
CHAPTER 5

Pain

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THE PROBLEM

Pain is a significant problem in patients with cancer and is often the most feared aspect of the disease. A multitude of pain guidelines exist to guide the management of cancer pain,²⁻³ and the World Health Organization (WHO) estimates that its ladder for cancer pain can adequately manage pain in approximately 80%–90% of patients.³ The health-care team has a professional and ethical responsibility to assess and adequately manage pain in patients throughout the cancer trajectory. Being aware of the incidence and etiology of cancer pain is important to recognize how this problem impacts every aspect of the cancer illness. Appreciating the global aspects of pain enables clinicians to identify high-risk patients and obtain a comprehensive pain assessment. Recognizing that the assessment should focus on the patient's perspective of pain, however it is defined, is critical in pain assessment.⁴ Finally, understanding the pathophysiology of pain enables healthcare professionals to use both pharmacologic and nonpharmacologic interventions that can interrupt pain signals along the pain pathway.

According to the International Association for the Study of Pain, pain is defined as “a sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage.”⁵ The definition reinforces the fact that pain is not just physical, but rather is a holistic experience. Total pain or global pain involves the interplay of physical, psychological, social, and spiritual factors that constructs each patient's unique pain experience. Total pain reinforces the inner-connectedness between the body, mind, and spirit. Healthcare professionals commonly focus on the physical pain but should be reminded that

pain is more than a physiologic process. Pain is psychological and can remind patients of their cancer and uncertainty of the future. Patients may even suppress pain in an effort to protect their family and deny pain due to fear of disease progression. Socially, patients may become isolated as pain keeps them from enjoying social activities and relationships. Spirituality can affect individual perception and intensity about pain, the significance of the meaning of pain, and the acceptance of the medical treatment plan. If total pain involves the physical, psychological, social, and spiritual domains, then the management of pain should likewise encompass all domains.⁶⁻⁸

Despite the full armamentarium of strategies available, cancer pain remains undertreated, and a multitude of barriers exist to its management. Data suggest that while a focus on cancer pain has existed for more than 20 years, pain is not adequately addressed, and misperceptions and limitations exist in pain-related knowledge and practice.⁹ Barriers comprise healthcare professionals, healthcare systems, and patients and families.

First, healthcare professionals have inadequate knowledge about pain assessment and management. A recent study indicated that the most common physician-related barriers to adequate cancer pain management were insufficient knowledge and inadequate opioid prescribing.¹⁰ A plethora of studies indicate that nurses' knowledge of pain assessment and management is also lacking, and only 49% of nurses in a recent study achieved a passing score of 80% or higher.¹¹ Lack of pain assessment is another major barrier, and has been considered the greatest barrier to adequate pain management.^{3,9,10} For nurses, The Joint Commission frequently cites lack of pain assessment in the hospital setting

TABLE 5-1

Glossary of Definitions	
Term	Definition
Pain	<ul style="list-style-type: none"> • A sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage⁶ • Whatever the experiencing person says it is existing whenever he or she says it does
Somatic Pain	<ul style="list-style-type: none"> • Pain arising from skin, muscle, tendon, joints, fasciae, and bones
Visceral Pain	<ul style="list-style-type: none"> • Pain arising from visceral organs such as the lungs, GI track, liver, gallbladder, kidneys, and bladder
Neuropathic Pain	<ul style="list-style-type: none"> • Pain arising from the peripheral or central nervous system
Types of Pain	
Acute Pain	<ul style="list-style-type: none"> • Pain that is self-limiting and resolves with healing of the underlying injury
Chronic Pain	<ul style="list-style-type: none"> • Persistent pain with pathology that is unable to explain the extension of pain beyond the expected period of healing
Persistent Pain	<ul style="list-style-type: none"> • Prolonged pain after a transient stimulus
Referred Pain	<ul style="list-style-type: none"> • Spread of pain to an uninjured tissue
Breakthrough Pain	<ul style="list-style-type: none"> • A transient exacerbation of pain that occurs either spontaneously, or in relation to a specific predictable or unpredictable trigger, despite relatively stable and adequately controlled background pain
End of Dose Pain	<ul style="list-style-type: none"> • Pain that occurs prior to the next dose of scheduled medication
Characteristics Used to Describe Pain	
Allodynia	<ul style="list-style-type: none"> • A painful response to a normally innocuous stimulus
Dysesthesia	<ul style="list-style-type: none"> • A spontaneous or evoked unpleasant and abnormal sensation
Hyperalgesia	<ul style="list-style-type: none"> • An increased response to a noxious stimulus
Hyperpathia	<ul style="list-style-type: none"> • Abnormal pain and exaggerated response, especially to a repetitive stimulus
Opioid-Related Terms ¹⁴	
Physical Dependence	<ul style="list-style-type: none"> • A state of adaptation that is manifested by a drug class specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of drug and/or administration of an antagonist.
Tolerance	<ul style="list-style-type: none"> • A state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more of the drug's effects over time.
Addiction	<ul style="list-style-type: none"> • Addiction is a primary, chronic, neurobiologic disease with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving.
Abstinence Syndrome	<ul style="list-style-type: none"> • Occurs with abrupt cessation or diminution of an opioid following chronic use

as a problem. Pain cannot be managed if it is not assessed. Fears about addiction may lead to inadequate prescribing, and confusion still exists about the differences between addiction, tolerance, and physical dependence (Table 5-1).¹²

Second, healthcare and regulatory systems fuel the problem. Providers fear scrutiny from regulatory agencies and may be reluctant to prescribe opioid analgesics.⁹ Most recently, risk evaluation and mitigation strategies (REMS) have added another layer to prescribing opioids for patients in need.¹³

Third, additional barriers have been noted throughout the last two to three decades for patients and families. Fears of addiction, failure to report pain, fear that pain is a sign of disease progression, perception that pain is an expected part of the disease, lack of knowledge about pain management options, lack of adherence due to side effects, and desire to be a “good” patient continue to prevail.^{9,14–16} Barriers may be compounded in patients who are older,¹⁷ female, of a minority race,¹⁸ and have less education and lower socioeconomic status.^{10,19}

INCIDENCE

A recent systematic review of more than 52 studies indicates that pain occurs in approximately 53% of patients with cancer, but the experience is highly variable and dependent upon the stage of disease, goals of treatment, and type of cancer.²⁰ Pain is more common in the advanced stages of the disease, with 59% to 64% of patients with metastatic or terminal disease reporting pain. Higher rates, up to 70%, were reported in earlier studies where pain was rated by a family member and not by the patients themselves. Families have been recognized to overestimate the amount of pain the patient is experiencing. For patients undergoing cancer treatment, 59% experience pain, and pain is also found to occur in 33% of patients' post curative treatment, so that it is a growing concern for disease-free cancer survivors. In regard to type of cancer, 70% of patients with head and neck cancer experienced the most pain, followed by 60% of those with gynecologic malignancies, 59% with gastrointestinal cancer (colon, esophageal, pancreatic), 55% with lung cancer, 54% with breast cancer, and 52% with urogenital cancer (prostate, bladder). In those patients who had pain, more than one-third assessed the pain as moderate to severe; as many as 43% rated their pain as moderate, and 26% rated their pain as severe.²⁰

A lack of consensus in the literature exists regarding which demographic characteristics predict the most pain. For example, the evidence on the prevalence of pain in older adults is conflicting. While some studies report an increased prevalence of pain in older adults,^{19,21} others find no difference.²⁰ Research studies on gender differences in cancer-related pain have also yielded inconsistent results.²²

ETIOLOGY

Cancer-related pain often results from three separate etiologies: from direct tumor involvement, diagnostic or therapeutic procedures, or cancer treatment. Cancer treatment-related pain can result from surgery, chemotherapy, biotherapy and targeted therapy, hormone therapy, and radiation therapy (Table 5-2). Patients may also experience pain that is unrelated to the cancer. Examples include arthritic pain, fibromyalgia, and chronic low back pain.

Pain related to any of the four causes can be somatic (e.g., bone pain), visceral (e.g., pancreas, liver), or neuropathic. Neuropathic pain can be peripheral or centrally mediated, and is usually caused by direct tumor invasion (approximately 64% of patients) or cancer treatment (approximately 20%).²³ Patients can also experience more than one type of pain. In a large international trial, 92.5% of the participating patients had one or more pains caused directly by the cancer and 20.8% of patients had one or more pains caused by cancer therapies.²⁴ A comprehensive

TABLE 5-2

Cancer-Related Pain Syndromes	
Etiology	Examples of Related Syndromes
Direct Tumor Involvement	Somatic pain
	• Bone pain – primary or metastases
	Visceral pain
Therapeutic and Diagnostic Procedures	• Ascites
	• Lymphedema
	• Obstruction
Cancer Treatment	• Organ related pain – pancreas, liver, abdominal viscera
	Neuropathic
	• Brachial or lumbosacral plexopathies
	Headache
	Therapeutic procedure-related
	• Pleurodesis
	• Post surgical pain
	Diagnostic procedure-related
	• Bone marrow aspirations
	• Lumbar puncture
Surgical	
• Post surgical pain	
• Pain following access device placement	
Chemotherapy	
• Arthralgias from flare reactions	
• Avascular necrosis from corticosteroid administration	
• Hemorrhagic cystitis	
• Mucositis	
• Peripheral neuropathy	
Hormone therapy	
• Arthralgias	
• Gynecomastia	
Biotherapy/Targeted Therapy	
• Acneiform rash	
• Bone pain related to growth factor administration	
Radiation therapy	
• Dermatitis	
• Enteritis	
• Mucositis	
• Plexopathies	

assessment is critical to determine the etiology of the pain and to identify whether patients are experiencing more than one type of pain—information that can help guide treatment decisions.

