisms. For example, decreased sensation, allodynia, hyperalgesia, or weakness may suggest neuropathic pain, whereas point tenderness over a bone may suggest malignant bony involvement. Current and previous pain management regimens should be evaluated, noting compliance, effectiveness, and adverse effects of therapies.

Validated self-reporting scales are useful tools to help characterize, rate, and monitor a patient's pain and response to therapy. The Agency for Healthcare Research and Quality,[21] the American Pain Society[22] and the World Health Organization[23] all identify assessment of pain through patient reporting as the most important factor in determining treatment. Their guidelines recommend using pain-rating scales in all patients who commence or change treatments in order to assess pain severity and relief. The most frequently used validated scales include the visual analog scale (VAS), the verbal rating scale (VRS), and the numerical rating scale (NRS).[24] In cases in which communication or cognitive ability are impaired, physical and behavioral signs of discomfort (ie, facial grimacing, vocalizations, changes in interpersonal interactions, body movements) can be used to assess the presence of pain; however, these methods may be limited in their assessment of pain intensity. In these cases, the Pain Assessment in Advanced Dementia (PAINAD) scale,[25] and for children, the Wong-Baker Faces Pain Rating Scale,[26] can be useful. It is also important to assess the way in which pain affects various aspects of a person's life, including activities of daily living, appetite, sleep, vitality, and relationships. More comprehensive tools that evaluate these functional dimensions include the Brief Pain Inventory,[27] the Memorial Symptom Assessment Scale,[28] and the Edmonton Symptom Assessment Scale.[29]

Given the reciprocal relationship between psycho-spiritual distress and physical pain, it is important for clinicians to perform an appropriate psychiatric and spiritual evaluation. While a thorough history and physical examination is the gold standard for the assessment of psycho-spiritual problems, an oncologist in a busy clinic setting might instead rely on staff-administered screening tools to provide an effective and time-efficient method to evaluate psycho-spiritual issues and identify patients who may benefit from further discussions, including a referral to mental health and spiritual care specialists. Useful clinical tools to assess physical and psycho-spiritual distress include the National Comprehensive Cancer Network Distress Thermometer for Patients[30] and the Alberta Health Services Screening for Distress tool.[31] Spiritual health may be further evaluated using FICA (Faith/Beliefs, Importance, Community, Address in care or action) and similar clinical tools.[32]

Delirium, depression, and anxiety are among the most common psychiatric problems that afflict cancer patients and are interconnected with pain management.[33,34] The Confusion Assessment Method is a brief screening tool for delirium that has been validated in many patient populations, including patients with advanced illnesses.[35] More detailed diagnostic tools, such as the Delirium Rating Scale Revised-98 and the Memorial Delirium Assessment Scale, can be used to confirm the diagnosis of delirium and monitor changes over time.[36] It is important to be attentive to the various delirium subtypes (hypoactive, hyperactive or mixed) and identify any reversible causes, such as dehydration, electrolyte abnormalities, infection, pain, and medications (ie, opioids, benzodiazepines, anticholinergics, steroids).

Depression can present as changes in mood, vitality, sleep, appetite, and weight, and is often linked to disease progression and diminshed quality of life. Depression screening tests that have demonstrated benefit in oncology patients include the Patient Health Questionnaire,[37] the Zung Depression Scale,[38] and the Beck Depression Inventory.[39] The Hospital Anxiety and Depression Scale is an efficient and commonly used screening tool for anxiety among cancer patients and can also help screen for depression.[40] A medication review is important as depression can be induced by certain medications, including corticosteroids, interferon, and drugs that block estrogen receptors (ie, tamoxifen).

Screening for substance abuse in patients and their families is another important component of the pain assessment. In the context of a serious public health problem in the United States in the last 15 years – a true epidemic of prescription opioid abuse and diversion – some experts are advocating for universal precautions (eg, substance abuse risk/screening) for all patients who are being prescribed opioids. Although many cancer pain management and palliative care clinicians disagree with this strategy for their patients, oncologists should at least be aware that some state medical boards and other agencies have taken fairly strong stances on this issue. Optimal evaluation and management of substance abuse involves a multidisciplinary team that includes social workers, psychologists, psychiatrists, chaplains, and mental health professionals who specialize in substance abuse. Screening tools, including the Screener and Opioid Assessment for Patients with Pain (SOAPP), the Opioid Risk Tool (ORT), and the Diagnosis, Intractability, Risk, and Efficacy (DIRE) inventory, can assist in evaluating the likelihood of inappropriate drug use in chronic pain patients. A comparative study on common screening methods for predicting aberrant drug-related behavior in chronic pain patients who received opioids demonstrated the highest sensitivity for the clinical interview and the SOAPP, followed by the ORT and the DIRE.[41] A treatment contract can be useful in establishing clear expectations for the physician and patient and in outlining the consequences of aberrant medication use. Such a contract may include spot urine toxicology screens, expectations for follow-up visits, management of medication supply, and requirement of joint management with a substance abuse specialist.

