

Chapter 77: Pain Management

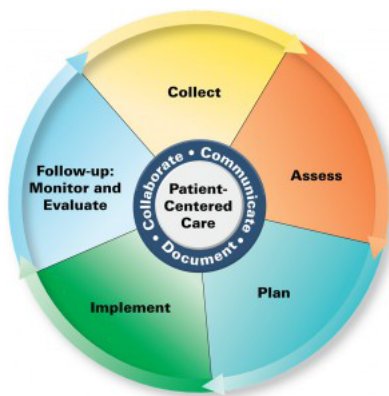
KEY CONCEPTS

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- 1 Understanding the pathogenesis of pain guides treatment and patient education.
- 2 It is important, whenever possible, to ask patients if they have healthcare pain, to identify the source of pain, and to assess the characteristics of the pain.
- 3 The etiology of pain may not always be identifiable.
- 4 Whenever possible, a multidisciplinary approach and nonpharmacologic strategies should be incorporated.
- 5 Chronic pain treatment should focus on self-management strategies and focus on active, rather than passive approaches.
- 6 Selection of nonopioids and opioids should be based on the characteristics and type of pain as well as individual patient factors.
- 7 Oral or topical analgesics are preferred over other dosage forms whenever feasible, but it is important to adjust the route of administration to the needs of the patient.
- 8 Patients taking analgesics should be monitored for response (analgesia, functionality, quality-of-life) and side effects.
- 9 Doses must be individualized for each patient and administered for an adequate duration of time. Around-the-clock regimens should be considered for acute and chronic pain. As-needed regimens should be used for breakthrough pain or when acute pain displays wide variability and/or has subsided greatly.
- 10 Consider a trial of opioids in those with severe pain that have failed nonpharmacologic and nonopioid treatment when the anticipated benefits are expected to outweigh the risks.
- 11 Use risk mitigation strategies (informed consent/patient agreements, urine drug monitoring [UDM], opioid overdose education and naloxone distribution, prescription drug monitoring program [PDMP] checks) prior to and periodically during opioid therapy, with frequency determined on the basis of patient risk and presence of aberrant drug-taking behaviors.

PATIENT CARE PROCESS

Patient Care Process for Pain Management



Collect

Patient-specific characteristics (eg, age, gender, pregnancy, ethnicity)

Pain and symptom-specific history (eg, onset, location, duration, characteristics, aggravating factors, alleviating factors, timing, and severity)

Patient history including current and past medications, nonpharmacologic trials, allergies or medication intolerance, and pertinent social history (eg, tobacco, alcohol, or recreational drug use)

Family history focusing on symptoms (ie, Rheumatoid arthritis) and social behavior (ie, alcoholism, recreational drug use)

Objective data including vitals, pertinent labs, targeted physical exam, and drug screen results

Assess

Presence of co-occurring mental health conditions (ie, depression, anxiety, or bipolar) which may confound treatment decisions

Aberrant drug-taking behaviors as evidenced by prescription drug monitoring programs (PDMP), urine drug screen results, and validated risk screening tools

Relative or absolute contraindications to the use of opioids, acetaminophen, antidepressants, anticonvulsants, nonsteroidal anti-inflammatory drugs (NSAIDs), or skeletal muscle relaxants

Chronicity of pain symptom (eg, acute or chronic), likely etiology (eg, neuropathic, musculoskeletal, or visceral), and severity

Plan*

Patient and symptom-specific lifestyle modification (eg, weight loss, smoking cessation, self-pacing, and pain-trigger avoidance; see [Table 77-2](#))

Nonpharmacologic treatment modalities (see [Table 77-3](#))

Drug therapy regimen including dose, route, frequency, and duration (see [Table 77-4](#))

Monitoring drug therapy regimen including efficacy (analgesic and functional improvement), toxicity, misuse, and ongoing necessity using tools such as urine drug screening, PDMP, and risk assessment tools (see [Table 77-14](#))

Patient education on safe use, storage, disposal, and risk mitigation following formal Risk Evaluation and Mitigation Strategies when available (see [Table 77-5](#))

Implement

Educate patient and/or caregiver regarding all elements of disease process and treatment plan, ensuring patient and/or caregiver understanding

Informed consent, including pain or treatment agreements when necessary

Schedule follow-up

Follow-up: Monitor and Evaluate

Attainment of treatment goals (eg, improved activity, improved sleep, improved work attendance)

Presence of adverse effects or aberrant drug-taking behaviors

Completion of validated risk assessment tools

Frequent review of PDMP

Patient adherence to all facets of treatment plan, including nonpharmacologic modalities

*Collaborate with patient, caregivers, and other healthcare professionals.

PRECLASS ACTIVITY

Preclass Engaged Learning Activity

Students are requested to watch the following videos on YouTube:

Understanding pain and what to do about it in less than 5 minutes—presented by Painaustralia

URL: <https://www.youtube.com/watch?v=RWMKucuejls&feature=youtu.be>

Tame the beast: It's time to rethink persistent pain — Lorimer Moseley, David Moen, Sam Chisholm

URL: <https://www.youtube.com/watch?v=ikUzvSph7Z4&feature=youtu.be>

INTRODUCTION

If we know that pain and suffering can be alleviated, and do nothing about it, then we ourselves, become the tormentors.

—Primo Levi¹ Humans have always known and sought relief from pain.² Today, pain's impact on society is still great, and pain remains a primary reason patients seek medical advice.³ In general, pain is defined as: “an unpleasant sensory and emotional experience associated with actual or potential tissue damage or

described in terms of such damage.”⁴ However, as pain is subjective, many clinicians define pain as “whatever the patient says it is.”

Regrettably, many healthcare providers do not receive adequate training in the treatment of pain. Therefore, understanding the pathophysiology of pain and maintaining a thorough understanding of both nonpharmacologic and pharmacologic treatment modalities are important factors in addressing pain control.

EPIDEMIOLOGY

Data presented in the Institute of Medicine report, “Relieving Pain in America” suggests that greater than 100 million persons in the United States live with chronic pain.⁵ Given that greater than 50% of persons reporting low back pain in the previous 3 months also reported interference with basic and complex activities, it is not surprising that the estimated economic burden of chronic pain alone exceeds 500 billion dollars (US) annually.⁵ In one year, an estimated 25 million Americans will experience acute pain due to injury or surgery, and one-third will experience severe chronic pain at some point in their lives.³ Unfortunately, despite much public attention, pain often remains inadequately or inappropriately treated.^{6,7}

PATHOPHYSIOLOGY

1 The pathophysiology of pain involves complex interactions between neural and immune networks within the peripheral and central nervous system in response to afferent sensory stimuli that produces the conscious experience we know as pain. It can be physiologic and protective (adaptive) or pathophysiologic and harmful (maladaptive).⁸ Pain is a complex interaction between biological processes (nociception) impacted by individual psychological and social determinates.