Clinicians should recognize that pain can occur throughout the cancer trajectory. While pain is most prevalent during the advanced stages of the disease, as noted, it can occur at diagnosis and throughout treatment. Pain in

TABLE 5-3

Disease Specific Chronic Pain Syndromes in Cancer Survivors		
Type of Cancer	Pain Syndromes	Characteristics
Anus	<ul style="list-style-type: none"> • Lumbosacral plexopathy 	<ul style="list-style-type: none"> • Radiating pain from the pelvis down the associated lower extremity
Breast	<ul style="list-style-type: none"> • Phantom breast pain • Intercostobrachial neuralgia • Neuroma • Lymphedema • Post-RT brachial plexopathy 	<ul style="list-style-type: none"> • Location of pain can be arm, neck, shoulder, chest wall, or breast • Pain can be localized or can radiate down the affected arm • Sensations include paresthesias, dysesthesias, hyperalgesias, and allodynia
Head and Neck	<ul style="list-style-type: none"> • Neck and shoulder pain • Facial, mouth, dental, mandibular pain 	<ul style="list-style-type: none"> • Can involve neck, shoulder, and myofascial pain • Pain includes loss of sensation and neuropathic pain syndromes
Lung	<ul style="list-style-type: none"> • Intercostal neuralgia 	<ul style="list-style-type: none"> • Sensations include paresthesias • Decreases over the course of a year
Prostate	<ul style="list-style-type: none"> • Chronic pelvic pain 	<ul style="list-style-type: none"> • Pain usually only present during urination or exacerbated during urination
Sarcoma	<ul style="list-style-type: none"> • Stump pain • Phantom limb pain (PLP) 	<ul style="list-style-type: none"> • Stump pain can be related to a poorly fitting prosthesis • PLP decreases over the course of a year; pain present at 1 year is likely to persist chronically

Source: Brant JM. Pain and discomfort. In: Lester JL, Schmitt P, eds. *Cancer Rehabilitation and Survivorship*. Pittsburgh: Oncology Nursing Society; 2011:37–48.

cancer survivors is being increasingly recognized. The most common cancer pain syndromes in cancer survivors are included in Table 5-3.

PATHOPHYSIOLOGY

The assessment and management of pain begins with an understanding of the pathophysiology of pain. While this process is more straightforward for acute pain, the mechanisms are less understood for chronic and cancer pain due to changes that occur within the nervous system over time, even without the pain stimuli.

Pain begins with transduction when a mechanical, thermal, or chemical stimulus triggers pain and initiates a cascade of events. At the time of injury, neuromediators such as prostaglandins, histamine, bradykinin, serotonin, and substance P flood the site of injury, initiating an inflammatory response.²⁵ Once the sensory nerve endings are stimulated, an action potential or depolarization occurs and transmits the painful message through primary afferent neurons in the peripheral nervous system and to the dorsal horn of the spinal cord. Within the spinal cord, neurotransmitters and other excitatory substances are released. Spinal neurons also release inhibitory amino acids such as gamma-aminobutyric acid (GABA) to inhibit presynaptic and postsynaptic nociceptive transmission, thereby modulating the pain sensation. Transmission continues to the brain stem and thalamus, eventually reaching higher

centers in the brain. The painful message finally reaches the cortical level of the brain, where perception of pain occurs. The thalamus also relays information to the limbic system, where affective responses of pain are mediated.²⁵

Past experience with pain, beliefs, and culture provide a contextual environment for interpretation of the pain. The brain, however, responds to the noxious stimuli to diminish perception through descending modulating mechanisms. Specifically, neurons within the pons and medulla descend to the dorsal horn and release serotonin, norepinephrine, and endogenous opioids at the dorsal horn of the spinal cord, which inhibit the transmission of pain impulses²⁶ (Figure 5-1).

Both pharmacologic and nonpharmacologic modalities assist in managing pain during the transduction, transmission, perception, and modulation processes. For example, corticosteroids and nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit prostaglandins in the periphery, disrupting transduction.²⁷ Topical capsaicin cream inhibits substance P.²⁸ Anticonvulsants such as gabapentin and pregabalin are nerve stabilizers and interrupt transmission of pain by preventing depolarization. Opioids work at the dorsal horn of the spinal cord by binding to receptors to prevent transmission to the higher brain centers. Psychosocial interventions and cognitive-behavioral therapy alter the amount of pain perceived by the brain.²⁹ Tricyclic antidepressants exert effects during modulation by blocking the reuptake of dopamine, serotonin, and norepinephrine within the synapse in the dorsal horn of the spinal cord.

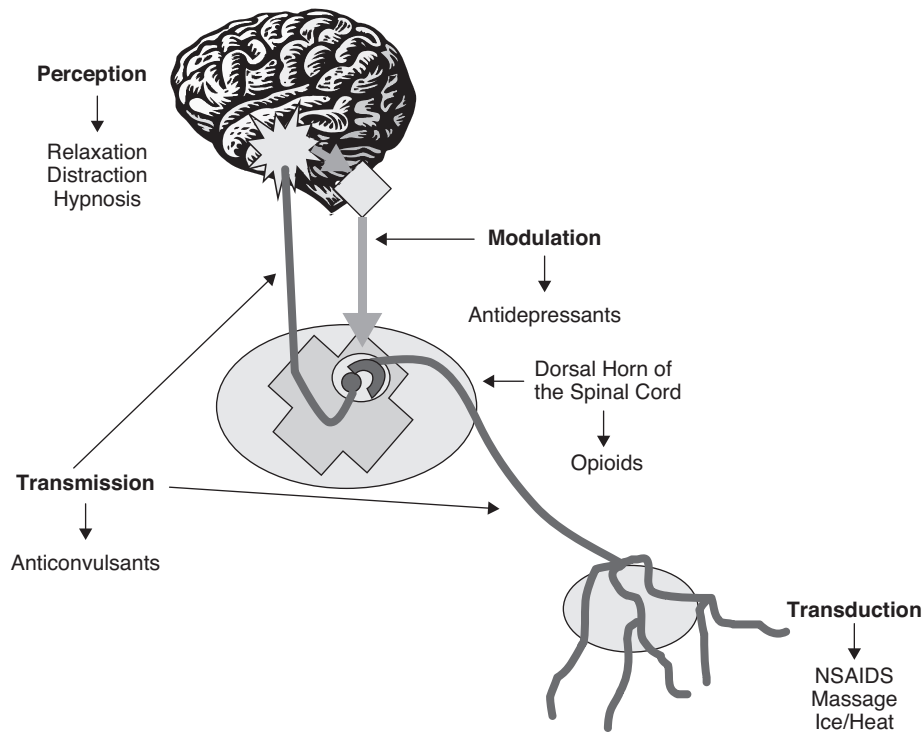


FIGURE 5-1

Pathophysiological Mechanisms of Pain and Pharmacologic Interventions.

Source: Brant JM. Strategies to manage pain in palliative care. In: O'Connor M, Lee S, Aranda S, eds. *Palliative Care Nursing: A Guide to Practice* (3rd ed.). Victoria, Australia: Ausmed; 2012:93–113.

CANCER PAIN PATHOPHYSIOLOGY

The pathophysiological mechanisms of cancer pain include both acute and chronic mechanisms. Acute pain can be described as pain that resolves with healing over time. Usually nociceptive, acute pain serves as a warning sign for impending injury. Psychological components are involved such as fear and depression, which can remodel the nervous system and provoke chronic pain.

Chronic pain, historically defined as pain that extends beyond 6 months or healing time, is now recognized as a complex phenomenon that no longer serves to protect function but rather disrupts sleep, activities of daily living, and quality of life. Chronic pain can be nociceptive, neuropathic, or both. In extreme situations, it can be accompanied by central sensitization, a state of spinal neuron excitability. “Wind-up” occurs as repeated stimulation of the nerve fibers causes an increase in dorsal horn neuron firing. When this occurs, pain progressively increases over time. Eventually, central inhibition is reduced in response to the pain, dorsal horn neuronal activity becomes spontaneous, and neurons that are usually mildly responsive are recruited to fire. This phenomenon can result in hyperalgesia, allodynia, persistent pain, and/or referred pain

(Table 5-1). The potential for central sensitization calls for an aggressive plan to manage pain in its current state to prevent “wind-up” and further sequale.²⁶

SYMPTOM ASSESSMENT

Pain assessment begins with an understanding of patients who may be at risk for developing pain, an understanding of patients who may be at risk for the under-treatment of pain, and a comprehensive history and physical exam. While it may be helpful to diagnostically determine the etiology of the pain, it is never a requirement for the management of pain. Because the patient’s report of pain is the most reliable indicator of its presence, it is the most significant assessment parameter.

RISK FACTORS

While pain is present in more than 50% of patients with cancer, some patients may be at greater risk.²⁰ As noted, a greater percentage of those patients with head and neck cancer have been found to have pain as well as those patients

with gynecologic or gastrointestinal malignancies. Patients whose disease has metastasized are also at increased risk.²⁰ Recognition of the disease characteristics that are associated with greater risk allows clinicians to anticipate potential problems and include pain management into the plan of care early, even prior to the onset of pain.