Treatment

The goal of cancer-related pain treatment is to enhance patient quality of life by providing sustained and effective pain relief with tolerable side effects. Pain treatments can be categorized into pharmacologic, nonpharmacologic, and interventional therapies. Pharmacologic therapies can be further divided into opioids, nonopioids, and adjuvants. There exist various types of opioids, including opioid receptor agonists, partial agonists, and mixed agonists-antagonists, with the agonist agents being the most effective and commonly used for analgesia. Of the various opioid receptors, the mu receptor is the most clinically relevant in terms of analgesia and related adverse effects.

Opioid selection should be individualized. Numerous splice variants of the mu receptor gene are thought to lead to clinical variability in opioid efficacy and adverse effects.[42] When selecting an opioid, clinicians should consider patients' past experiences with opioids, including both analgesic benefit and tolerability. For opioid naïve patients, starting with one of the pure mu receptor agonists while monitoring for both clinical benefit and adverse effects would be a reasonable approach. Indeed, the most appropriate opioid for a patient is the one that works best for them. Opioids have multiple routes of administration and are produced in long- and short-acting formulations (Tables 2 and 3). Because opioids alter pain perception and signal transmission, they can have an analgesic effect in different types of pain syndromes, regardless of the under-

TABLE 2 Immediate-release oral opioids

Opioid	Dose, mg	Routes	Interval, h	Onset, min	Peak, min	Half-life, h
Morphine sulfate	15, 30	PO, IV, SL, SC, PR	q3-6	15-60	60-90	2-4
Hydromorphone	2, 4, 8	PO, IV, SL, SC, PR	q3-4	15-30	30-90	2-3
Oxycodone	5, 10, 15, 20, 30	PO, SL, PR	q3-4	15-30	60-90	2-3
Methadone[a]	5, 10, 40	PO, IV, SL, SC, PR	q4-12	30-60	30-90	12-150
Hydrocodone/ acetaminophen	2.5/325, 5/325, 7.5/325, 10/325	PO	q4-6	30-60	60-90	4.5
Codeine	15, 30, 60	PO	q4-6	15-30	60-90	2-4
Tramadol	50	PO	q4-6	60	120	6-8

IV, intravenously; SC, subcutaneous; SL, sublingual; PO, by mouth; PR, by rectum

[a]Dilute methadone when using subcutaneous route secondary to local irritation.

lying pathophysiology.[43] Most opioids have similar initial adverse effects, such as sedation and nausea, which typically resolve after a few days. Other, more serious adverse effects that clinicians and patients should be aware of include confusion, nightmares, hallucinations, urinary retention, myoclonus, dizziness, and dysphoria. In general, opioids should be used cautiously in patients who are in acute pain with impaired ventilation, bronchial asthma, or raised intracranial pressure; however, the same caveats should not typically limit dose titrations in chronic cancer pain management.[44] In the case in which an opioid is ineffective despite increased doses or its side effects become unmanageable, it would be appropriate to rotate to a different opioid.

Commonly used pure mu receptor agonists include morphine, hydromorphone, oxycodone, hydrocodone, fentanyl, and methadone. Although morphine was traditionally considered the gold standard for opioids, there does not seem to be a demonstrable difference in effectiveness among the different opioids.[45] Hydromorphone is a derivative of morphine that is about 5-10 times more potent than morphine. Oxycodone is a synthetic opioid that is slightly more potent than oral morphine and seems to have similar adverse effects to morphine and hydromorphone. Hydrocodone is found in combination products with acetaminophen and ibuprofen, and a liquid cough formulation exists in combination with homatropine. Fentanyl is a highly lipid-soluble opioid that has a long-acting transdermal formulation that provides an alternate route of administration in patients for whom ingestion of oral medications may be difficult or impossible. The absorption of transdermal fentanyl can be affected by edema, body temperature, and fat content.[46] Although other opioids have active metabolites that can cause neurotoxicity in the setting of renal impairment, fentanyl and methadone are safer alternatives in patients with renal failure because they do not have active metabolites.

Long-acting opioids, or controlled-release opioids, can provide greater pain relief in patients whose pain is not optimized with short-acting opioid formulations. Controlled-release opioids should not be used in opioid naive patients, and clinicians and patients should be aware of the associated risks of opioid addiction and misuse, which can lead to overdose and death. There are various controlled-release opioid formulations available (Table 3), including hydromorphone, oxycodone, and morphine. In patients who have difficulty swallowing, 2 morphine formualtions, Avinza and Kadian, would be of benefit as they can be sprinkled, whereas other controlled-release opioids should not be crushed. Another controlled-release opioid, oxymorphone (Opana ER), should be taken 1 hour before or 2 hours after meals, because its peak varies with food intake.