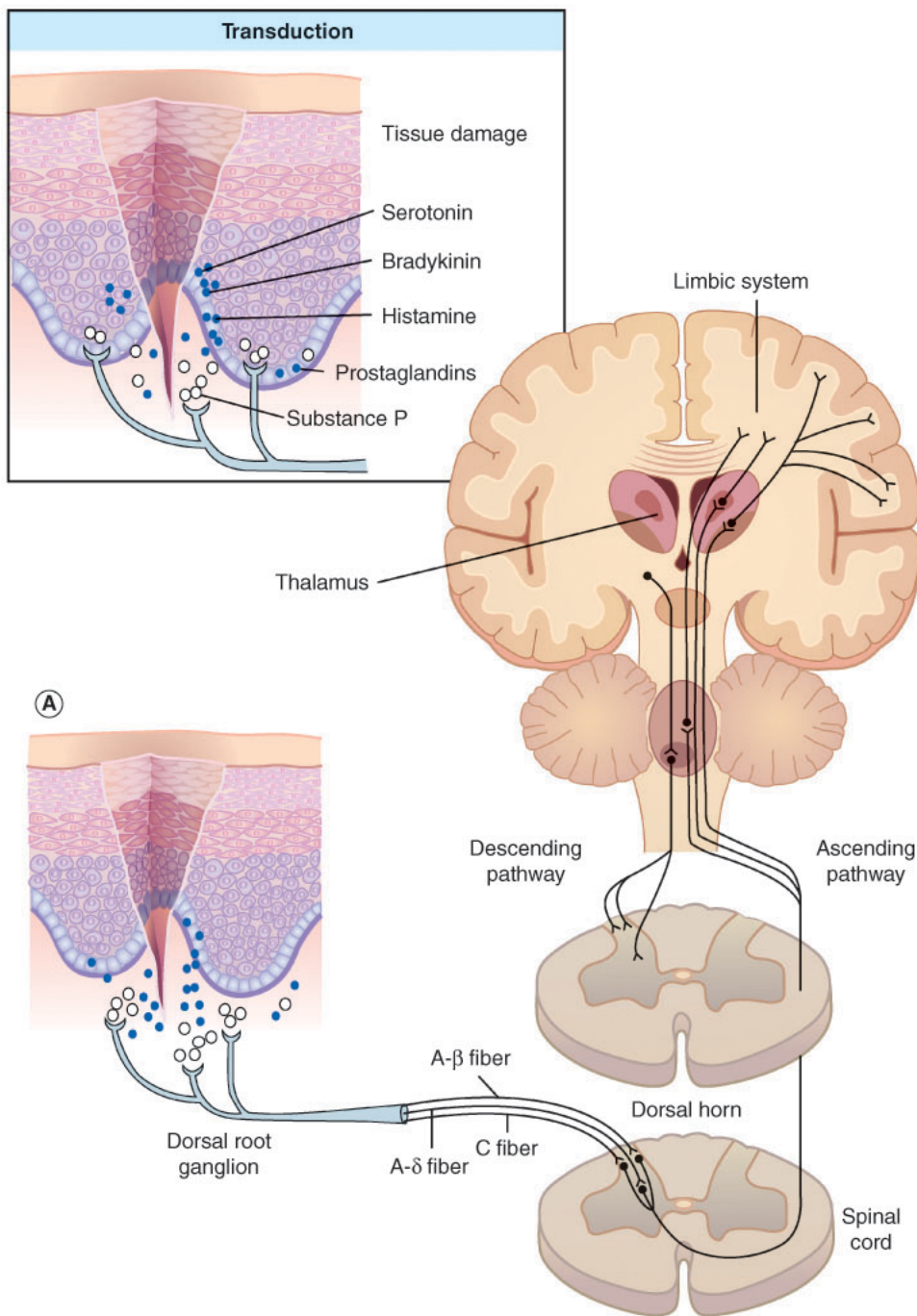
Adaptive Pain

The pain experienced from noxious stimuli involving temperature extremes, mechanical trauma, or chemical irritation is called nociceptive pain which is a primitive evolutionary mechanism to protect our body from actual or potential tissue injury. Pain that occurs as a result of unavoidable tissue damage (trauma or surgery) creates sensitization at and adjacent to the site of tissue injury. This process also engages the immune system, and is called inflammatory pain. Nociceptive and inflammatory pains are both adaptive and protective. The physiological processing of pain occurs within a neurotransmission circuit via a number of steps known as transduction, conduction, transmission, modulation, and perception.⁸

Transduction

The first step leading to the sensation of pain is stimulation of specialized nerve fiber receptors known as *nociceptors*. These high-threshold receptors are found in both somatic and visceral structures and help to discriminate between noxious and innocuous stimuli. Nociceptors are activated and subsequently sensitized by mechanical, thermal, and chemical stimuli.⁸ The underlying mechanism of these noxious stimuli (which in and of themselves may sensitize/stimulate the receptor) may be the release/activation of numerous cytokines and chemokines that sensitize and/or activate the nociceptors (Fig. 77-1).⁸⁻¹⁰

Figure 77-1
Schematic representation of nociceptive pain. (Used with permission from Pasero C, Portenoy R. *Neurophysiology of pain and analgesia and the pathophysiology of neuropathic pain*. In: McCaffery M, Pasero C, eds. *Pain Assessment and Pharmacologic Management*. St. Louis: Mosby, 2011:4–5, Figure 1–2. Copyright © 2011 from Elsevier.).



Source: JT DiPiro, GC Yee, LM Posey, ST Haines, TD Nolin, VL Ellingrod. Pharmacotherapy: A Pathophysiologic Approach. 11th Edition. Copyright © McGraw-Hill Education. All rights reserved.

Conduction

Nociceptor activation leads to the conversion of a chemical signal into an electrical signal. This requires voltage-gated sodium channels, which produce the generation of action potentials that are conducted along primary afferent A-δ and C-polymodal nerve fibers to the dorsal horn of the spinal cord.^{11,12} Stimulation of large-diameter, sparsely myelinated A-δ fibers evokes sharp, well-localized pain, whereas stimulation of unmyelinated, small-diameter C fibers produces aching, poorly localized pain.¹³

Transmission

These afferent, nociceptive pain fibers synapse in various layers (laminae) of the spinal cord's dorsal horn and convert the electrical signal back into a chemical signal by releasing excitatory neurotransmitters, such as glutamate and substance P. The N-type voltage-gated calcium channels regulate the release of these excitatory neurotransmitters. The complex array of events that influence pain can be explained in part by the interactions between neuroreceptors and neurotransmitters that take place in this synapse. Pain signals reach the brain through a host of ascending spinal cord pathways, which include the spinothalamic tract.¹³ Other sensory information is also carried along these pathways. Thus, pain is influenced by many factors supplemental to nociception, which prevents simple schematic representation. The thalamus acts as a relay station within the brain, as these pathways ascend and pass the impulses to higher cortical structures where pain can be processed further.¹³

Modulation

The brain and spinal cord modulate pain through a number of intricate processes. Pain transmission may be facilitated by neurotransmitters such as glutamate or substance P to make the signals stronger and the pain more intense. Alternatively, the signal can be attenuated/inhibited by descending pathways that consist of endogenous opioids (eg, enkephalins and β -endorphins), γ -aminobutyric acid (GABA), norepinephrine, or serotonin.^{14,15} Like exogenous opioids, endogenous peptides bind to opioid receptor sites and modulate the transmission of pain impulses.¹⁴ Other receptor types also can influence this system, and blockade of *N*-methyl-D-aspartate (NMDA) receptors may increase the mu (μ)-receptors' responsiveness to opiates.¹⁶

Perception

The complex interplay between ascending excitatory and descending inhibitory pathways is thought to culminate in a conscious experience that takes place in higher cortical structures. While not well understood, we do know cognitive and behavioral functions can modify pain. Thus, relaxation, distraction, meditation, and guided mental imagery may strongly influence pain perception and decrease pain.^{17,18} In contrast, conditions such as depression or anxiety often worsen pain.¹⁹

Immune System Impact on Pain Signaling

Over the past two decades research has demonstrated that a two-way communication exists between neurons and immune cells within the central nervous system (CNS), especially astrocytes and microglia. Microglia are the equivalent of a macrophage within the CNS.^{16,20} Their activation within the CNS in response to nerve injury (both in the periphery and CNS) leads to a complex cascade of events that appears to be responsible for the ongoing pain seen in neuropathic pain conditions. Activated microglia may also play a role in the development of opioid tolerance and opioid-induced hyperalgesia. Evidence is emerging that the interface between immune cells and neurons in the CNS plays a significant role in the maintenance of chronic pain and may offer attractive new potential therapeutic targets.²¹

Maladaptive (Pathologic) Pain

1 Pathophysiologic pain is distinctly different from nociceptive pain, in that it becomes disengaged from noxious stimuli or healing and often is described in terms of chronic pain. This type of pain is a result of damage or abnormal functioning of the peripheral nervous system (PNS) and/or CNS.¹⁶ Maladaptive pain can be neuropathic pain, in which there is ongoing peripheral nerve injury (eg, postherpetic neuralgia, painful diabetic neuropathy, or chemotherapy-induced neuropathy), or in the CNS (eg, following an ischemic stroke or with multiple sclerosis). Maladaptive pain may also be centralized, where no nerve injury or inflammation exists, but a centrally mediated disturbance in pain processing within the CNS leads to pain hypersensitivity and subsequently spontaneous pain. Classic examples are fibromyalgia, irritable bowel syndrome, temporomandibular joint disorder, and myofascial pain syndrome. Chronic pain states are often mixed with all three mechanisms (nociceptive, neuropathic, and centralized) simultaneously.²² These pain syndromes are frequently challenging to diagnose and difficult to treat. In addition, the pain reported is often not commensurate with physical exam findings or imaging results, which may result in undertreatment and ultimately inadequate pain relief.