Some patient populations may also be at increased risk for under-treatment of pain, such as minority patients, older adults, and patients with a disease of addiction. Minority patients, especially those who speak English as a second language, may be at increased risk due to lack of communication and other biases. In one study, pain was underestimated in 64% of Hispanics and 74% of African Americans. Inadequate pain assessment was named as the primary gap for minority patients and linked to inadequate pain management.¹⁸ Lay educators and others who speak the patient's language can assist with the overall assessment and education about pain.¹⁹

Older adults are another high-risk population. Loss of hearing and visual acuity may impede communication, as may dementia and memory loss. Despite these challenges, clinicians should recognize that self-assessment pain scales can often be used reliably in older patients with mild to moderate dementia, and even in some individuals with severe dementia. Behavioral scales should be used only in patients who cannot complete a self-assessment.³⁰ Behavioral scales can detect possible pain, but currently no standardized scale exists and existing tools are in early development. Guidelines for assessing pain in older adults are included in Table 5-4.

Patients with a disease of addiction are another high-risk population for under-treatment of pain and for misuse of opioid analgesics.³¹ Lack of trust, provider lack of knowledge about addiction, and opiophobia may interfere with optimal management. Active substance abuse brings about additional challenges, as providers attempt to manage pain without contributing to the problem of addiction.³² In addition to the pain assessment, clinicians will need to assess for risks of addiction. Behaviors that are less predictive of aberrancy include drug hoarding, aggressive demands for higher doses, occasional unsanctioned dose escalation, psychiatric side effects, and requests for specific drugs. Behaviors more predictive of aberrancy include selling and forging prescriptions, concurrent illicit drug use, multiple prescription losses, multiple dose escalations, stealing drugs, using a nonsanctioned route of administration, and repeated resistance to the recommended treatment plan.³³ Outcomes of opioid therapy in patients with a disease of addiction should include the four "A's": (1) analgesic response or pain relief, (2) activities of daily living or physical, social, and emotional functioning, (3) adverse effects of the prescribed analgesics, and (4) aberrant drug-seeking behaviors suggesting active addiction.³³ Ongoing communication and assessment are keys to maintaining comfort while preventing misuse, abuse, and diversion.

TABLE 5-4

Five Step Approach to Pain Assessment in Older Adults

Step 1	Attempt to obtain a self-report of pain. Options include: <ul style="list-style-type: none"> • "0–10" scale • Verbal descriptor scale • Vertical pain thermometer
Step 2	If unable to use a self-report, search for potential causes of the pain: <ul style="list-style-type: none"> • Trauma • Bladder distention • History of chronic pain • Decubitus ulcer • Progressive cancer
Step 3	Observe patient behaviors using a behavioral rating scale. Types of pain behaviors include: <ul style="list-style-type: none"> • Facial expressions • Verbal and vocal indicators • Body movements • Change in interpersonal interaction • Change in activity pattern or routine • Mental status change Nonverbal tool examples for use in older adults: <ul style="list-style-type: none"> • Assessment of Discomfort in Dementia Protocol (ADD) • Checklist of Nonverbal Pain Indicators (CNPI) • Doloplus 2 • Nursing Assistant-Administered Instrument to Assess Pain in Demented Individuals (NOPPAIN) • Pain Assessment Scale for Seniors with Severe Dementia (PACSLAC) • Pain Assessment in Advanced Dementia Scale (PAINAD)
Step 4	Ask family members to aid in the assessment. Ask about: <ul style="list-style-type: none"> • Typical behavior • Changes in behavior – families can detect subtle changes • Changes in cognition
Step 5	If Step 1 through Step 4 suggests the patient may be in pain: <ul style="list-style-type: none"> • ASSUME PAIN PRESENT • Use an analgesic trial and assess if there is a decrease in potential pain behaviors or improved cognition

Source: Data from American Geriatrics Society. Pharmacological management of persistent pain in older persons. *Pain Med.* 2009;10(6):1062–1083. ; Herr K, Bjoro K, Decker S. Tools for assessment of pain in nonverbal older adults with dementia: a state-of-the-science review. *J Pain Symptom Manage.* 2006;31(2):170–192.

SELF-ASSESSMENT AND PAIN HISTORY

The patient's report of pain is the most valuable component of a comprehensive pain assessment, and pain should be managed according to the patient's report of pain. Onset, location, duration, characteristics, aggravating factors, relieving factors, and treatment (OLDCART) can be used to systematically assess the physiological components of the pain (Table 5-5). Information should be gathered for each

TABLE 5-5

Comprehensive Pain Assessment	
Domain	Pain Assessment Components
Physical	<ul style="list-style-type: none"> • Onset – When did the pain start? • Location – Where is the pain located? Is there more than one location? • Duration – How often does the pain occur? Is it constant or intermittent? How long does the pain last? <ul style="list-style-type: none"> ○ Breakthrough pain (BTP) <ul style="list-style-type: none"> ■ Follow OLDCART assessment ■ Number of episodes per day ■ Incident versus idiopathic <ul style="list-style-type: none"> • Differentiate from end of dose pain ■ Onset and duration of BTP episodes ■ How the BTP responds to pharmacologic and nonpharmacologic interventions • Characteristics – How does the pain feel? What words would you use to describe the pain? <ul style="list-style-type: none"> ○ Intensity <ul style="list-style-type: none"> ■ 0-10 scale preferred ■ Verbal descriptor scale (mild, moderate, severe) ■ Others: pain thermometer, visual analog scale, nonverbal scales as indicated ○ Patient descriptors can aid in diagnosing the pain syndrome. <ul style="list-style-type: none"> ■ Somatic pain (e.g. bone pain) – well localized, constant, dull, aching, gnawing ■ Visceral pain (e.g. abdominal pain) – poorly localized, can be referred, described as cramping, stretching, fullness ■ Neuropathic pain (e.g. peripheral neuropathy) – described as burning, numb, radiating, shock-like • Aggravating Factors – What makes your pain worse? <ul style="list-style-type: none"> ○ Movement – walking, other ○ Positional – sitting, standing, lying down ○ Miscellaneous activity – coughing, sneezing, urinating, moving bowels • Relieving Factors – What makes your pain better? <ul style="list-style-type: none"> ○ Analgesics ○ Positioning, splinting, modifying activity ○ Nonpharmacologic modalities – ice, heat, massage, TENS, cognitive behavioral strategies • Treatment – What treatments have you tried to control the pain? How are they working? How do the treatments affect the pain intensity? <ul style="list-style-type: none"> ○ Pharmacologic ○ Nonpharmacologic
Psychological	<ul style="list-style-type: none"> • The meaning of pain to the patient and family • History of anxiety, depression, or other psychological illness • Cognition, including confusion or delirium • Usual coping strategies in response to pain • Psychological responses to pain and illness such as depression, anxiety, and fear • Beliefs about opioids, addiction, and other concerns • Willingness to try complementary modalities such as cognitive behavioral therapy
Social	<ul style="list-style-type: none"> • Functional assessment: Interference of pain on daily living including physical or social withdrawal from activity • Family communication and response to illness • Support system • Economic impact of the pain and its treatment (e.g. ability to afford analgesics)
Spiritual/ Existential	<ul style="list-style-type: none"> • Spiritual beliefs related to pain and illness • Presence of a spiritual community and its role related to pain and illness • Influence of religion or spirituality on coping with pain • Use of traditional medicine in healing

Source: Data from Brant JM. The global experience of cancer pain. *Asian Pacific J Cancer Prev*. 2010;11(MECC supplement):7–12.

pain location. Aspects of the pain to be considered include both intensity and characteristics.

The pain intensity can be ascertained by asking the patient, “On a 0–10 scale, with 0 being no pain and 10 being the worst possible pain, what is your pain?” Quantifying the pain assists in communication between the patient, family, and healthcare team, and can measure the patient response to the interventions. The pain management plan of care can then be modified based on the patient’s response. When patients are unable to provide a “0–10” response, alternative assessment tools are available, such as a verbal descriptor scale, pain thermometer, and pain faces scale. A nonverbal pain assessment scale should be used for patients who cannot provide a self-assessment of pain. Duration of the pain can determine whether controlled-release or immediate-release opioids should be employed.^{4,34}

One type of intermittent pain—breakthrough pain (BTP)—requires individual assessment. Breakthrough pain is defined as “a transient exacerbation of pain that occurs either spontaneously, or in relation to a specific predictable or unpredictable trigger, despite relatively stable and adequately controlled background pain” (p. 332).³⁵ Onset, location, duration, characteristics, aggravating and relieving factors, and treatment response of the BTP episodes should be examined.³⁵

Pain characteristics include the patient’s description of the pain. Descriptors can help identify the etiology of the pain, which aids in the pharmacologic management. For example, if the patient complains of numbness and tingling of the feet following taxane therapy, the clinician assumes peripheral neuropathy and employs analgesics such as anti-convulsants. Aggravating and relieving factors as identified by the patient roll into the pain management plan of care. For example, if a patient complains of pain with movement and activity, analgesics should be given at the appropriate time prior to the activity so that comfort can be attained. Response to treatment should be evaluated on an ongoing basis as well so that therapy can be tailored accordingly. In addition to the physiological assessment, psychological, social, and spiritual influences on pain should be examined.⁸

A number of assessment tools are available to report the elements of the pain assessment. The Brief Pain Inventory (BPI) is a tool that can measure both pain intensity and interference of pain with daily functioning. The tool has established validity and reliability in measuring pain across cultures and has been translated in several different languages.³⁶ Additional scales such as the Edmonton Symptom Assessment Scale and the Rotterdam Symptom Checklist include the measurement of pain along with other global symptoms.³⁷

Many healthcare settings are beginning to incorporate electronic pain assessment tools into practice. Electronic tools allow field prompts that guide the clinician through the assessment, ensuring consistency and comprehension.