Methadone acts as an opioid receptor agonist and an NMDA (N-methyl-d-aspartate) receptor antagonist, and also blocks the reuptake of serotonin and norepinephrine. Given its various mechanisms of action, methadone can be effective in multifaceted pain syndromes involving both somatic and neuropathic pain, although there are conflicting results in neuropathic pain studies.[47,48] Given methadone's variable and long half-life, clinicians should be watchful for adverse events as a result of drug accumulation.[49] Methadone's pharmacokinetics can be especially variable in cancer patients because methadone binds avidly to alpha1-glycoproteins, the levels of which are increased in cancer patients, which can lead to a decrease in unbound methadone and a delayed onset of effect.[49] Because methadone is metabolized primarily by CYP3A4, clinicians should be aware of other medications that may inhibit or induce the CYP3A4 enzyme. Methadone can prolong the QTc interval, so QTc monitoring may be warranted in appropriate settings.[50] Recent guidelines suggest that methadone should be prescribed only by clinicians who are familiar with its use, such as palliative medicine, pain, and addiction medicine specialists.[50]

There are other weaker agents, such as codeine and tramadol. Codeine is an opioid alkaloid whose action is dependent on its metabolism to the active form, morphine. Because of codeine's genetic variability in its rate of metabolism, its use should be individualized.[51] Tramadol is a synthetic analog of codeine that has shown efficacy in neuropathic pain,[52] but has no anti-inflammatory activity. It can increase the risk of seizures and serotonin syndrome because it is also a monoamine reuptake inhibitor. Unlike the stronger opioids, there is a "ceiling effect" for these medications, that is, above a certain threshold dose, there is no additional analgesic effect but there is still the potential for adverse effects.

TABLE 3 Controlled-release opioids

Opioid	Dose	Intervals, h
Duragesic (Fentanyl)	12, 25, 50, 75, 100 mcg	48-72
Avinza (Morphine)	30, 45, 60, 75, 90, 120 mg	24
Kadian (Morphine)	10, 20, 30, 50, 60, 80, 100, 200 mg	12-24
MS Contin (Morphine)	15, 30, 60, 100, 200 mg	8-12
Oramorph SR (Morphine)	15, 30, 60, 100 mg	8-12
Opana ER (Oxymorphone)	5, 10, 20, 30, 40 mg	12
Exalgo (Hydromorphone)	8, 12, 16 mg	24
Oxycontin (Oxycodone)	10, 15, 20, 30, 40, 60, 80 mg	12

Commonly used nonopioid medications include nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen. NSAIDs can be quite effective in controlling pain caused by inflammatory processes and/or bone metastasis but can have potential adverse effects, such as gastrointestinal bleeding, platelet dysfunction, and renal failure.[53] Patients with a history of gastritis or gastrointestinal bleeds should either be on a combination of a nonselective NSAID with a proton pump inhibitor or switched to a selective cyclooxygenase (COX2) inhibitor.[54] It is important to note that COX2 inhibitors do not protect against renal failure and may present an increased risk of thrombotic cardiovascular events.[55] Acetaminophen can also be an effective analgesic for cancer pain, but should be used cautiously in patients with hepatic impairment.

Adjuvant analgesics are medications that are not primarily indicated for pain management but can be an effective analgesic in various pain syndromes. Commonly used adjuvants that are used to treat neuropathic pain include anticonvulsants, antidepressants, corticosteroids, ketamine, and cannabinoids. Gabapentin is the most commonly used anticonvulsant for neuropathic pain and can have an added analgesic effect when used in combination with tricyclic antidepressants such as nortriptyline.[56] Its main side effects are somnolence and dizziness. Whereas gabapentin's bioavailability decreases at higher doses (60%-80% percent bioavailability at 100 mg every 8 hours vs 27% at 1600 mg every 8 hours), the gabapentin analog pregabalin is linearly absorbed in all doses.[57,58] Hence, pregabalin may be a more effective alternative to gabapentin in patients requiring higher doses of the medication. Serotonin norepinephrine reuptake inhibitors, such as venlafaxine and duloxetine, are recommended along with gabapentin and pregabalin as first-line treatments for diabetic neuropathic pain.[59]