The mechanism responsible for pain of this nature may be the nervous system's dynamic nature. Nerve damage or certain disease states may cause both peripheral (eg, alteration in nociceptive nerve fiber sensitivity, alteration of sodium channels, collateral sprouting of nerve fibers) and central (eg, hyperexcitability of central neurons or central sensitization, NMDA-glutamate receptor activation, central disinhibition) changes in neurotransmission leading to increased pain.^{14,16} Pain circuits may rewire themselves both anatomically and biochemically (often referred to as neural plasticity), and this produces a mismatch between pain stimulation and inhibition, potentially resulting in a progressive increase in the discharge of dorsal horn neurons.²³ The end result is chronic pain, where patients may present with episodic or continuous pain transmission (often described as burning, tingling, shock-like, or shooting), exaggerated painful response to normally noxious stimuli (hyperalgesia), and/or painful response to normally non-noxious stimuli (allodynia).^{13,24,25} This change over time may help explain why this type of pain often manifests long after the injury or when no actual injury is identified.

CLASSIFICATION OF PAIN

1 2 3 It is helpful in guiding assessment and treatment of pain to classify or subdivide the presenting symptoms into types of pain. There are numerous ways of classifying pain, such as by type of pain (eg, nociceptive, neuropathic, inflammatory), by pain intensity (eg, mild, moderate, or severe), or most commonly by duration of pain (eg, acute, subacute, or chronic pain).

Acute Pain

2 3 Acute pain is a beneficial physiologic process, serving its adaptive purpose by warning individuals of disease states and potentially harmful situations. Unfortunately, severe, unremitting, under-treated acute pain, when it outlives its biologic usefulness, can produce many deleterious effects. Aside from unnecessary suffering, poorly treated acute pain has also been shown to increase one's risk for the development of chronic pain syndromes.²⁶ Acute pain is typically short in duration, lasting less than 30 days. It is often due to an identifiable cause and is usually nociceptive in nature with common causes including surgery, acute illness, trauma, labor, medical procedures, and cancer or cancer treatment.²⁷

Chronic Pain

5 Under normal conditions, acute pain subsides quickly as the healing process decreases the pain-producing stimuli; however, in some instances, pain persists for months to years, leading to a chronic pathologic pain state with features quite different from those of acute pain (Table 77-1).^{27,28} In many cases the exact etiology of

pain may not be identifiable; therefore, chronic pain can be classified as either being associated with cancer (cancer pain) or from noncancer etiologies (chronic noncancer pain). Chronic noncancer pain is often a result of changes to nerve function and transmission, thus making treatment more challenging.²⁹

TABLE 77-1

Characteristics of Acute and Chronic Pain

Characteristic	Acute Pain	Chronic Pain
Relief of pain	Highly desirable	Highly desirable
Dependence and tolerance to medication	Unusual	Common
Psychological component	Usually not present	Often a major problem
Organic cause	Common	May not be present
Environmental/family issues	Small	Significant
Insomnia	Unusual	Common component
Treatment goal	Cure	Functionality
Depression	Uncommon	Common

Data from References 27 and 33.

Cancer Pain

1 2 4 Pain associated with potentially life-threatening conditions is often called malignant pain or in the case of cancer, cancer pain.³⁰ This type of pain includes both chronic and acute (eg, breakthrough pain) components and often has multiple etiologies. This pain may be caused by the disease itself (eg, tumor invasion, organ obstruction), associated with treatment (eg, chemotherapy, radiation, and surgical incisions), or as a result of diagnostic procedures (eg, biopsy).³⁰ Breakthrough cancer pain may be *idiopathic* (no known precipitating factors), *incident* (due to a predictable cause), or *end of dose failure* (predictable worsening of pain at the end of an analgesic's pharmacodynamic efficacy).³¹ Regardless of duration of pain, or suspected underlying etiology, a standardized approach to evaluation of a pain complaint is imperative. Cancer pain crises, frequently considered an acute pain overlaying an ongoing chronic pain, should be considered a medical emergency.

CLINICAL PRESENTATION

2 4 A patient-oriented approach is essential, and symptom assessment methods for pain should not differ from those used in other medical conditions.³² Therefore, a comprehensive history and physical examination is imperative to evaluate underlying diseases and possible other contributing factors.²⁷ This includes asking if the patient has pain and identifying the source of pain when possible; however, the absence of a discreet etiology should not preclude appropriate treatment.²⁷ A baseline characterization of pain should be obtained using a symptom assessment mnemonic (eg, OLDCARTS or SOCRATES).³³ Ongoing assessment should occur using a consistent and validated method (ie, Wong Baker Faces Scale, Brief Pain Inventory, Numeric Rating Scale, or the Pain-Enjoyment-General Activity Scale).³⁴

CLINICAL PRESENTATION: ACUTE AND CHRONIC PAIN**Acute Pain****General**

Look for obvious distress (eg, trauma). In infants, presentation may include changes in feeding habits, increased fussiness, or being inconsolable. Those with dementia may exhibit changes in eating habits, increased agitation, calling out. Attention also must be given to mental/emotional factors that alter the pain threshold. Anxiety, depression, fatigue, anger, and fear are noted to lower this threshold, whereas rest, mood elevation, sympathy, distraction, and understanding raise the pain threshold symptoms.

Can be described as sharp, dull, shock-like, tingling, shooting, radiating, fluctuating in intensity, and varying in location (these occur in a timely relationship with an obvious noxious stimuli).

Signs

Hypertension, tachycardia, diaphoresis, mydriasis, and pallor, but these signs are *not diagnostic*.

In some cases there are no obvious physical signs.

Comorbid conditions usually not present.

Outcome of treatment generally predictable.

Laboratory Tests

Pain is always subjective.

There are no specific laboratory tests for pain.

Pain is best diagnosed based on patient description and history.

Chronic Pain

General

Can appear to have no noticeable suffering. Attention also must be given to mental/emotional factors that alter the pain threshold. Anxiety, depression, fatigue, anger, and fear are noted to lower this threshold, whereas rest, mood elevation, sympathy, distraction, and understanding raise the pain threshold.

Symptoms

Can be described as sharp, dull, shock-like, tingling, shooting, radiating, fluctuating in intensity, and varying in location (these often occur *without* a temporal relationship with an obvious noxious stimuli).

Over time, the pain stimulus may cause symptoms that completely change (eg, sharp to dull, obvious to vague).

Signs

Hypertension, tachycardia, diaphoresis, mydriasis, and pallor are seldom present.

In most cases there are *no* obvious signs.

Comorbid conditions are often present (eg, insomnia, depression, and anxiety).

Outcome of treatment is often unpredictable.

Laboratory Tests

Pain is always subjective.

Pain is best diagnosed based on patient description and history.