Electronic self-report tools are also available for patients to rate pain and other symptoms prior to clinic visits.³⁸

OBJECTIVE ASSESSMENT

While self-assessment of pain is the most reliable indicator of its existence, objective assessment can further identify the etiology of the pain and guide treatment options. Both physical and diagnostic evaluations are critical in identifying and then treating the underlying causes of the pain.

Physical Assessment

A physical assessment includes a head-to-toe examination with a focus on the neurological assessment. Initially, the clinician should observe the patient and identify overt signs of pain such as splinting or grimacing and more subtle signs of pain such as fatigue, exhaustion and sleep deprivation, and signs of depression that often cluster with pain.³⁹ The site of the pain should be assessed using observation, palpation, percussion, and, if indicated, auscultation. Color changes, edema, and tenderness with palpation and percussion assist in pinpointing the specific area.

Tests (brush, pinch, pin prick, and/or scratch) should be conducted to assess for allodynia, hyperalgesia, or hyperesthesia (see Table 5-1 for definitions). Sensory evaluation can detect different types of neuropathy. Reduced sensation to vibration as detected with a tuning fork or loss of proprioception can indicate large neuronal fiber damage. Small-diameter neuronal fiber damage is indicated by changes in temperature sensation and touch sensation using the pin-prick test.

Motor abnormalities or deficits and lack of coordination can also indicate neurologic problems. The musculoskeletal system should be observed, and causes of pain identified. Body posture, gait, and lack of symmetry can indicate compensation for pain and could lead to further sequela. Patients may also limit range of motion when pain is severe. For example, women post mastectomy can develop a painful frozen shoulder if range of motion is not maintained.⁴⁰

Diagnostic Evaluation

Radiographic exams can diagnose the underlying problem of the pain. Computed tomography (CT) scans can visualize tumor progression, magnetic resonance imaging (MRI) allows good visualization of nerve impingement and central nervous system involvement, and bone scans detect the extent of bony metastases. Laboratory analyses such as an increase in tumor marker levels and liver enzymes can also suggest pain related to progressive disease. The extent of the diagnostic work-up is related to the patient’s goals of care. As goals move toward palliation, clinicians rely more

on the patient's self-assessment and history. However, when pain can be ameliorated by radiation therapy or other cancer treatment modalities, the diagnostic evaluation is essential to obtain prior to the palliative treatment.⁴⁰

DEGREES OF TOXICITY

The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) includes comprehensive descriptive terminology to measure symptoms related to cancer and the manifestations of cancer treatment.⁴¹ Within the CTCAE, which is often used to measure toxicity related to clinical trials, various types of pain are differentiated. While the overall CTCAE scale ranges from 0 to 5, pain is measured using a 0 to 3 scale where 0 is no pain, 1 is mild pain, 2 is moderate pain limiting instrumental activities of daily living (ADLs), and 3 is severe pain limiting self-care. One benefit of the criteria is the all-inclusive list of pain syndromes represented. The list reminds clinicians of the multitude of pain syndromes that can be experienced by patients with cancer. A limitation of the CTCAE is the lack of detail to each of the ratings, thereby limiting its usefulness. Clinicians should be reminded that these criteria are staging systems of pain but should not replace the pain assessment.

SYMPTOM MANAGEMENT STRATEGIES

PREVENTIVE STRATEGIES

A number of interventions can be employed to prevent pain in some patients. First, patients should be reminded to take analgesics as prescribed, often around the clock (ATC) to maintain a therapeutic blood level of the opioid and to prevent pain. Breakthrough pain medication should be taken, if possible, at the first indication of pain. For patients with predictable incident pain, the opioid analgesic should be employed at an appropriate interval according to the pharmacokinetics of the medication prior to the activity. This ensures that the opioid is peaking during the painful activity.

Novel strategies are also being investigated in the prevention of postoperative pain. For many patients with cancer, surgery is the initial painful experience. The use of preemptive analgesia is important to prevent peripheral and central sensitization, thereby preventing wind-up and postoperative injury. NSAIDs, gabapentin, and opioids are commonly used, but more research is needed to determine the optimal dose and schedule for these preemptive agents.^{42,43}

Bone-modifying agents, which are now standard treatment in patients with lytic bone lesions, can prevent skeletal events such as fractures and subsequent bone pain related to

bony metastases. Bisphosphonates such as pamidronate and zoledronic acid inhibit osteoclast-mediated bone resorption. Denosumab is a novel bone-modifying monoclonal antibody that binds to a protein called RANKL, which is responsible for the production, function, and survival of osteoclasts.⁴⁴

THERAPEUTIC APPROACHES

Anticancer Treatment

Surgery, antineoplastic therapy, and radiation therapy can all be used to decrease tumor burden, thereby alleviating pain. While some cancer therapies can cause significant side effects and should be carefully weighed according to patient goals and disease status, other therapies are associated with few sequelae and may be considered even toward the end of life.

Surgery can be employed to resect tumor away from surrounding organs, bones, and nerves to prevent disease complications and alleviate pain. Specific surgical interventions for vertebral metastases include vertebroplasty and kyphoplasty. Both procedures can be performed with minimal invasion, are well tolerated, and can provide timely reduction in pain.^{45,46} Bowel resection, decompression laminectomy, and renal stent placement are additional surgical procedures employed to manage pain caused by cancer.

Antineoplastic therapy such as chemotherapy, targeted therapy, biological therapy, and hormonal therapy may decrease tumor burden, thereby alleviating pain. However, the goal of antineoplastic therapy is rarely pain control, as the side effects of the treatment often outweigh benefits.

Radiation therapy is commonly employed to manage painful bone metastases. One study revealed that approximately 25% of patients achieved complete pain relief at 1 month and more than 50% at 4 weeks. The median duration of complete pain relief was 12 weeks.⁴⁷ Radioisotopes are another strategy for pain control in patients with disseminated bone metastases. Patients may experience a complete reduction in pain over 1 to 6 months. Pancytopenia is a common side effect and should be considered in terms of the risk-benefit ratio.⁴⁸

Pharmacologic Treatment

Pharmacologic therapy is the mainstay of cancer pain management. The approach is multimodal, using a variety of agents that interrupt the pain pathway and the transmission of pain to the brain. WHO has developed a three-step analgesic ladder that guides the pharmacologic management of pain (Figure 5-2). The ladder suggests that when pain occurs, prompt administration of nonopioids

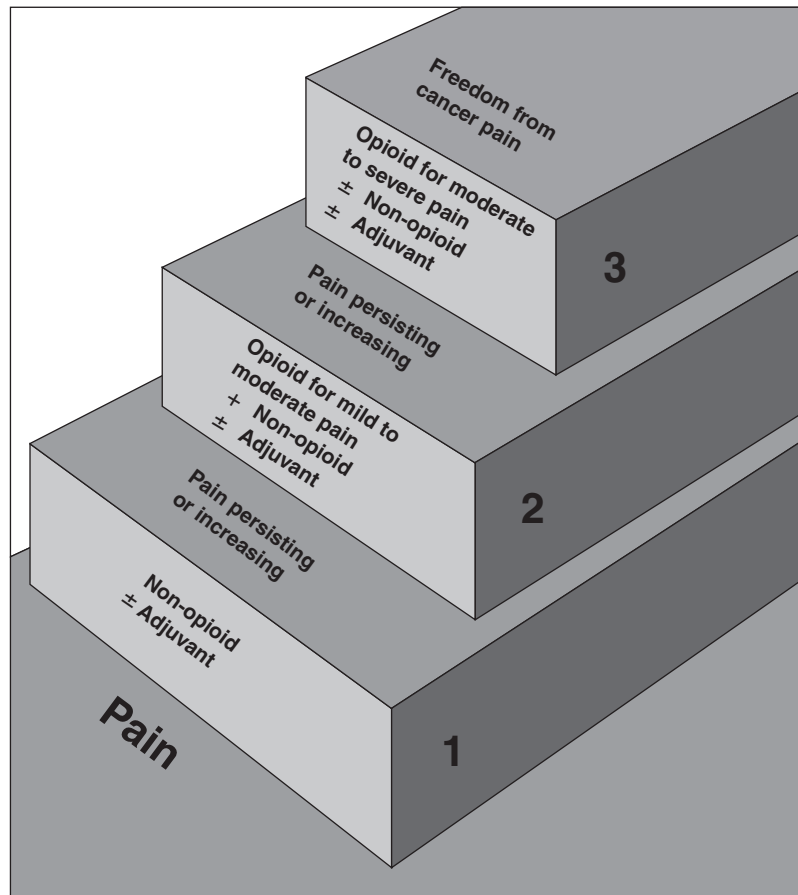


FIGURE 5-2

World Health Organization Analgesic Ladder.

Source: World Health Organization, 1990. Used with permission.

should occur, followed by mild opioids (e.g., hydrocodone) as needed and then strong opioids (e.g., morphine) until the patient is comfortable. Adjuvants, also known as co-analgesics, should be used in all three steps to treat specific pain syndromes and the symptoms associated with pain such as anxiety and depression. To maintain freedom from pain, the WHO ladder recommends that analgesics be given ATC. Using the ladder with the right drugs and dosages is inexpensive and is 80%–90% effective.³

Nonopioids Nonopioids, which include acetaminophen, aspirin, and NSAIDs, constitute Step 1 of the WHO ladder. Acetaminophen is often used in combination with opioids for cancer pain management. The mechanism of action for acetaminophen is poorly understood, but it appears to work primarily in the central nervous system. It has fewer adverse gastrointestinal (GI) effects compared to the NSAIDs and lacks antiplatelet effects. Studies suggest that acetaminophen may increase blood pressure⁴⁹ and may contribute to over anticoagulation^{50,51} when administered with warfarin.