Tricyclic antidepressants can be useful for neuropathic pain with the added benefit of improving mood and sleep; however, their use may be limited in the elderly because of its anticholinergic effects and it should also be avoided in patients with glaucoma and those who are suicidal.[60] Corticosteroids reduce inflammation, inhibit prostaglandin production, and reduce neuronal excitability, which makes it particularly useful in metastatic bone pain and neuropathic pain caused by spinal cord or nerve plexus compression.[61] Corticosteroids also provide the additional benefits of improved appetite, malaise, and nausea. Transdermal lidocaine has been approved by the US Food and Drug Administration for postherpetic neuralgia, but may also be effective in other neuropathic pain conditions, including postmastectomy pain syndrome and diabetic neuropathy.[62] Ketamine is a pure NMDA antagonist that has been shown to improve neuropathic cancer pain;[63] potential adverse effects include sedation, delirium, and hallucinations, especially at higher doses. Although data in cancer pain is limited, cannabinoids have been shown to be of benefit in neuropathic pain in HIV-positive patients.[64]

In addition to NSAIDs and corticosteroids, bone-metabolism modifying agents can help relieve cancer-related bone pain. Bisphosphonates inhibit osteoclast activity and can provide relief from metastatic bone pain. The American Society of Clinical Oncology recommends using pamidronate or zoledronic acid; however, these medications should be avoided in the setting of renal failure, and patients should be aware that both medications can initially worsen the pain due to an acute phase reaction.[65] The RANK-L inhibitor denosumab prevents bone resorption and osteoclast maturation and activation. Denosumab can improve bone pain, is not renal toxic, and causes fewer episodes of acute phase reactions compared with zolendronic acid.[66] Calcitonin reduces bone resorption, and although the evidence is scarce for its effectiveness in treating cancer-related bone pain, it is generally well tolerated.[67]

Various nonpharmacologic modalities can also help treat cancer-related pain. There are many studies supporting the use of cognitive and behavioral therapy (CBT) for chronic pain management;[68] however, results are mixed for the effectiveness of CBT in cancer-related pain.[69,70] Acupuncture, therapeutic massage and exercise can also be effective in managing all types of cancer-related pain.[71,72] Transcutaneous electrical nerve stimulation, topical heat, and ice therapy are other topical therapies that can provide pain relief with few adverse effects. Mind-body interventions such as biofeedback, diversion of attention, relaxation breathing, meditation, and music and art therapy can all be useful in managing cancer pain.[73]

Interventional therapies are also available to treat cancer-related pain, and are particularly effective in severe cases that are refractory to systemic analgesics and cases in which intolerable side effects limit medication use. Celiac plexus blocks can provide long-lasting benefit for 70%-90% of patients with pancreatic and other abdominal malignancies,[74] and hypogastric plexus blocks can be effective in chronic cancer-related pelvic pain.[75] Intrathecal pumps deliver opioids directly into the subarachnoid space, achieving equianalgesic effect at much lower doses than do systemic administrations, thereby decreasing the risk of opioid dose-related adverse effects.

External beam radiation can be an effective treatment option for localized metastatic bone pain. It provides pain relief in 50% and 75% of patients at 2 and 4 weeks, respectively, after treatment, and for most patients, pain relief lasts for 3 months.[76] Single fraction radiation is recommended over multiple-fraction regimens for the treatment of metastatic bone pain.[77] There is no difference in the duration of or time to pain relief between single large fraction radiation and conventional radiation treatments involving mul-

tiple fractions; however, there is a higher retreatment rate in single fraction radiation.[78] Patients should also be aware of a possible transient increase in pain at the treatment site, which may be decreased with NSAIDs or corticosteroids.[79]

In cases in which optimal pain relief is not achieved despite medication and interventional therapies, surgical procedures, such as cordotomy and myelotomy, may be of benefit. Cordotomy is indicated for unilateral medically intractable cancer pain below the level of C5 and can provide immediate pain relief in over 90% of patients; although, the analgesic effect decreases to 40% after 1 year.[80] Vertebroplasty can be effective in vertebral compressions from bone metastasis,[81] and kyphoplasty has been demonstrated to be safe and effective in bone pain associated with multiple myeloma.[82] Case reports have suggested a high success rate in pain control for patients with malignant compression fractures and indicate pain relief within 48 hours after vertebroplasty.[83]

There are a number of barriers to effective cancer-related pain management, including physician-related barriers, patient-related barriers and society and tradition-related barriers.[84] A review of empirical research on these barriers in the literature identified the most significant patient-related barriers were patient reluctance to report pain and adhere to treatment recommendations.[85] The most prominent physician-related barriers were insufficient physicians' knowledge about cancer pain management, inadequate patterns of pain assessment, and inadequate opioid prescription. A large multicenter study that surveyed physicians identified a number of critical barriers to effective cancer pain management (Table 4) with 76% of physicians designating poor pain assessment as the single most important barrier to adequate pain management.[86]

TABLE 4 Barriers to management of cancer pain[a]

Inadequate pain assessment
Patient reluctance to report pain
Patient reluctance to take opioids
Physician reluctance to prescribe opioids
Inadequate staff knowledge about pain management
Nursing staff reluctance to give opioids
Excessive state regulation of analgesics
Lack of access to professional methods
Lack of psychological support services
Lack of equipment
Lack of neurodestructive procedures
Lack of access to wide range of analgesics