There are *no* specific laboratory tests for pain; however, history and/or diagnostic proof of past trauma (eg, computed tomography) may be helpful in diagnosing etiology. General labs that may be considered include vitamin D, thyroid stimulating hormone (generalized or widespread pain), and B12 (neuropathic pain).

Data from Reference 27.

TREATMENT

Achieving desired pain management outcomes includes both nonpharmacologic and pharmacologic strategies.

Desired Outcomes

4 **5** The primary goal of pain treatment depends on the type of pain present and should be tailored to individual patients and circumstances (see “[Patient Care Process](#)” section). For example, a desired outcome in the acute postoperative setting may be to achieve a level of pain relief that allows the patient to attain certain functional goals, such as deep breathing or participation in physical therapy. In comparison, the goals in chronic noncancer pain may be to improve or maintain the patient's level of functioning, decrease pain perception, reduce the use of medications when possible, and improve the patient's quality of life. Treatment goals for cancer pain or other forms of malignant pain may include adequate pain relief such that a patient can tolerate diagnostic and therapeutic manipulation and permit the patient to function at a level that will allow freedom of movement and choice while minimizing adverse effects of chosen analgesics.³¹

Nonpharmacologic Therapy

2 **3** **5** The use of nonpharmacologic therapies in the management of pain should always be considered first-line therapy, either alone or in combination with appropriate analgesics. It is important to target all aspects of the biopsychosocial model when treating pain. Collaborating with other professions who are trained to provide nonpharmacologic approaches is essential. In addition, focusing on active therapies over passive therapies is encouraged. The evidence basis for many of the nonpharmacologic approaches is in evolution and the results of these approaches can have varied efficacy based on the skill of the individual applying the modality, as well as the type of pain being treated.

A variety of nonpharmacologic approaches are available. These include physical therapy, manipulation, formal exercise programs, weight loss, and diet changes (Table 77-2).³⁵⁻³⁷ There are a variety of complementary and integrative approaches with evidence in pain treatment and include acupuncture, Tai chi, yoga, mindfulness, meditation, relaxation, and biofeedback.³⁸

TABLE 77-2
Nonpharmacologic Approaches to the Treatment of Pain

• Exercise • Physical therapy • Diet ◦ Anti-inflammatory ◦ Elimination • Weight loss • Electroanalgesia: application of electrical stimulation to various areas that range from noninvasive to highly invasive ◦ Noninvasive: transcutaneous electrical nerve stimulation (TENS) ◦ Minimally invasive: percutaneous electrical nerve stimulation (PENS) ◦ Highly invasive: spinal cord stimulation (SCS) • Interventional approaches
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Data from Reference 37.

5 Simple interventions (eg, education or introductory information about expected discomfort or pain after certain procedures) reduce patient distress and help reduce post-procedure pain.³⁹ Psychological techniques (eg, cognitive-behavioral therapy, relaxation training, mindfulness-based stress reduction) have proven effective in reducing pain-related disability and improving global functioning in patients with numerous types of chronic pain.⁴⁰

Electroanalgesia involves the application of electrical stimulation to various locations and range from noninvasive (eg, transcutaneous or percutaneous electrical nerve stimulation) to highly invasive (implanted spinal cord stimulation).^{37,41} Transcutaneous electrical nerve stimulation (TENS) may reduce pain by enhancing natural descending inhibitory pathways within the central nervous system. Evidence to date suggests that the frequency of the electrical stimulation delivered, presence or absence of systemic analgesics, and the type of underlying pain may affect the overall efficacy of this treatment.⁴² Complementary and integrative approaches to the treatment of chronic pain are outlined in Table 77-3.⁴³⁻⁴⁵

TABLE 77-3

Complementary and Integrative Approaches for Chronic Pain

Intervention	Description	Evidence	Safety
Tai Chi	Low-impact Mind body exercise Started in China Slow mindful movement with attention to breathing and relaxation	Osteoarthritis Chronic low back pain Fibromyalgia	Minor musculoskeletal aches and pains
Yoga	From India Blend of meditation, breathing, and physical postures	Osteoarthritis Rheumatoid Arthritis Kyphosis Fibromyalgia Low back pain Neck pain	Similar to musculoskeletal pain associated with PT ^a Discuss with provider/yoga instructor if glaucoma or osteoporosis
Acupuncture	Stimulation of certain points of the body typically with the insertion of needles into the skin East Asian	<i>Acute:</i> Post-surgical pain (reduces opioid dose) Migraine Acute/subacute LBP ^b Ankle sprain <i>Chronic:</i> CLBP ^c Osteoarthritis (knee, hip, general) TMD ^d Headache Migraine Neck pain Shoulder pain Peripheral neuropathy (diabetic, HIV ^e , Bell's palsy, CTS ^f)	Low risk for adverse effects Minor: itching, relaxation, tired Rare: pneumothorax, infections (associated with poor training)
Massage	Soft tissue manipulation	<i>Acute:</i> Postoperative pain <i>Chronic:</i> CLBP ^c Neck pain Knee osteoarthritis Heel pain Epicondylitis	Low risk for adverse effects

Intervention	Description	Evidence	Safety
Mindfulness, meditation, and relaxation	A variety of mind-body practices free of judgment Examples: mindfulness-based stress reduction (MBSR), cognitive behavioral therapy (CBT), pain-coping skills training (PCST), diaphragmatic breathing, progressive muscle relaxation, hypnosis, acceptance and commitment therapy, music therapy, guided imagery	<i>Acute:</i> Burn patients (music therapy) Acute/procedural pain (music therapy, hypnosis, guided imagery) <i>Chronic:</i> LBP ^b (MBSR, CBT, Chronic pain (music therapy, CBT, guided imagery, ACT, progressive relaxation) Headache (mindfulness and relaxation, MBSR) Fibromyalgia (relaxation, guided imagery) Knee pain (PCST) Osteoarthritis (PCST, guided imagery) Rheumatoid arthritis (PCST, guided imagery) Diabetic neuropathy (mindfulness/meditation) TMD ^d (relaxation)	Rare adverse reactions (psychiatric patients, epilepsy, hx of trauma)
Biofeedback	Mind-body practice in which patients are connected to a device that measures their bodily functions (BP, HR, RR) and use the information to alter thoughts and behaviors	Tension/migraine headache CLBP ^c Fibromyalgia Shoulder pain	No to low risk of adverse reactions
Manipulation	Treatment of spine and other joints	Osteoarthritis (hip, knee, ankle, plantar fasciitis, ankle, shoulder, epicondylitis) LBP ^b CTS ^f TMD ^d	Musculoskeletal aches and pains Uncommon serious adverse reactions (cervical artery dissection, stroke, neck injury)

Data from References 37, 38, 43, 44 and 45.