Hepatotoxicity is a serious side effect of acetaminophen, and doses should not exceed 4000 mg per day.² Recent evidence suggests that even lower doses may be associated with an increased risk of hepatotoxicity.⁵²

Aspirin, one of the oldest nonopioid analgesics, is rarely used in cancer pain management. It has been replaced with newer NSAIDs that have more favorable efficacy.

NSAIDs are widely used in cancer pain management and are especially indicated for inflammatory, bone, and joint-related pain.²⁷ Evidence suggests that using acetaminophen and NSAIDs together is superior compared to either drug alone.⁵³ They work by inhibiting cyclooxygenase (COX), a catalyst enzyme responsible for converting arachidonic acid (a cell-wall fatty acid) to prostaglandin (PGE₂), prostacyclin (PGI₂), and thromboxane A₂ (TXA₂). By blocking COX and subsequent prostaglandin production in the central and peripheral nervous systems, NSAIDs reduce inflammation. Two types of COX exist. Cyclooxygenase-1 is found in most human tissues, including the GI tract, platelets, and kidneys, whereas COX-2

is concentrated primarily in the kidneys, central nervous system, and peripheral tissues during painful and inflammatory states. Therefore, prostaglandins protect the gastrointestinal tract, allow for platelet aggregation, and provide vasodilation for adequate blood flow in the kidneys and other tissues. Inhibiting cyclooxygenase and subsequent prostaglandin production produces the significant side effects exhibited, including GI toxicity, bleeding, and renal compromise.²

NSAIDs are categorized according to their ability to inhibit both COX-1 and COX-2 (nonselective) or selectively COX-2. The majority of NSAIDs are nonselective, and celecoxib is the only selective COX-2 inhibitor currently approved by the Food and Drug Administration. While all NSAIDs can produce GI side effects including ulceration, bleeding, and perforation, evidence suggests that the COX-2 NSAIDs exhibit fewer GI effects compared to the nonselective NSAIDs. Patients should take NSAIDs with food to minimize these effects. In addition, COX-2 NSAIDs do not inhibit platelet function. One limitation is their increased risk of prothrombotic and related cardiovascular events. Central nervous system effects such as short-term memory loss, loss of concentration, decreased attention span, and confusion can also occur, likely due to prostaglandin inhibition in the central nervous system.^{2,54}

Opioids Opioids are the mainstay of cancer pain management and are included in both Step 2 and Step 3 of the WHO analgesic ladder. Opioids work by binding to mu (μ), kappa (κ), and delta (δ) receptors at the dorsal horn of the spinal cord and in the peripheral nervous system. While several opioids are available for use, agonist-antagonist opioids are not recommended for cancer pain control due to their psychomimetic effects and ceiling dose. These opioids that bind to κ and/or λ antagonize μ , which can precipitate withdrawal in patients taking pure μ agonists. Meperidine is one μ agonist that is not recommended in cancer pain management. Its toxic metabolite, normeperidine, can accumulate and cause central nervous system toxicity and seizures.²

Individual response to opioids occurs and can be explained by the polymorphic *OPRM1* gene that has multiple μ receptor subtypes. Approximately 20% to 30% of the population has heterozygous changes in alleles of the *OPRM1* gene, influencing pain sensitivity. Patients with the *OPRM1* GG genotype require higher doses of morphine compared to those patients with the *OPRM1* AA genotype.⁵⁵ Thus opioid therapy should be tailored per patient response. Patients also report better response from other opioids, but little is known about these individual variations. Following is a discussion of the opioids used to control cancer pain, and a summary of opioids is included in Table 5-6.

Morphine is the standard of comparison for all opioids and is efficacious in the management of cancer pain.⁵⁶ It is available via oral, suppository, and parenteral routes of administration, with the oral formulation being available in both controlled- and immediate-release preparations. Because of its poor oral bioavailability, the onset of effect for the immediate-release version is at least 30 minutes; it is 90 minutes for the controlled-release product.

Morphine is metabolized in the liver through glucuronidation to morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G). M3G antagonizes morphine and is thought to be responsible for many of the adverse effects of the drug such as myoclonus, hallucinations, and hyperalgesia. M6G is more potent than the morphine itself and can add to the overall analgesic effect, which can increase over time with retention of the metabolites. Both metabolites can accumulate in patients with renal compromise, resulting in possible oversedation and an increase in other toxicities. The dose of morphine should be lowered in patients with renal insufficiency or an alternative opioid should be considered.²

Morphine is associated with additional side effects. It causes histamine release, which can lead to bronchospasm and hypotension. Anaphylaxis can also occur in patients with sulfa allergies when given morphine parenterally due to the presence of sulfites. Respiratory depression can occur and respiratory acidosis can result in increased morphine delivery to the brain and further respiratory compromise. Orthostatic hypotension, pruritus, and nausea and vomiting are additional side effects.

Oxycodone is 1.5 times stronger than morphine and is a useful oral opioid for the control of cancer pain. It is available in the pure form or combined with acetaminophen. Clinicians should use the pure form for BTP when the acetaminophen dose exceeds 4000 mg/day. Oxycodone is metabolized by CYP2D6 to oxymorphone, but the parent drug is responsible for the analgesic effect.⁵⁷

Oxymorphone is a newer, synthetic and lipophilic opioid that is 10 times more potent than morphine. Drug-drug reactions with this agent are rare due to its lack of CYP2D6 or CYP3A4 metabolism. Its reduced histamine release can also be an advantage for patients who complain of histamine-related side effects such as pruritus and headache.⁵⁷

Hydrocodone is a commonly used opioid but lacks usefulness in chronic cancer pain management due to its combination with acetaminophen. It is metabolized by CYP2D6 into hydromorphone. It is suggested in the literature that hydrocodone is a prodrug, so those patients who lack CYP2D6 may not achieve the full analgesic benefit; however, human studies of this effect are sparse.

Hydromorphone is a semi-synthetic opioid that is 7 to 10 times stronger than morphine. The recent approval of a sustained-release preparation has expanded the role of hydromorphone in managing cancer pain. While this

TABLE 5-6

Opioids Used to Manage Cancer Pain					
Opioid	Preparations	Equianalgesic Ratios		Common Side Effects	Comments
		Oral	IV		
Morphine	<ul style="list-style-type: none"> • Oral: Controlled release (CR), Immediate release (IR), Oral solution • Rectal • Parenteral (IV or SC) • Intraspinal preservative free (PF) 	30	10	<ul style="list-style-type: none"> • Respiratory depression • Nausea and vomiting • Pruritis • Orthostatic hypotension • Urinary retention • Constipation 	<ul style="list-style-type: none"> • Standard for opioid comparison • Metabolites M3G and M6G can accumulate with renal compromise • Histamine release can cause bronchospasm and hypotension • Parenteral forms contain sulfites; patients with sulfa allergies may experience anaphylaxis
Fentanyl	<ul style="list-style-type: none"> • Transdermal (TD) • Transmucosal • Nasal • Parenteral: IV, SC • Intraspinal PF 	–	0.1	<ul style="list-style-type: none"> • Similar to morphine 	<ul style="list-style-type: none"> • Highly lipophilic • Onset and duration of action variable and dependent on route • TD onset 12 hours, peak 24–48 hours; potency of 25 ug TD fentanyl equal to approximately 30–75 mg morphine/day; remains in system approximately 24 hours after discontinuation • Transmucosal onset usually within 15 minutes • Nasal onset within 5 minutes • Parenteral onset within 5–10 minutes • Metabolized by CYP3A4 • Should not cut or tamper with the patch; heating the patch can cause overdose and death
Hydrocodone	<ul style="list-style-type: none"> • Oral: IR with acetaminophen or aspirin, oral solution 	30	–	<ul style="list-style-type: none"> • Similar to morphine 	<ul style="list-style-type: none"> • Proposed as a prodrug that must be metabolized by CYP2D6 enzyme prior to achieving an analgesic effect; patients who are CYP2D6 deficient may achieve less clinical benefit with codeine, but studies are sparse
Hydromorphone	<ul style="list-style-type: none"> • Oral: CR, IR • Rectal • Parenteral: IV, SC • Intraspinal PF 	7.5	1.5	<ul style="list-style-type: none"> • Similar to morphine • Not associated with histamine release 	<ul style="list-style-type: none"> • May be preferred in patients with renal insufficiency • Extensive metabolism by the liver to primarily H3G and to some extent H6G; M3G accumulation can cause allodynia, myoclonus, and seizures in animal models
Oxycodone	<ul style="list-style-type: none"> • Oral: CR, IR with and without acetaminophen, oral solution 	20	–	<ul style="list-style-type: none"> • Similar to morphine 	<ul style="list-style-type: none"> • 1.5 times more potent than morphine • Parenteral preparation unavailable • Metabolized by CYP2D6; drug-drug interactions may occur with 2D6 inhibitors
Oxymorphone	<ul style="list-style-type: none"> • Oral: CR, IR • Parenteral: IV, SC • Rectal 	10	1	<ul style="list-style-type: none"> • Similar to morphine • Reduced histamine effect 	<ul style="list-style-type: none"> • To be administered on an empty stomach; food increases the maximum concentration • Do not administer with alcohol • No CYP450 drug-drug interactions

(continued)

TABLE 5-6

Opioids Used to Manage Cancer Pain (continued)					
Opioid	Preparations	Equianalgesic Ratios		Common Side Effects	Comments
		Oral	IV		
Methadone	<ul style="list-style-type: none"> • Oral: long acting • Rectal • Parenteral 	See separate equianalgesic table		<ul style="list-style-type: none"> • Similar to morphine • High risk of respiratory depression due to long half-life • QTc prolongation with doses > 100 mg/day 	<ul style="list-style-type: none"> • Contraindicated in moderate and severe hepatic impairment • Dose reduce in patients with renal compromise and mild hepatic impairment • May be useful in patients with a morphine allergy or in those who experience itching or headache with other opioids • Long half-life (up to 150 hours) allows for less frequent dosing but accumulation of drug • NMDA antagonism may be beneficial to prevent tolerance and manage neuropathic pain syndromes • Metabolized by P450 with potential for drug-drug interactions • Only experienced practitioners with substantial knowledge of methadone pharmacokinetics should prescribe methadone

agent has two metabolites (similar to morphine), hydromorphone-3-glucuronide (H3G) and hydromorphone-6-glucuronide (H6G), studies are sparse regarding the clinical effects of these metabolites. Hydromorphone lacks histamine release so is also helpful in patients who report histamine-related side effects.