[a]Adapted from van Roenn et al[86]

Summary

Uncontrolled pain is one of the most feared and debilitating symptoms among cancer patients, and many suffer unnecessarily from suboptimal pain control. Pain can affect all aspects of a patient's life, and each individual has a unique experience in how they manage, cope and respond to their pain and related treatments. Hence, achieving adequate pain relief involves a proper assessment of psychosocial, spiritual and physical pain issues, matched with an individualized treatment plan involving pharmacologic, nonpharmacologic and procedural therapies when appropriate. Indeed, the optimal context in which pain management occurs is within a multidisciplinary health care team, involving oncologists, pain management and palliative medicine specialists, nurses, chaplains, social workers, physical and occupational therapists, complementary and alternative medicine specialists, psychiatrists, psychologists, surgeons, and radiologists. Providing adequate pain relief can help ease the overall burden of disease among oncology patients while helping them tolerate cancer-directed therapies and achieve the most optimal quality of life throughout all phases of the disease process.

References

1. van den Beuken-van Everdingen MH, de Rijke JM, Kessels AG, Schouten HC, van Kleef M, Patijn J. Prevalence of pain in patients with cancer: a systematic review of the past 40 years. Ann Oncol. 2007;18:1437-1449.
2. Winslow M, Seymour J, Clark D. Stories of cancer pain: a historical perspective. J Pain Symptom Manage, 2005;29:22-31.
3. Fisch MJ et al. Prospective, observational study of pain and analgesic prescribing in medical oncology outpatients with breast, colorectal, lung, or prostate cancer. Journal of Clinical Oncology. 2012;30:1980-1988.
4. Deandrea S, Montanari M, Moja L, Apolone G. Prevalence of undertreatment in cancer pain. A review of published literature. Ann Oncol. 2008;19:1985-1991.
5. Lopez G, Reddy SK. Pain assessment and management. In: Yennurajalingam S, Bruera E, eds. Oxford American Handbook of Hospice and Palliative Medicine. New York, NY: Oxford University Press; 2011:32.
6. Cherny N. Pain assessment and cancer pain syndromes. In: Hanks G, Cherny NI, Christakis NA, Fallon M, Kaasa S, Portenoy RK, eds. Oxford Textbook of Palliative Medicine. 4th ed. New York, NY; Oxford University Press; 2010:600.
7. Peuckmann V, Ekholm O, Rasmussen NK, et al. Chronic pain and other sequelae in long-term breast cancer survivors: nationwide survey in Denmark. Eur J Pain. 2009;13:478-485.
8. Wolf S, Barton D, Kottschade L, Grothey A, Loprinzi C. Chemotherapy-induced peripheral neuropathy: prevention and treatment strategies. Eur J Cancer. 2008;44:1507-1515.
9. Ververs JM, et al. Risk, severity and predictors of physical and psychological morbidity after axillary lymph node dissection for breast cancer. Eur J Cancer. 2001;37:991-999.
10. Akechi T, Okuyama T, Sugawara Y, Nakano T, Shima Y, Uchitomi Y. Major depression, adjustment disorders, and post-traumatic stress disorder in terminally ill cancer patients: Associated and predictive factors. J Clin Oncol. 2004;22:1957-1965.
11. Breitbart W, Rosenfeld B, Pessin H, et al. Depression, hopelessness, and desire for hastened death in terminally ill patients with cancer. JAMA. 2000;284:2907-2911.
12. Massie MJ, Gagnon P, Holland JC. Depression and suicide in pa-