Pharmacologic Therapy

Appropriate Patient Selection

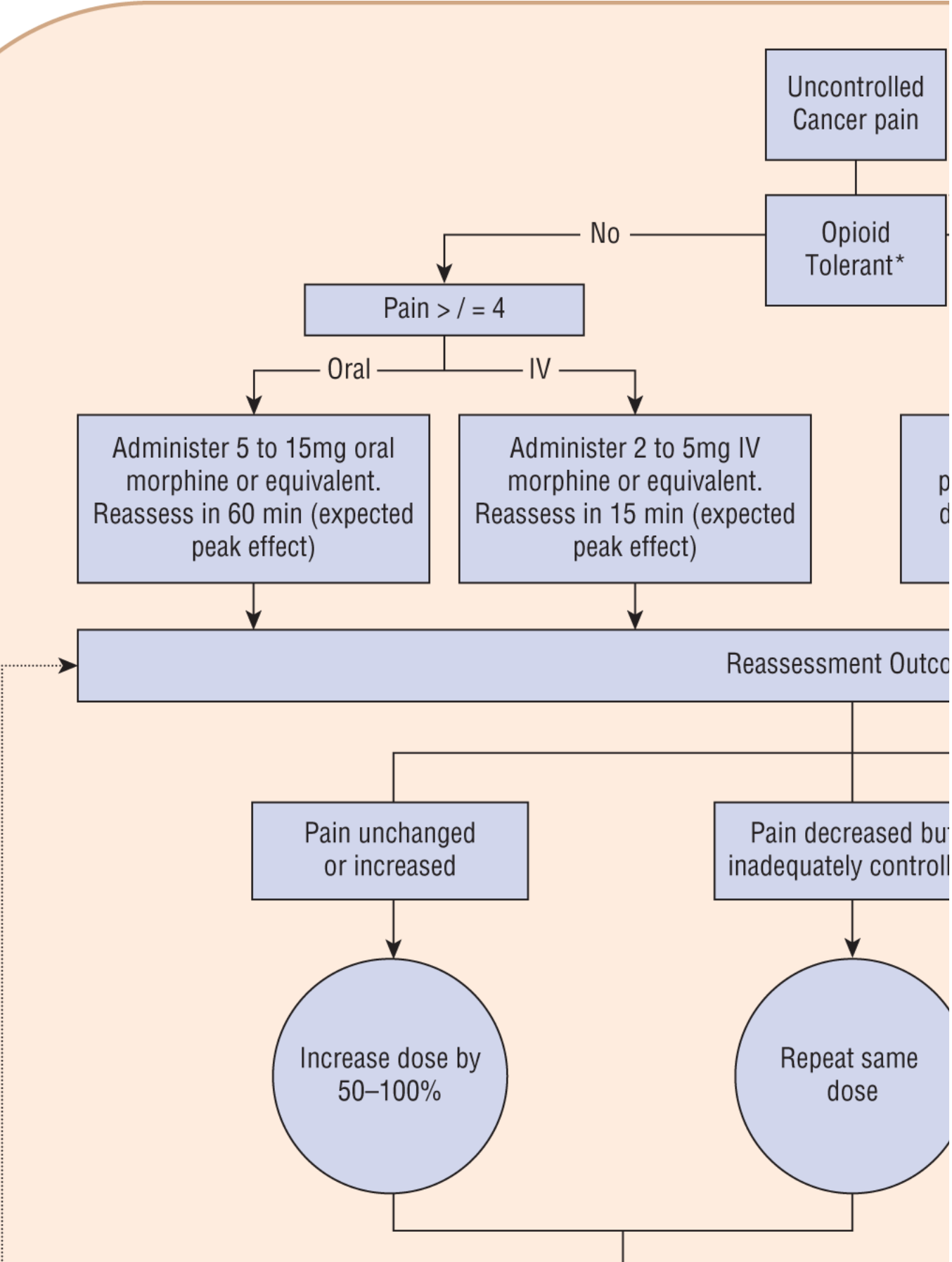
6 7 8 9 Pharmacologic treatment is often considered the cornerstone of pain management. However, proper patient selection using a benefit-to-risk assessment is crucial when determining the optimal therapeutic plan for an individual patient. The potential for benefit with each pharmacologic option, as well as the risk of adverse effects, must be assessed.

Patient Selection Considerations in Acute or Cancer Pain

9 10 11 10 The World Health Organization (WHO) recommends a three-step ladder approach using the nonopioids as initial treatment and escalating treatment to either “weak” or “strong” opioids based on pain intensity ratings (ie, mild, moderate, or severe).⁴⁶ However, patient-specific factors, for example, renal or liver dysfunction that would potentially limit treatment with many nonopioid therapies, may lead clinicians to initiate therapy with an opioid to optimize pain relief while minimizing adverse effects. Acute cancer pain crises should be considered a medical emergency. For this we recommend using the approach of the National

Comprehensive Cancer Network guidelines on Adult Cancer Pain (Fig. 77-2).³¹ Inadequate analgesia, opioid-related adverse effects, or loss of an administration route may require rotation to another opioid analgesic. The process for equianalgesic opioid rotation is provided in Table 77-4.⁴⁷

Figure 77-2
Algorithm for cancer pain crisis. (Adapted from National Comprehensive Cancer Center Adult Pain Guidelines.).



After 2–3 cycles of dosing, consider switching to IV opioid (if titration occurred with PO), maximize adjuvant analgesics, consider opioid rotation, consider pain specialist consultation

* Other daily oral opioid doses for consideration of tolerance includes codeine 15 25mcg, hydromorphone 8mg, methadone 20mg, oxycodone 30mg, oxymorphone

Table adapted from reference XX

Source: JT DiPiro, GC Yee, LM Posey, ST Haines, TD Nolin, VL Ellingrod. Pharmacotherapy: A Pathophysiologic Approach. 11th Edition.

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TABLE 77-4

Steps for Equianalgesic Opioid Calculation

- Step 1.** Use the equianalgesic dose chart in [Table 77-11](#) for a first estimate of the dose of the new drug that is equianalgesic to the old drug.
- Step 2.** Record the total dose of each opioid given during the past 24 hours. If both parenteral and oral doses of the same opioid were given, calculate a separate total for each.
- Step 3.** Divide each 24-hour total by the equianalgesic dose in [Table 77-11](#) for that opioid and route, converting the dose into equianalgesic dose units. Add the equianalgesic dose units for all drugs and routes (ie, some clinicians prefer to convert all opioid doses to “oral morphine equivalents” prior to calculating new target dose).
- Step 4.** Estimate the dose of the new drug by multiplying the sum obtained in Step 3 by the equianalgesic dose for the new drug and route (see example below*).
- Step 5.** Modify the initial estimate based on the clinical situation and the specific drugs involved. Factors that enter into this process include the following:
- Effective analgesia, intolerable adverse effects: Calculate the dose of the new opioid as outlined in Steps 1-4. Reduce target dose by 25% to 50% to account for lack of cross-tolerance between various opioids.
 - Ineffective analgesia, no intolerable adverse effects: Calculate the dose of the new opioid as outlined in Steps 1-4. Reduction in target dose outlined in (a) may be disregarded depending on clinical situation and patient-specific variables. Those with severe pain on regularly scheduled opioids for >5 days may have their dose increased by 30% to 50% or an increase equal to the use of supplemental PRN medication per day averaged over the previous 2 to 3 days. Consider more conservative increases (ie, 10% to 20%) in the first few days of therapy in those who have less severe pain or who are frail. Dose increases are safest after steady state has been approached (typically 5 to 6 half-lives).
- Step 6.** Should PRN dosing of immediate release drug be necessary for break-through pain, provide 10% to 15% of total daily dose of new opioid every 3 to 4 hours depending on individual opioid's duration of analgesia.
- Step 7.** Reassess patient frequently following opioid rotation (48 to 72 hours following dose change).

Data from Reference 47.

Patient Selection Considerations in Chronic Noncancer Pain

3 4 5 5 7 8 9 10 11 In all cases of chronic noncancer pain, an integrated systematic approach with a strong emphasis on patient–clinician relationships is essential. Patients and clinicians must realize that optimal treatment may take months or even years to achieve. Opioids are often a treatment of last resort in chronic noncancer pain and initiated as a time-limited trial to see if there is an improvement in the patient's function while overall tolerability is being assessed. Although long-term opioid therapy can be effective for individual patients in carefully considered situations, limited data exists to support such practice.^{36,48} Chronic opioid therapy in this setting requires careful patient selection with judicious attention to risk factors (eg, prior substance abuse disorder history, family history of substance abuse, younger age, male gender, and certain co-occurring mental health conditions) associated with misuse and abuse of these agents to evaluate the balance between potential benefit of therapy and the potential risks in the individual patient.