Methadone is a synthetic, lipophilic, pure μ opioid agonist that has a long history in the management of cancer pain. It also has a role in addiction maintenance, which sometimes creates a stigma for this opioid. In addition to its pain-relieving properties, methadone demonstrates N-methyl-D-aspartate (NMDA) antagonism, which may confer benefits in the management of neuropathic pain syndromes⁵⁸; however, a recent Cochrane review indicated that methadone was not superior to morphine.⁵⁹ Additional studies are needed in this area. Antagonizing the NMDA receptor has also been shown to prevent opioid tolerance, central nervous system desensitization, and hyperalgesia.

Although methadone has several advantages, its high affinity for protein and subsequently long half-life can lead to oversaturation, respiratory depression, and fatal overdose when not accurately prescribed. The increased use of methadone over the last decade has resulted in a number of deaths that prompted the Food and Drug Administration to revise the package insert for methadone in 2006 to include clearer dosing guidelines.⁶⁰ Only clinicians with

in-depth knowledge of methadone's pharmacokinetic profile should prescribe this opioid.

Fentanyl is a strong, lipophilic μ agonist commonly used for cancer pain management. Its pharmacokinetics varies significantly depending on the route of administration. When given transdermally (TD), fentanyl must first saturate the subcutaneous tissue prior to onset of pain relief, which usually occurs at approximately 12 hours. Short-acting analgesics should be used judiciously when initiating TD fentanyl because of this lag in onset. Titration should occur only at steady state, which is reached at 72 hours after administration. Some patients who experience end-of-dose failure prior to the three-day patch change may need to change the patch every two days. Transdermal fentanyl is contraindicated in opioid-naïve patients. Parenteral fentanyl, whose effect both peaks and dissipates rapidly, is used to manage acute and intractable cancer pain. Acute pain includes postoperative pain and mucositis-induced pain.²

Transmucosal fentanyl is an additional entry in the armamentarium for the management of breakthrough cancer pain. Its ease of use and rapid onset are especially beneficial for patients with idiopathic and sudden-onset BTP. Patients report a faster time to pain relief and greater reduction in pain compared to placebo and immediate-release opioids.^{61,62} Several preparations exist, including a lollipop, buccal tablet, sublingual tablet, and buccal film.

The products vary to some extent in their oral bioavailability, onset, and efficacy.⁶³

Nasal fentanyl spray is the newest rapid-onset fentanyl product on the market. It demonstrates an even faster onset to pain relief (as early as 5 minutes) compared to the transmucosal fentanyl products. The product is designed using a pectin-based technology. When the drug comes into contact with mucosal surfaces (the nasal mucosa in this situation), it forms a gel that allows rapid absorption, yet prevents runoff.

Clinicians should keep in mind that dosing with these rapid-onset fentanyl products is unlike that other

immediate-release opioids. Titration occurs by using the lowest dose available and titrating gradually upward to efficacy rather than basing the BTP dose on a percentage of the 24-hour opioid dose.^{64,65}

Opioids can cause a variety of side effects. While tolerance occurs over time for some side effects such as respiratory depression, other effects, such as constipation, persist throughout treatment. Prevention of side effects is critical. Untoward side effects can affect patient adherence, pain control, and quality of life. The most common opioid-related side effects and strategies for management are included in Table 5-7.

TABLE 5-7

Opioid Side Effects: Pathophysiology and Management		
Side Effect	Pathophysiology	Management Strategies
Constipation	<ul style="list-style-type: none"> • Decrease in normal bowel peristalsis, gastric and pancreatic secretions, increase anal tone • Tolerance to constipation does not develop 	<ul style="list-style-type: none"> • Prevention is the key • Bowel stimulant (e.g. senna) ± a stool softener for prophylaxis • Other options: polyethylene glycol, magnesium citrate, lactulose, dioctyl sodium sulfosuccinate • Methylnaltrexone – reverses opioid receptors in the GI tract
Nausea and Vomiting	<ul style="list-style-type: none"> • Stimulation of the chemoreceptor trigger zone (CTZ) • Tolerance usually develops within one week. 	<ul style="list-style-type: none"> • Antiemetics around the clock for up to one week if nausea/vomiting occurs with opioids • Rotate opioids if tolerance does not develop
Psychomimetic Effects: sedation, delirium, confusion, agitation, and restlessness	<ul style="list-style-type: none"> • Stimulation of the central nervous system. • May be related to co-analgesics and/or disease process; not always opioid-induced 	<ul style="list-style-type: none"> • Attempt to identify the cause and modify pharmacologic agents as able • Psychostimulants to counteract sedation • Haloperidol or an antipsychotic for restlessness or agitation.
Pruritis	<ul style="list-style-type: none"> • Histamine release of some opioids, most commonly morphine 	<ul style="list-style-type: none"> • Antihistamines to counteract pruritis • Nalbuphine may counteract pruritis if associated with intraspinal opioids • Rotate opioids if pruritis persists
Myoclonus	<ul style="list-style-type: none"> • Generalized or focal sudden, brief, involuntary movements caused by muscle contraction • Can result from the accumulation of the opioid metabolites such as the M₃G metabolite of morphine 	<ul style="list-style-type: none"> • Opioid rotation may help • Administer agents to counteract myoclonus <ul style="list-style-type: none"> ○ Midazolam infusion starting at 1 mg/hour and titrate upward, shorter half-life than lorazepam and compatible with morphine ○ Lorazepam 1–4 mg Q 4 hours as needed or via continuous infusion ○ Dantrolene 50–100 mg per day is an alternative to benzodiazepines that causes less sedation
Respiratory Depression	<ul style="list-style-type: none"> • Most common in opioid naive patients and with opioid dose titration. 	<ul style="list-style-type: none"> • Prevention is the key; individualize opioid therapy • Determine if respiratory depression is due to opioid, a co-analgesic, or the dying process. • For life-threatening respiratory depression related to the opioid: dilute 0.4 mg naloxone in 10 cc normal saline and administer 1 cc every 2–5 minutes; do not administer naloxone too quickly as this can precipitate breakthrough pain and a pain crisis.

Co-analgesics Co-analgesics are agents that have independent analgesic activity, enhance the efficacy of other pain-relieving agents, or counteract analgesic adverse events. These agents were initially approved for another indication but now have a role in the management of pain—often in the form of neuropathic pain, which can be difficult to control. Categories of some of the more common agents include α_2 -adrenergic agonists, antidepressants, anticonvulsants, benzodiazepines, corticosteroids, local anesthetics, muscle relaxants, NMDA antagonists, and stimulants.² A summary of co-analgesics is included in Table 5-8.

Alpha₂-Adrenergic Agonists. Clonidine, an antihypertensive agent, can be used to alleviate neuropathic pain; however, limited data on this indication exist. Clonidine can be administered via the oral, transdermal, or intraspinal route but should be used only in refractory pain due to the limited evidence supporting its use as an analgesic.²

Antidepressants. Antidepressants are commonly used in the management of neuropathic pain syndromes such as chemotherapy-induced peripheral neuropathy, postherpetic neuralgia, and malignant nerve infiltration. They also are used as adjuvants in the management of depression and insomnia associated with pain. The agents are thought to work during pain modulation by blocking the reuptake of serotonin, norepinephrine, and/or dopamine at the dorsal horn of the spinal cord. Other theories suggest a role in nerve membrane stabilization and NMDA antagonism effects.² Studies suggest that one in three patients treated with a tricyclic antidepressant or venlafaxine will experience moderate relief. Limited evidence exists regarding the use of serotonin-specific antidepressants (SSRIs) to manage pain.⁶⁶

Anticonvulsants. Anticonvulsants have become first-line agents in the management of neuropathic pain, but are also helpful in a variety of other pain syndromes, including headaches. Gabapentin is used most commonly due to its cost, efficacy, and favorable toxicity profile. Adult dosing starts at 100 mg to 300 mg at bedtime and can be titrated every three days up to 3600 mg per day in three divided doses.² A novel once-daily long-acting gabapentin is now approved for postherpetic neuralgia. Carbamazepine is used less commonly, but some studies suggest it is as efficacious as gabapentin in the management of chronic neuropathic pain. Approximately two-thirds of patients report at least one adverse effect with this drug.⁶⁷ Pregabalin is the newest anticonvulsant used for neuropathic pain. Dosing is simpler than with gabapentin, and titration can occur more rapidly. As a result, the therapeutic effect may be reached earlier.²

Benzodiazepines. Benzodiazepines help relieve muscle spasm and anxiety associated with pain. They are commonly associated with oversedation and respiratory

depression, especially when administered with opioids. While helpful in some patients, these agents should be used with caution due to their side-effect profile.