tients with cancer. J Pain Symptom Manage. 1994;9:325-340.
13. Gorin S, Krebs P, Badr H. Meta-analysis of psychosocial interventions to reduce pain in patients with cancer. J Clin Oncol. 2012;30:539-547.
14. Puchalski C, Ferrell B, Virani R, et al. Improving the quality of spiritual care as a dimension of palliative care: the report of the Consensus Conference. J Palliat Med. 2009;12:885-904.
15. Chochinov HM, Hack T, Hassard T, Kristjanson LJ, McClement S, Harlos M. Understanding the will to live in patients nearing death. Psychosomatics. 2005;46:7-10.
16..Grant R, Papadopoulos SM, Sandler HM, Greenberg HS. Metastatic epidural spinal cord compression: current concepts and treatment. J Neurooncol. 1994;19:79-92.
17. Abrahm JL. A physician's guide to pain and symptom management in cancer patients. 3rd ed. Baltimore, MD: John's Hopkins University Press; 2014:181.
18. Abrahm JL. A physician's guide to pain and symptom management in cancer patients. 3rd ed. Baltimore, MD: John's Hopkins University Press; 2014:182.
19. Abrahm JL. A physician's guide to pain and symptom management in cancer patients. 3rd ed. Baltimore, MD: John's Hopkins University Press; 2014:181-182.
20. Von Roenn JH, Cleeland CS, Gonin R, Hatfield a K, Pandya KJ. Physician attitudes and practice in cancer pain management. A survey from the Eastern Cooperative Oncology Group. Ann Intern Med. 1993;119:121-126.
21. Jacox A, Carr DB, Payne R, et al. Agency for Health Care Policy and Research, US Department of Health and Human Services, Public Health Service. Rockville, MD. Management of cancer pain. Clinical Practice Guideline No 9. AHCPR Publication No. 94-0592. http://www.ncbi.nlm.nih.gov/books/NBK52307/?report=reader#!po=25.0000. Released March 1994. Accessed September 22, 2015. [Provided for historical reference only, information may be out of date.]
22. Gordon DB, Dahl JL, Miaskowski C, et al. American pain society recommendations for improving the quality of acute and cancer pain management: American Pain Society Quality of Care Task Force. Arch Intern Med. 2005;165:1574-1580.
23. Zech DFJ, Grond S, Lynch J, Hertel D, Lehmann KA. Validation of World Health Organization Guidelines for cancer pain relief: a 10-year prospective study. Pain. 1995;63:65-76.
24. Jost L, Roila F. Management of cancer pain: ESMO Clinical Practice Guidelines. Ann Oncol. 2010;21(suppl 5):v257-v260.
25. Abrahm JL. A physician's guide to pain and symptom management in cancer patients. 3rd ed. Baltimore, MD: John's Hopkins University Press; 2014:169-170.
26. Garra G, Singer AJ, Taira BR, et al. Validation of the Wong-Baker FACES pain rating scale in pediatric emergency department patients. Acad Emerg Med. 2010;17:50-54.
27. Cleeland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory. Ann Acad Med Singapore. 1994;23:129-138.
28. Portenoy RK, Thaler HT, Kornblith AB, et al. The Memorial Symptom Assessment Scale: an instrument for the evaluation of symptom prevalence, characteristics and distress. Eur J Cancer. 1994;30A:1326-1336.
29. Chang VT, Hwang SS, Feuerman M. Validation of the Edmonton Symptom Assessment Scale. Cancer. 2000;88:2164-2171.
30. NCCN distress thermometer for patients. http://www.nccn.org/patients/resources/life_with_cancer/pdf/nccn_distress_thermometer.pdf. Released 2013. Accessed September 22, 2015.
31. Alberta Health Services Screening for Distress tool. http://www.albertahealthservices.ca/frm-18125.pdf. Revised March 2013. Accessed September 24, 2015.
32. Puchalski C, Ferrell B, Virani R, et al. Improving the quality of spiritual care as a dimension of palliative care: the report of the Consensus Conference. J Palliat Med. 2009;12:885-904.
33. Fang CK, Chen HW, Liu SI, Lin CJ, Tsai LY, Lai YL. Prevalence, detection and treatment of delirium in terminal cancer inpatients: a prospective survey. Jpn J Clin Oncol. 2008;38:56-63.
34. Mitchell AJ, Chan M, Bhatti H, et al. Prevalence of depression, anxiety, and adjustment disorder in oncological, haematological, and palliative-care settings: a meta-analysis of 94 interview-based studies. Lancet Oncol. 2011;12:160-174.