Risk Mitigation Strategies

10 11 In addition to identifying and managing risk prior to initiation (eg, misuse, abuse, or respiratory depression), specific strategies should be employed once treatment with an opioid analgesic has been initiated.^{36,49} Opioid risk mitigation consists of judicious dose monitoring, regular and random urine drug monitoring, patient informed consent via treatment agreements, pill counts, and frequent review of prescription drug monitoring programs, to name a few.⁵⁰ The Centers for Disease Control and Prevention (CDC) have published guidelines to assist clinicians in balancing harms versus benefit of long-term opioid therapy and are

summarized in [Table 77-5](#).⁵¹ Opioid/pain stewardship refers to opioid risk mitigation on a patient panel or system level and aims to ensure safe and effective use of these agents.⁷ Harm reduction, including the co-prescribing of opioid antagonists, is discussed in-depth within [Chapter 82](#) “Substance-Related Disorders: Overview and Depressants, Stimulants, and Hallucinogens.”

TABLE 77-5
Key Recommendations of the Centers for Disease Control and Prevention Guideline for Prescribing Opioids for Chronic Pain

1. Nonpharmacologic and nonopioid modalities are preferred.
 2. If opioid analgesia is warranted, establish realistic treatment goals.
 3. Discuss the known risks and realistic benefits of opioid analgesics prior to initiation.
 4. Immediate-release opioids are preferred over CR/LA opioid formulations.
 5. Use the lowest effective dose of opioid possible. Use caution at any dosage, and carefully reassess evidence of benefit versus risk when exceeding ≥50 MME/day and avoid increasing dose ≥90 MME/day without careful justification.
 6. Opioid analgesia should be used for the shortest duration possible. In most cases, 3 days is sufficient for acute pain. More than 7 days will rarely be required for most acute pain indications.
 7. Clinicians should regularly evaluate the benefits and harms of ongoing opioid analgesia within 1 to 4 weeks of initiation and at least every 3 months when ongoing opioid therapy is required. Consider taper and discontinuation when harm risk outweighs benefit potential.
 8. Careful evaluation of opioid overdose risk should be assessed frequently, and naloxone co-prescribed at opioid doses of ≥50 MME/day or when patients are exposed to concurrent opioid analgesia and benzodiazepines.
 9. Prescription drug monitoring programs should be reviewed at opioid initiation and periodically, ranging from every prescription to at least every 3 months.
 10. Clinicians should use urine drug screening prior to initiating opioid therapy and periodically when ongoing therapy is warranted.
 11. Concurrent prescribing of opioid analgesics and benzodiazepines should be avoided when possible.
 12. When Opioid Use Disorder is recognized or suspected, clinicians should offer evidence-based treatment such as medication-assisted therapy (ie, methadone or buprenorphine/naloxone) in combination with behavioral therapies.

Data from Reference 36.

Co-Analgesics

5 6 7 Co-analgesics represent a diverse group of pharmacologic agents with individual characteristics that make them useful in the management of pain, but these agents typically are not classified as analgesics. Examples of co-analgesics include antidepressants and anticonvulsants. Chronic pain that has a neuropathic component (eg, diabetic neuropathy) often requires co-analgesic therapy. Anticonvulsants (eg, gabapentin, pregabalin, which may decrease neuronal excitability), tricyclic antidepressants and serotonin and norepinephrine reuptake inhibitor antidepressants (eg, nortriptyline, duloxetine, venlafaxine—which block the reuptake of serotonin and norepinephrine, thus enhancing pain inhibition), and topically applied local anesthetics (which decrease nerve stimulation) all have demonstrated efficacy in managing various chronic pain conditions.⁵²

Nonopioid Analgesics

Acetaminophen and Nonsteroidal Anti-inflammatory Drugs

5 6 7 Analgesics should be initiated with the most effective agent having the fewest potential adverse effects. Acetaminophen and NSAIDs are often preferred first-line therapies in the treatment of mild-to-moderate pain, although the efficacy of acetaminophen has recently been called into question ([Table 77-6](#)).^{53,54} The exact mechanism of acetaminophen is not completely understood but likely involves central prostaglandin modulation.⁵⁵ The NSAIDs inhibit formation of varying prostaglandins produced in response to noxious stimuli, thereby decreasing neuronal pain transmission received by the CNS.³⁸ While acetaminophen is still considered a first-line therapy for some mild pain conditions, in some pain-related disease states, such as osteoarthritis, NSAIDs, either oral or topical, may be preferred.^{56,57} In addition, NSAIDs may be useful in the management of cancer-related bone pain and for short-term relief in the management of chronic low back pain.^{58,59}

Nonopioid Analgesics

Class and Generic Name (Brand Name)	Approximate Half-Life (h)	Usual Dosage Range (mg)	Maximal Dose (mg/day)
Salicylates			
Acetylsalicylic acid ¹ –aspirin (various)	0.25	325-1,000 every 4-6 hours	4,000
Choline and magnesium trisalicylate (various)	9-17	1,000-1,500 every 12 hours	3,000
		750 every 8 hours (elderly)	
Diffunisal (Dolobid, various)	8-12	500-1,000 initial 250–500 every 8-12 hours	1,500
Salsalate (various)	1	1,000 every 12 hours or 500 every 6 hours	3,000
Para-aminophenol			
Acetaminophen ¹ (Oral: Tylenol, various; Parenteral: Ofirmev)	2-3	325-1,000 every 4-6 hours	4,000 ²
			Dosing for peds lower based on weight
Fenamates			
Meclofenamate (various)	0.8–3.3	50–100 every 4–6 hours	400
Mefenamic acid (Ponstel)	2	Initial 500 250 every 6 hours (max. 7 days)	1,000 ³
Pyranocarboxylic acid			
Etodolac (various) (immediate release)	7.3	200–400 every 6–8 hours	1,000 1,200 with extended-release product
Acetic acid			
Diclofenac potassium (Cataflam, various, Flector [patch] Voltaren Gel, Pennsaid [solution])	1.9	In some patients, initial 100, 50 three times per day	150 ⁴
		Patch available: to be applied twice daily to painful area (intact skin only), Gel and solution dosing joint specific	
Propionic acids			
Ibuprofen ¹ (Motrin, Caldolor, various)	2–2.5	200-400 every 4-6 hours Injectable, 400–800 every 6 hours (infused over 30 min)	3,200 ⁵ 2,400 ⁵ 1,200 ⁶
Fenoprofen (Nalfon, various)	3	200 every 4-6 hours	3,200
Ketoprofen (various)	2	25-50 every 6-8 hours	300
			200 with extended-release product
Naproxen (Naprosyn, Anaprox, various)	12–17	500 initial	1,000 ³
		500 every 12 hours or	
		250 every 6-8 hours	

Class and Generic Name (Brand Name)	Approximate Half-Life (h)	Usual Dosage Range (mg)	Maximal Dose (mg/day)
Naproxen sodium ¹ (Aleve, various, combined with esomeprazole [Vimovo])	12–17	In some patients, 440 initial ⁶ 220 every 8–12 hours ⁶	660 ⁶
Pyrrolizine carboxylic acid			
Ketorolac—parenteral (Toradol, various)	5–6	30 ⁷ –60 (single IM dose only)	30 ⁷ –60
		15 ⁷ –30 (single IV dose only)	15 ⁷ –30
		10 ⁷ –30 every 6 h (IV dose) (max. 5 days)	60 ⁷ –120
Ketorolac—oral, indicated for continuation with parenteral only (various)	5–6	10 every 4–6 h (max. 5 days, which includes parenteral doses)	40
Ketorolac—nasal spray, indicated for acute, moderate to moderately severe pain		In non-elderly patients, initial oral dose of 20	126
		1 spray (15.75 mg) in each nostril every 6–8 hours in adults <65 years and weight ≥50 kg	
Pyrazols			
Celecoxib (Celebrex)	11	Initial 400 followed by another 200 on first day, then 200 twice daily (note some recommend maintenance doses of 200 mg/day due to cardiovascular concerns)	400

¹Available both as an over-the-counter preparation and as a prescription drug.

²Food and Drug Administration maximum dose. OTC maximum dose 3,000 mg daily. Lower with weight-based dosing in pediatric patients.

³Up to 1,250 mg on the first day.