Corticosteroids. Corticosteroids work by inhibiting prostaglandins and decreasing inflammation caused by tumor or other causes. They are used in a variety of nociceptive and neuropathic pain syndromes, including pain caused by lymphedema, spinal cord compression, brain tumors, and bone metastases. Long-term side effects can be substantial and include hyperglycemia, fluid retention and weight gain, osteoporosis, Cushing syndrome, myopathy, and psychosis. Side effects should be carefully weighed against the benefits of treatment.^{2,68}

Local Anesthetics. Local anesthetics are another useful type of co-analgesic for some pain syndromes. They are commonly employed in procedure-related pain such as bone marrow aspiration, pleurodesis, and lumbar puncture. Topical anesthetics such as EMLA are used to prevent pain associated with implantable port access and venipuncture procedures. The topical lidocaine 5% patch is approved for treating pain related to postherpetic neuralgia, but other uses exist, including management of postmastectomy pain and peripheral neuropathy. The patch should be worn for 12 hours and then removed for 12 hours. Several patches can be applied at once, and systemic effects are minimal.⁶⁹ Systemic administration of local anesthetics is also effective in relieving some neuropathic pain syndromes.⁷⁰

Muscle Relaxants. Skeletal muscle relaxants are a helpful short-term strategy for pain related to musculoskeletal conditions. Treatment should not continue past a few weeks, as the efficacy of long-term treatment has not been established. Sedation is the most common side effect.⁷¹

NMDA Antagonists. Blocking the NMDA receptor suggests prevention of tolerance and hyperalgesia as well as efficacy in neuropathic pain management. Methadone has some NMDA antagonism. Other agents include dextromethorphan, which is combined with morphine in a novel agent. Ketamine, an anesthetic agent, is also an NMDA antagonist that can be given orally, intravenously, and intraspinally. Its therapeutic index is narrow, however, and side effects include sedation and hallucinations. NMDA antagonists are typically used for refractory neuropathic pain that is not responsive to opioids, antidepressants, and anticonvulsants.^{72,73}

Stimulants. Stimulants are commonly used to counteract sedation caused by opioids and other pain-relieving agents. Methylphenidate is one option. Doses should be administered in the morning and before noon to prevent insomnia at night. Modafinil is a newer stimulant. Other options include caffeine, dextroamphetamine, and atomoxetine.² Other miscellaneous agents available as co-analgesics include antihistamines, antispasmodics, cannabinoids, and

TABLE 5-8

Co-Analgesics Used in Cancer Pain Management				
Drug Class	Daily Adult Starting Dose (Range)	Routes of Administration	Adverse Effects	Indications
Alpha-2-Adrenergic Agonists	Clonidine 0.1 mg qday	PO, TD, Intraspinal	Hypotension	Neuropathic pain
Tricyclic Antidepressants	Amitriptyline 10–25 mg hs Nortriptyline 10–25 mg hs Desipramine 10–25 mg hs	PO	Sedation, anticholinergic effects, cardiotoxicity, orthostatic hypotension, confusion, weight gain	Neuropathic pain, such as burning pain, poor sleep
Serotonin Norepinephrine Reuptake Inhibitor Antidepressants	Duloxetine 20 mg qday Venlafaxine 37.5 mg qday	PO	Duloxetine associated with nausea Venlafaxine associated with ECG changes	Neuropathic pain Treat depression and anxiety that exacerbate pain
Anticonvulsants	Gabapentin 100 mg qday or tid Gabapentin ER 300 mg qday Pregabalin 150 mg qday Carbamazapine 100–200 mg bid Clonazepam 0.5–1 mg hs, bid or tid	PO	Sedation, dizziness, ataxia, impaired concentration, peripheral edema Pregabalin associated with weight gain	Neuropathic pain, such as shooting pain Gabapentin CR for post-herpetic neuralgia
Benzodiazepines	Alprazolam 0.25 mg tid Clonazepam 0.5 mg tid Diazepam 1 mg bid Lorazepam 0.5 mg bid	PO, IV	Sedation, respiratory depression	Relieve anxiety and muscle spasm associated with pain
Corticosteroids	Dexamethasone: 2–4 mg tid, qid, or qday; may give up to 100 mg IV bolus for pain crises Methylprednisolone: 10 mg bid	PO/IV/SC	“Steroid psychosis,” dyspepsia, hyperglycemia, Cushingoid syndrome long-term	Cerebral edema, spinal cord compression, bone pain, neuropathic pain, visceral pain
Local Anesthetics	Mexiletine 150 mg qday Lidocaine infusion: 2 mg/kg over 30 minutes Lidocaine 5% patch Capsaicin cream: 0.025% tid	PO IV TD Topical	Lightheadedness, arrhythmias	Neuropathic pain
Muscle Relaxants	Cyclobenzaprine 5 mg tid Carisoprodol 350 mg tid Tizanidine 2 mg hs Metaxalone 400 mg tid	PO	Sedation, dizziness,	Musculoskeletal pain, indicated short-term (2 weeks or less)
N-Methyl-D-aspartate antagonists	Dextromethorphan: 15–20 mg tid Ketamine: 0.1 mg/kg	PO IV	Confusion, hallucinations, sedation	Neuropathic pain
Stimulants	Methylphenidate 2.5–5 mg qAM Dextroamphetamine 10 mg qday Modafinil 100 mg qAM	PO	Anxiety, agitation, insomnia	Counteract sedation caused by other analgesics
Antispasmodic	Baclofen 5 mg tid	PO	Muscle weakness, cognitive changes	Musculoskeletal pain and spasms
Bone Modifying Agents	Pamidronate 60–90 mg over 2 hours q 4 weeks Zoledronic acid 4 mg over 15 minutes q 4 weeks Denosumab 120 mg q 4 weeks	IV infusion SC	Pain flare, osteonecrosis of the jaw	Osteolytic bone pain, prevention of skeletal events

(as previously mentioned) bisphosphonate and radionucleotides. Treating the underlying cause of the pain and symptoms associated with the pain will increase success of the treatment plan.

Routes of Administration The simplest and most effective route of administration should be employed for each individual patient. The oral route is often the first choice for administration, but when it is not intact, other routes must be considered. Transdermal administration is another simple route and is especially helpful for patients who cannot take oral medications or cannot remember to take analgesics around the clock. Use of the transmucosal and nasal routes is becoming increasingly more common with greater use of the rapid-onset fentanyl products for breakthrough cancer pain. Their advantage is the fast onset that occurs following administration. Intravenous and subcutaneous routes can also be employed, especially for patients who have intractable pain uncontrolled with administration of pain relief via simpler routes.

Intraspinal routes of administration, including epidural and intrathecal routes, are additional options. Epidural administration can occur in the acute setting for postoperative pain or in patients with pain that is refractory to other routes. For refractory pain, the epidural catheter is usually tunneled at the waist line and attached to an infusion pump that delivers a continuous infusion of opioid and/or co-analgesic. An optional bolus dose can be programmed into the pump for patients who have BTP. The intrathecal route offers another option for refractory intractable pain. Due to the high risk of infection, this route often involves the placement of an intrathecal pump that delivers a continuous opioid dose to the patient. Because of the smaller doses required for intraspinal administration of opioids, side effects are minimal and patient satisfaction is high.^{46,74} Intraspinal delivery poses some challenges, however. This route requires specialized care and resources that may not be available in all settings. The plan of care should be carefully weighed individually with the patient and family.

Analgesic Prescribing Principles Analgesics should be administered starting at the lowest, most effective dose to treat the pain. Age, renal function, and other individual characteristics should be taken into consideration when choosing opioids and co-analgesics and when dosing and adjusting analgesics. Titration of opioids should be judicious according to patient response and side effects. Opioid dosing and titration guidelines are included in Table 5-9. For patients whose pain does not respond to escalating analgesic doses or when patients experience intolerable side effects, changing the route of administration or rotating opioids is recommended. Guidelines for opioid rotation are included in Table 5-10.

TABLE 5-9

Opioid Dosing and Titration Guidelines

- Individualize treatment based on personal characteristics and opioid tolerance.
- Initiate therapy at the lowest and most effective dose.
- Give each opioid a fair trial by titrating judiciously to therapeutic efficacy or until the patient experiences untoward side effects.
 - Titrate opioids by approximately 25–33% for moderately controlled pain
 - Titrate opioids by up to 100% for intractable pain
- Administer analgesics around the clock if pain is constant.
- Administer shorter acting analgesics for breakthrough pain (BTP).
 - BTP dose should be 5–15% of the 24 hour opioid dose (not applicable for rapid onset fentanyl products and methadone)
 - For patients established on methadone, 10% of the 24 hour methadone dose is recommended for BTP
- Use the simplest route of administration possible.
- Prevent and treat side effects.
- Consider opioid rotation with untoward side effects.
- Do not abruptly withdraw opioid as this will precipitate a withdrawal syndrome.
 - To discontinue opioids, decrease the dose by 10–25% daily to prevent abstinence syndrome
- Consider an intraspinal route of administration with uncontrolled pain, especially pain that occurs at or below the waist.

Invasive Therapeutic Approaches

In addition to analgesics, nerve blocks, nerve stimulators, and other procedural interventions are options for the management of cancer-related pain. These interventions are often used as adjuncts to pharmacologic therapy.