35. Ryan K, Leonard M, Guerin S, Donnelly S, Conroy M, Meagher D. Validation of the confusion assessment method in the palliative care setting. Palliat Med. 2009;23:40-45.
36. Trzepacz PT, Mittal D, Torres R, Kanary K, Norton J, Jimerson N. Validation of the Delirium Rating Scale-revised-98: comparison with the delirium rating scale and the cognitive test for delirium. J Neuropsychiatry Clin Neurosci. 2001;13:229-242.
37. Kroenke K, Spitzer RL, Williams JBW. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med. 2001;16):606-613.
38. Passik SD, Kirsh KL, Donaghy KB, et al. An attempt to employ the Zung Self-Rating Depression Scale as a 'lab test' to trigger follow-up in ambulatory oncology clinics: criterion validity and detection. J Pain Symptom Manage. 2001;21:273-281.
39. Dozois DJA, Dobson KS, Ahnberg JL. A psychometric evaluation of the Beck Depression Inventory-II. Psychol Assess. 1998;10:83-89.
40. Luckett T, Butow PN, King MT, et al. A review and recommendations for optimal outcome measures of anxiety, depression and general distress in studies evaluating psychosocial interventions for English-speaking adults with heterogeneous cancer diagnoses. Support Care Cancer. 2010;18:1241-1262.
41. Moore TM, Jones T, Browder JH, Daffron S, Passik SD. A comparison of common screening methods for predicting aberrant drug-related behavior among patients receiving opioids for chronic pain management. Pain Med. 2009;10:1426-1433.
42. Fallon M, Cherny N, Hanks G. Opioid analgesic therapy. In: Hanks G, Cherny NI, Christakis NA, Fallon M, Kaasa S, Portenoy RK, eds. Oxford Textbook of Palliative Medicine. 4th ed. New York, NY; Oxford University Press; 2010:662.
43. Paice JA. Opioid pharmacotherapy. In: Berger AM, Shuster JL, von Roenn JH, eds.
Principles and practice of palliative care and supportive oncology. 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2013;23.
44. Fallon M, Cherny N, Hanks G. Opioid analgesic therapy. In: Hanks G, Cherny NI, Christakis NA, Fallon M, Kaasa S, Portenoy RK, eds. Oxford Textbook of Palliative Medicine. 4th ed. New York, NY; Oxford University Press; 2010:685-686.
45. Chou R, Clark E, Helfand M. Comparative efficacy and safety of long-acting oral opioids for chronic non-cancer pain: a systematic review. J Pain Symptom Manage. 2003;26:1026-1048.
46. Heiskanen T, Mätzke S, Haakana S, Gergov M, Vuori E, Kalso E. Transdermal fentanyl in cachectic cancer patients. Pain. 2009;144:218-222.
47. Morley JS, Bridson J, Nash TP, Miles JB, White S, Makin MK. Low-dose methadone has an analgesic effect in neuropathic pain: a double-blind randomized controlled crossover trial. Palliat Med. 2003;17:576-587.
48. Nicholson AB. Methadone for cancer pain. Cochrane Database Syst Rev. 2007;(4):CD003971. http://www.ncbi.nlm.nih.gov/pubmed/17943808. Accessed September 22, 2015.
49. Paice JA. Opioid pharmacotherapy: principles and practice of palliative care and supportive oncology. 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2013:28.
50. Chou R, Cruciani RA, Fiellin DA, et al. Methadone safety: a clinical practice guideline from the American Pain Society and College on problems of drug dependence, in collaboration with the Heart Rhythm Society. J Pain. 2014;15:321-337.
51. Gasche Y, Daali Y, Fathi M, et al. Codeine intoxication associated with ultrarapid CYP2D6 metabolism. N Engl J Med. 2004;351:2827-2831.
52. Harati Y, Gooch C, Swenson M, et al. Double-blind randomized trial of tramadol for the treatment of the pain of diabetic neuropathy. Neurology. 1998;50:1842-1846.
53. McNicol E, Strassels SA, Goudas L, Lau J, Carr DB. NSAIDS or paracetamol, alone or combined with opioids, for cancer pain. Cochrane Database Syst Rev. 2005;(1):CD005180.
54. Laine L. Gastrointestinal effects of NSAIDs and coxibs. J Pain Symptom Manage. 2003;25(suppl 2):S32-S40.
55. DeMaria AN, Weir MR. Coxibs – beyond the GI tract: renal and