⁴Up to 200 mg on the first day.

⁵Some individuals may respond better to 3,200 mg as opposed to 2,400 mg, although well-controlled trials show no better response; consider risk versus benefits when using 3,200 mg/day.

⁶Over-the-counter dose.

⁷Dose for elderly and those under 50 kg (110 lbs).

FDA, Food and Drug Administration; h, hours; IM, intramuscular; IV, intravenous; ND, no data.

Data from References 47 and 95.

6 7 8 Studies comparing the efficacy of individual NSAIDs have failed to identify greater efficacy of any NSAID compared to another. Therefore, the choice of a particular agent often depends on availability, cost, pharmacokinetics, pharmacologic characteristics, and the side-effect profile. Because of the large interpatient variability in response to individual NSAIDs, it is considered rational therapy to switch to another member of this class if there is inadequate response after a sufficient therapeutic trial of any single agent.⁴⁷ The duration of a sufficient trial has not been well defined; however, typically, an NSAID should be continued for a minimum of 1 month prior to evaluating the need to switch agents. Chronic use of NSAIDs may result in serious gastrointestinal (GI), renal, and cardiac toxicity. More recent data lessens the concerns of increased risk of cardiovascular events with celecoxib, a cyclooxygenase (COX)-2 selective NSAID, compared to other nonselective NSAIDs.^{60,61} Topical NSAIDs may offer similar efficacy as oral NSAIDs with improved safety and tolerability in the treatment of small or superficial joint arthritis.^{62,63} Appropriate patient selection for NSAID therapy is critical to ensure optimal benefit while minimizing potential adverse effects.

Anticonvulsants

6 7 8 The anticonvulsants frequently employed for pain are presented in Table 77-7.^{64–71} Carbamazepine and oxcarbazepine block voltage-gated sodium channels and potentiate the effects of GABA and is considered the drug of choice for trigeminal neuralgia according to multiple guidelines.^{52,65,72,73} The primary metabolic pathway for carbamazepine is CYP3A4. The active metabolite, carbamazepine 10,11-epoxide, auto-induces its own metabolism, making titration difficult. Carbamazepine is associated with many drug–drug interactions through induction of CYP3A4, CYP1A2, CYP2B6, CYP2C9, and CYP2C19. Common side effects during initiation include dizziness, drowsiness, unsteadiness, nausea, and vomiting and can be avoided with low starting doses. Serious dermatologic reactions can occur,

including toxic epidermal necrolysis and Stevens–Johnson syndrome (SJS). The risk of dermatological adverse effects is higher in patients who come from Asian descent with an inherited variant, HLA-B*1502, so in at-risk ethnicities, patients should be tested for this allele before initiation of carbamazepine.⁷⁴ Rare cases of aplastic anemia and agranulocytosis are also associated with carbamazepine use so a CBC should be monitored during therapy. Hyponatremia is also reported, which requires regular monitoring of sodium.⁷⁵ Cardiovascular effects include hyper/hypotension, congestive heart failure, edema, arrhythmias, atrioventricular block. Elevation in hepatic enzymes should be monitored periodically during treatment.⁷⁶

TABLE 77-7

Co-analgesics: Anticonvulsants

Medication	MOA	Role	Dosing	Notes
Carbamazepine and carbamazepine XR	Inhibits voltage-gated sodium channels, potentiate GABA	Trigeminal neuralgia Neuropathic pain	Initial dose: 100 mg PO BID Titrate dose by 100 mg PO BID Target dose: 300–900 mg/day Maximum dose: 1,200 mg/day	Significant drug–drug interactions Monitor CBC, LFTs, sodium level Recommended testing HLA-B ¹ 502 in patients with Asian ancestry Therapeutic drug levels only indicated for high-dose therapy to avoid toxicity. No correlation between analgesia and serum drug concentration
Gabapentin	Inhibition $\alpha 2\delta$ subunit of the voltage-gated calcium channel leading to decreased release of excitatory neurotransmitters including glutamate, norepinephrine, and substance P	PHN ¹ Neuropathic pain Perioperative pain	100–300 mg steps Increase every 3–5 days as tolerated by 100–300 mg increments	Median dose for response 1,600–2,400 mg/day Risk of misuse/abuse Requires renal dose adjustment
Gabapentin (Gralise)	Refer to gabapentin	PHN ¹	Take once daily with evening meal Day 1: 300 mg Day 2: 600 mg Day 3–6: 900 mg Days 7–10: 1,200 mg Days 11–14: 1,500 mg Day 15: 1,800 mg Maximum dose: 1,800 mg/day	Refer to gabapentin
Gabapentin enacarbil	Refer to gabapentin	PHN ¹ Restless leg syndrome (RLS) ¹	Initial dose: 600 mg PO QAM × 3 days Titrate dose: 600 mg PO BID Maximum dose: 1,200 mg/day	Refer to gabapentin
Lamotrigine	Inhibits sodium channels	Neuropathic pain (4th line Canadian NP guidelines, specialist setting NICE guidelines)	Initial 25 mg PO daily Titrate q2weeks to 50 mg/day, 100 mg/day, and 200 mg/day Maximum dose: 400 mg/day	Stevens–Johnson syndrome
Oxcarbazepine	Inhibits sodium channels	Trigeminal neuralgia (EFNS) Neuropathic pain (specialist setting NICE guidelines)	Initial: 150 mg PO BID Titrate by 300 mg q3 days Target dose: 300–600 mg BID Max dose: 1,800 mg/day	Improved tolerability and less drug–drug interactions compared to CBZ
Oxcarbamazepine XR	Refer to oxcarbazepine	(See above under oxcarbamazepine)	Initial dose: 600 mg PO daily Titrate by 600 mg/day weekly Maximum: 2,400 mg/day	Refer to oxcarbazepine

Medication	MOA	Role	Dosing	Notes
Pregabalin	Refer to gabapentin	DPN ¹ Fibromyalgia ¹ Neuropathic pain associated with spinal cord injury ¹ Neuropathic pain PHN ¹ Perioperative pain	Initial dose: 150 mg/day in 2 or 3 divided doses Titrate dose by 300 mg/day at 1 week Maximum dose: varies by indication. Overall 600 mg/day	Refer to gabapentin
Pregabalin CR	Refer to gabapentin	DPN ¹ PHN ¹	Initial dose: 165 mg daily Maximum dose: 330 mg/day (DPN) or 330–660 mg/day (PHN)	Refer to gabapentin
Topiramate and Topiramate XR	Inhibits voltage-gated sodium channels, AMPA/kainite subtype of glutamate receptor, and carbonic anhydrase; increases activity of GABA-A receptor	Alcohol use disorder Migraine prophylaxis Neuropathic pain (fourth-line Canadian NP guidelines, specialist setting NICE guidelines)	Initial dose: 25 mg PO daily × 1 week Titrate by 25-50 mg week Target dose: 50 mg PO BID (migraine ppx) or 200-400 mg/day neuropathic pain	Monitor serum bicarbonate and renal function Increase risk for kidney stones Weight loss Decreased sweating/hyperthermia Hyperammonemia

¹FDA-approved indication.

All anticonvulsants associated with increased risk for suicidal thoughts and behaviors.

Data from References 95 and 64.