A celiac plexus block is recommended as an option for patients with pain related to pancreatic cancer. The treatment involves neurolysis of the celiac plexus nerve, which innervates the pancreas. The procedure is most easily performed using an endoscopic ultrasound, which allows for better visualization of the celiac plexus. While results with this approach are mixed, many patients report better pain control and a reduction of opioid use.^{75,76}

Transcutaneous nerve stimulation (TENS) is a noninvasive option but has produced mixed results. While some studies show little effect, others suggest a benefit with TENS.⁷⁷ The National Comprehensive Cancer Network (NCCN) guidelines recommend using TENS in addition to pharmacologic therapy.⁴

Sympathetic nervous system blockade and vertebroplasty are additional options for pain control.⁴⁶

Nonpharmacologic Management

A plethora of nonpharmacologic modalities exist to complement the pharmacologic management of pain. A growing body of evidence demonstrates the impact of nonpharmacologic

TABLE 5-10

Opioid Rotation
<ol style="list-style-type: none"> 1. Calculate the current opioid dose: <ol style="list-style-type: none"> a. Add the amount of all opioids given over a 24 hour period for the past 2–3 days <ol style="list-style-type: none"> i. Morphine Day 1 total: 60 mg every 8 hours + MSIR 15 mg (6 doses) = 270 mg ii. Morphine Day 2 total: 60 mg every 8 hours + MSIR 15 mg (7 doses) = 285 mg b. Take the average from the past 2–3 days <ol style="list-style-type: none"> i. $270 \text{ mg} + 285 \text{ mg} = 555 \text{ mg} \div 277.5 \text{ mg/day}$ or approximately 280 mg 2. Calculate the equianalgesic dose of the new opioid based on the equianalgesic table. <ol style="list-style-type: none"> a. $\frac{30 \text{ mg morphine}}{20 \text{ mg oxycodone}} = \frac{280 \text{ mg morphine}}{x \text{ mg oxycodone}}$ b. Cross multiply: $30x = 5600$, $x = \text{approximately } 187 \text{ mg oxycodone per day}$ 3. Consider decreasing the dose of the new opioid by 25–50% due to lack of cross tolerance <ol style="list-style-type: none"> a. Consider current degree of pain relief; may be unnecessary to reduce the dose if pain is intractable b. Consider 50% reduction with older age, minority race, comorbidities, and risk factors for oversedation; decrease dose if risk factors exist c. Consider 25% reduction if the patient does not have risk factors as stated above <ol style="list-style-type: none"> i. Patient is opioid tolerant and 50 years old without comorbidities; pain control good but rotation performed due to confusion possibly related to morphine <ul style="list-style-type: none"> • $187 \text{ mg} \times .75 \text{ (dose reduce by 25\%)} = 140 \text{ mg oxycodone/day}$ 4. Depending on the opioid, divide the 24 hour dose in every 12 hour or every 8 hour intervals; does not apply for transdermal fentanyl <ol style="list-style-type: none"> a. $140 \text{ mg} \div 2 \text{ doses per day} = 70 \text{ mg every 12 hours}$ 5. Increase breakthrough medication to equal 5–15% of 24 hour dose <ol style="list-style-type: none"> a. $140 \text{ mg} \times .05 \text{ (5\%)} = 7 \text{ mg}$; oxycodone given in 5 mg increments so dose would equal 10–15 mg oxycodone immediate release every 3 hours as needed for breakthrough pain 6. Methadone rotation: <ol style="list-style-type: none"> a. Calculate the 24 hour current opioid dose in morphine equivalents using an equianalgesic table (as above) b. Calculate the methadone dose based on the morphine equivalents: <ol style="list-style-type: none"> i. < 90 mg morphine equivalents/day: 1:4 methadone to morphine ii. 90 mg to 100 mg morphine equivalents/day: 1:8 methadone to morphine iii. > 300 mg morphine equivalents/day: 1:12 methadone to morphine iv. > 800 mg morphine equivalents/day: 1:15–20 methadone to morphine c. Divide the methadone dose at 8 hour fixed intervals d. May use 10% the 24 hour methadone dose for breakthrough pain

modalities such as institutional initiatives, educational interventions, cognitive-behavioral therapy, massage, and others. While the results of most of these studies are mixed, these modalities may provide some benefit and should be incorporated as able into practice.

Institutional quality initiatives have had mixed results in improving pain. Continued efforts are needed with studies that standardize the intervention and dose of various interventions so that improvement efforts can be replicated for improvement.⁷⁸ Patient education is a key component of nursing care. Evidence suggests that patient education has positive effects on pain intensity and patient knowledge about pain.⁷⁹ Cognitive-behavioral therapy such as that focusing on distraction, relaxation, and positive mood can decrease anxiety associated with pain and has been shown to improve pain intensity scores.⁸⁰ The NCCN guidelines recommend training in cognitive-behavioral therapy to improve pain and associated symptoms.⁸¹ Music

therapy in another complementary intervention that may improve pain intensity and decrease opioid requirements.⁸² Therapeutic touch, massage, hypnosis, and exercise are additional measures that can be offered and employed based on patient preference.

NURSING IMPLICATIONS

Nurses play a direct role in the assessment and management of pain for patients across the cancer trajectory. Nursing interventions have a direct effect on pain care quality and pain outcomes, reinforcing pain as a nursing-sensitive patient outcome. These outcomes include changes in function, physical and psychosocial symptoms, safety, and costs. Pain is an important nursing-sensitive patient outcome in that nursing care can have a direct impact on the quality of pain assessment and management. The frequency of

pain assessment, components of pain assessment, attitudes toward patients' pain, timeliness of analgesic administration, nonpharmacologic modalities, and patient education are all influenced by nursing care.⁸³ Quality measurement of pain care and nursing-sensitive patient outcomes related to pain management should occur on an ongoing basis. The Pain Care Quality Survey is one tool incorporating a subscale that measures the quality of nursing care.⁸⁴

Overall, nurses have a primary responsibility to deliver quality pain care. Being armed with evidence-based information on the assessment and management of pain is the first step. However, knowledge alone does not ensure quality pain management. In addition, nurses have a responsibility to practice according to the best evidence available. Implementation of evidence-based strategies requires ongoing commitment and advocacy for patient comfort and well-being.

PATIENT SELF-CARE

Patient self-care is important in producing safe and efficacious pain management. Nurses have a primary responsibility in providing both written and verbal instructions to patients regarding when to report pain, what to report about their pain, and how the pain management plan of care works, including how to take medications safely. For example, differentiating between long-acting and short-acting opioids (which can be confusing for patients) and describing each analgesic's purpose is an important part of the pain management plan of care. The benefits of good pain management should be reinforced so that the patient and family are aware that comfort is an essential component of healing and quality of life. See Appendix 5A for a Self-Care Guide to assist patients in describing their pain to the healthcare provider and strategies for prevention and management of pain. Overall, the more that patients and families are informed about their care, the more likely they are to have positive pain outcomes.

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Pain

Patient Name: _____

This guide provides suggestions on how to report, prevent, and treat your pain. It includes a log to record information about your pain. Keeping a pain diary will help your doctors and nurses better manage your pain.

Description

Pain is often feared by people with cancer, but good treatment is available to provide relief for most patients. Pain can contribute to many problems, such as sleep problems, depression, and a decrease in activity. Getting pain relief will allow you a better quality of life.

It is important to report your pain so that your doctor and nurse can treat it effectively. Here are the things you should report about your pain:

- Where the pain is located
- How much the pain hurts (try to rate your pain on a 0 to 10 scale with 0 being no pain and 10 being the worst possible pain)
- What kind of pain you have (e.g., aching, sharp, dull, numb)
- How your pain changes over time (e.g., constant, on and off)
- What makes the pain worse
- What makes the pain better
- What you have tried to manage the pain—both medicines and nonmedicines such as massage and ice

Sometimes patients and families do not report pain. Here are some reasons why:

- They may not want to bother the doctor.
- They may believe that pain is a part of having cancer.
- They may believe that pain is a sign that the cancer is getting worse and fear getting bad news.

Remember, however, that your comfort is important to your doctor and nurse.

Prevention

The best way to treat pain is to prevent it from getting too bad. Here are some ways to prevent pain:

- Take your medicines as ordered.
 - Some pain medicines are scheduled. They work over a long period of time, and you should take them on time to keep the pain from coming back.
 - Some pain medicines can be taken as needed—for example, every 4 hours. Take the pain medicine before the pain gets too bad. Waiting too long will mean you will have to “catch up” on the pain medicine.

- Constipation is a side effect of opioid pain medicines. Take stool softeners and laxatives to prevent constipation. Constipation can make your pain worse. Report constipation to your doctor or nurse when it is not controlled.
- Report other side effects from the pain medicine. Most side effects can be treated.

Management

You are a partner in your pain management. Here are some tips for your comfort:

- Keep a pain diary. Include the items listed above in your diary.
- If you are having pain, be ready to discuss your pain at each office visit.
- Call the doctor or nurse if your pain is not controlled.
- Prevent constipation by taking stool softeners and laxatives.
- Try nondrug treatments for your pain. Relaxation, guided imagery, and distraction can help you to relax and take thoughts away from the pain. Massage may relieve muscle tension and stress that can increase pain. Warm rice bags or ice can help some patients.

Follow-up

Talk to your doctor and nurse when your pain is not controlled. Do not wait for your next office visit if your pain is not well controlled.

Phone Numbers

Nurse: _____ Phone: _____
Doctor: _____ Phone: _____