cardiovascular issues. J Pain Symptom Manage. 2003;25(suppl 2):S41-S49.
56. Gilron I, Bailey JM, Tu D, Holden RR, Jackson AC, Houlden RL. Nortriptyline and gabapentin, alone and in combination for neuropathic pain: a double-blind, randomised controlled crossover trial. Lancet. 2009;374:1252-1261.
57. Bockbrader HN, Wesche D, Miller R, Chapel S, Janiczek N, Burger P. A comparison of the pharmacokinetics and pharmacodynamics of pregabalin and gabapentin. Clin Pharmacokinet. 2010;49:661-669.
58. Abrahm JL. A physician's guide to pain and symptom management in cancer patients. 3rd ed. Baltimore, MD: John's Hopkins University Press; 2014:266.
59. Attal N, Cruccu G, Baron R, et al. EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. Eur J Neurol. 2010;17:1113-1123.
60. Nersesyan H, Slavin K V. Current aproach to cancer pain management: availability and implications of different treatment options. Ther Clin Risk Manag. 2007;3:381-400.
61. Abrahm JL. A physician's guide to pain and symptom management in cancer patients. 3rd ed. Baltimore, MD: John's Hopkins University Press; 2014:262.
62. Devers A, Galer BS. Topical lidocaine patch relieves a variety of neuropathic pain conditions: an open-label study. Clin J Pain. 2000;16:205-208.
63. Bell RF, Eccleston C, Kalso E. Ketamine as adjuvant to opioids for cancer pain. A qualitative systematic review. J Pain Symptom Manage. 2003;26:867-875.
64. Abrams DI, Jay CA, Shade SB, et al. Cannabis in painful HIV-associated sensory neuropathy: a randomized placebo-controlled trial. Neurology. 2007;68:515-521.
65. Van Poznak CH, Temin S, Yee GC, et al. American Society of Clinical Oncology executive summary of the clinical practice guideline update on the role of bone-modifying agents in metastatic breast cancer. J Clin Oncol. 2011;29:1221-1227.
66. Cleeland CS, Body J-J, Stopeck A, et al. Pain outcomes in patients with advanced breast cancer and bone metastases: results from a randomized, double-blind study of denosumab and zoledronic acid. Cancer. 2013;119:832-838.
67. Portenoy RK. Treatment of cancer pain. Lancet. 2011;377:2236-2247.
68. Eccleston C, Williams AC de C, Morley S. Psychological therapies for the management of chronic pain (excluding headache) in adults. Cochrane Database Syst Rev. 2009;(2):CD007407.
69. Vilela LD, Nicolau B, Mahmud S, et al. Comparison of psychosocial outcomes in head and neck cancer patients receiving a coping strategies intervention and control subjects receiving no intervention. J Otolaryngol. 2006;35:88-96.
70. Dalton JA, Keefe FJ, Carlson J, Youngblood R. Tailoring cognitive-behavioral treatment for cancer pain. Pain Manag Nurs. 2004;5:3-18.2004.
71. O'Regan D, Filshie J. Acupuncture and cancer. Auton Neurosci Basic Clin. 2010;157:96-100.
72. Calenda E. Massage therapy for cancer pain. Curr Pain Headache Rep. 2006;10:270-274.
73. Bardia A, Barton DL, Prokop LJ, Bauer BA, Moynihan TJ. Efficacy of complementary and alternative medicine therapies in relieving cancer pain: a systematic review. J Clin Oncol. 2006;24:5457-5464.
74. Eisenberg E, Carr DB, Chalmers TC. Neurolytic celiac plexus block for treatment of cancer pain: a meta-analysis. Anesth Analg. 1995;80:290-295.
75. Plancarte R, de Leon-Casasola OA, El-Helaly M, Allende S, Lema MJ. Neurolytic superior hypogastric plexus block for chronic pelvic pain associated with cancer. Reg Anesth. 1997;22:562-568.
76. Abrahm JL. A physician's guide to pain and symptom management in cancer patients. 3rd ed. Baltimore, MD: John's Hopkins University Press; 2014:273.
77. Lutz S, Berk L, Chang E, et al. Palliative radiotherapy for bone metastases: an ASTRO evidence-based guideline. Int J Radiat Oncol Biol Phys. 2011;79:965-976.
78. Steenland E, Leer J, Van Houwelingen H, et al. The effect of a single fraction compared to multiple fractions on painful bone metastases: a global analysis of the Dutch Bone Metastasis Study. Radiother Oncol. 1999;52:101-109.
79. Shaiova L, Farber L, Aggarwal S. Difficult pain syndromes: neuropathic pain, bone pain, and visceral pain. In: Berger AM, Shuster JL, von Roenn JH, eds. Principles and practice of palliative care and supportive oncology. 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2013:14.
80. Mannes A, Kim P, Lonser R. Interventional approaches to pain In: Berger AM, Shuster JL, von Roenn JH, eds. Principles and practice of palliative care and supportive oncology. 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2013:62.
81. Mannes A, Kim P, Lonser R. Interventional approaches to pain In: Berger AM, Shuster JL, von Roenn JH, eds. Principles and practice of palliative care and supportive oncology. 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2013:61.
82. Zou J, Mei X, Gan M, Yang H. Kyphoplasty for spinal fractures from multiple myeloma. J Surg Oncol. 2010;102:43-47.
83. Jensen ME, Kallmes DK. Percutaneous vertebroplasty in the treatment of malignant spinal disease. Cancer J. 2002;8:194-206.
84. Fazeny B, Muhm M, Hauser I, et al. Barriers in cancer pain management. Wien Klin Wochenschr. 2000;112:978-981.
85. Jacobsen R, Liubarskiene Z, Møldrup C, Christrup L, Sjøgren P, Samsanaviciene J. Barriers to cancer pain management: a review of empirical research. Medicina (Kaunas). 2009;45:427-433.
86. Von Roenn JH, Cleeland CS, Gonin R, Hatfield a K, Pandya KJ. Physician attitudes and practice in cancer pain management. A survey from the Eastern Cooperative Oncology Group. Ann Intern Med. 1993;119:121-126.
87. Cherny N. Pain assessment and cancer pain syndromes. In: Hanks G, Cherny NI, Christakis NA, Fallon M, Kaasa S, Portenoy RK, eds. Oxford Textbook of Palliative Medicine. 4th ed. New York, NY; Oxford University Press; 2010:605-621.