Oxcarbazepine is the keto derivative of carbamazepine and is metabolized to an active metabolite, 10-monohydroxy oxcarbazepine, which does not undergo Phase I metabolism in the liver. This is advantageous for oxcarbazepine with reduced drug–drug interactions and side effects compared to carbamazepine.⁷⁶ The most common side effects include dizziness, somnolence, diplopia, fatigue, nausea, vomiting, ataxia, abnormal vision, headache, nystagmus, tremor, and abnormal gait. Other adverse effects include hyponatremia, angioedema or anaphylactic reactions, pancytopenia, agranulocytosis, and leukopenia.⁷⁵ Serious dermatological reactions (SJS, TEN) may also occur and may be associated with HLA-B*1502.⁷⁴ It is estimated that about 20% to 30% of those patients who are hypersensitive to carbamazepine will be hypersensitive to oxcarbazepine as well. In addition to its role in trigeminal neuralgia, the National Institute for Health and Care Excellence (NICE) guidelines list oxcarbazepine for the treatment of neuropathic pain in a specialist setting as fourth-line treatment.^{52,73,77}

Gabapentinoids, including gabapentin and pregabalin, are common anticonvulsants used in the treatment of neuropathic pain. There are numerous formulations available with varying indications that may include diabetic peripheral neuropathy (DPN), postherpetic neuralgia (PHN), fibromyalgia, neuropathic pain associated with spinal cord injury (SCI), and restless legs syndrome (RLS). Based on several neuropathic pain treatment guidelines, gabapentinoids are considered first-line medications for the treatment of neuropathic pain.^{64–66,73} Other roles for gabapentinoids include perioperative pain management as a part of a multimodal approach or “enhanced recovery after surgery” (ERAS) protocols. These agents, however, were not included in the ERAS Society guidelines due to inconclusive evidence.^{78–85} In general, evidence has not supported the use of gabapentinoids for the prevention of chronic post-surgical pain.⁸⁶ There are negative findings for pregabalin in acute and chronic sciatica as well as gabapentin and pregabalin for nonspecific low back pain.^{87,88}

Gabapentinoids do not, as their name may suggest, alter gamma-aminobutyric acid (GABA) binding, uptake, metabolism, or degradation though their pharmacology does lead to GABA-mimetic effects. Primary pharmacodynamic effects are due to inhibition of voltage-gated calcium channels specifically by binding to the presynaptic $\alpha_2\delta$ subunit. This results in decreased release of excitatory neurotransmitters glutamate, norepinephrine, and substance P.⁷¹

Common adverse effects, namely dizziness and sedation, can be mitigated with slow dose titration. Gabapentinoids may lead to peripheral edema and weight gain and may be dose-limiting adverse effects. All anticonvulsants have been associated with increased risk for suicidal thoughts and behavior. Recently, there have been increasing reports of gabapentinoid misuse and abuse, which has resulted in some states classifying them as controlled substances.^{89,90} Gabapentinoids are cleared renally and have recommended renal dose adjustments as well as supplemental doses after hemodialysis.⁹¹

Several neuropathic pain guidelines place lamotrigine as a fourth-line agent or medication for use in a specialist setting.^{52,65,73} The mechanism of action of lamotrigine is not entirely known but thought to be related to inhibition of voltage-gated sodium channels. One of the main concerns with the use of lamotrigine is the possibility of life-threatening rash. To minimize the risk of a rash, the dose is titrated slowly (ie, every 2 weeks). If any signs of rash appear, lamotrigine should be discontinued immediately, although other fatal or life-threatening hypersensitivity reactions can occur as lamotrigine is also associated with blood dyscrasias and aseptic meningitis. More common adverse effects include dizziness, nausea, headache, insomnia, somnolence, fatigue, rhinitis, abdominal pain, diplopia, ataxia, blurred vision. Utilizing lamotrigine is further complicated by the potential for multiple drug–drug interactions.

For neuropathic pain, topiramate is listed as a fourth-line agent by the Canadian Pain Society guideline and for use in specialist settings by the NICE guidelines.^{65,73} Topiramate is commonly used as a prophylactic medication for migraines and has data supporting its use in radicular low back pain.^{92,93} It has four components to its proposed mechanism of action including inhibition of voltage-gated sodium channels, increased effects of GABA_A receptors, blocking AMPA/kainate subtype of glutamate receptors, and inhibiting carbonic anhydrase enzyme. Topiramate has numerous warnings and precautions including secondary angle closure glaucoma, metabolic acidosis, hyperammonemia and encephalopathy, kidney stones, oligohydrosis, hypo/hyperthermia, and cognitive dysfunction. Renal dose adjustments are recommended with a creatinine clearance (CrCl) <70 mL/min (1.17 mL/s) and topiramate is removed via hemodialysis, so supplemental doses are needed. Adverse effects most associated with discontinuation of therapy in studies of migraine patients included paresthesia, fatigue, nausea, difficulty with concentration/attention, insomnia, anorexia, and dizziness. Dose-related side effects include paresthesia, fatigue, nausea, anorexia, dizziness, difficulty with memory, diarrhea, weight loss, concentration/attention problems, and somnolence.

Antidepressants

6 7 8 Select antidepressants have long been used for their anti-nociceptive effects (Table 77-8).^{94–96} Most tricyclic antidepressants (TCAs) are FDA-approved for major depressive disorder (MDD) aside from clomipramine (obsessive compulsive disorder) and imipramine (MDD and childhood enuresis). In general, however, the TCAs are often used for the treatment of neuropathic pain. The Canadian Pain Society, the Neuropathic Pain Special Interest Group (NeuPSIG) of the International Association for the Study of Pain, and the European Federation for Neurological Societies (EFNS) list TCAs as first-line options for neuropathic pain.^{52,64,65} The NICE guidelines list amitriptyline as a first-line option for neuropathic pain.⁷³ Interestingly, the American Diabetes Association does not list TCAs as first-line because they are not FDA approved for this indication.⁶⁶ Other evidence-based uses of TCAs include low back pain, fibromyalgia, and migraine prophylaxis.⁶⁸

Co-analgesics: Antidepressants

Medication	Mechanism of Action (MOA)	Role	Dosing	Notes
Tricyclic antidepressants (TCA)				
Amitriptyline Desipramine Imipramine Nortriptyline	Inhibits reuptake serotonin and norepinephrine which in turn inhibits descending pain pathway Analgesic effects independent of antidepressant effects and lower doses needed for analgesic effects compared to MDD doses	Fibromyalgia Low back pain Migraine prophylaxis Neuropathic pain	Initial: 10–25 mg PO QHS Titrate by 10-25 mg q3-7 days Maximum: 150 mg	Secondary amines (desipramine, nortriptyline) less anticholinergic activity = less ADE Multiple cardiac ADE (including QTc prolongation, orthostatic hypotension, arrhythmias, tachycardia) Doses > 100 mg/day associated with sudden cardiac death Lowers seizure threshold
Serotonin norepinephrine reuptake inhibitors (SNRI)				
Duloxetine	Inhibits reuptake serotonin and norepinephrine which in turn inhibits descending pain pathway Analgesic effects independent of antidepressant effects	Chronic musculoskeletal pain (low back pain [LBP], osteoarthritis) ¹ Diabetic peripheral neuropathy (DPN) ¹ Fibromyalgia ¹ Chemotherapy-induced neuropathic pain (CINP)	Initial: 30 mg PO daily × 1 week (2 weeks if elderly) Target dose: 60 mg PO daily Maximum dose: 120 mg/day though limited evidence for doses >60 mg providing additional benefit in pain	Avoid CrCl < 30 mL/min (0.50 mL/s) Avoid chronic liver disease or cirrhosis Hypertension Hyponatremia Increased risk of bleeding (GI and CNS)
Milnacipran	Inhibits reuptake serotonin and norepinephrine which in turn inhibits descending pain pathway Analgesic effects independent of antidepressant effects	Fibromyalgia ¹	Day 1: 12.5 mg PO daily Days 2-3: 12.5 mg PO BID Days 4-7 25 mg PO BID Then increase to 50 mg PO BID Target dose: 100 mg/day Maximum dose: 200 mg/day	Avoid CrCl <30 mL/min (0.50 mL/s) Caution with severe hepatic impairment Increase risk for bleeding
Venlafaxine	Inhibits reuptake serotonin and norepinephrine which in turn inhibits descending pain pathway Analgesic effects independent of antidepressant effects	Chemotherapy-induced neuropathy DPN Fibromyalgia LBP Migraine prophylaxis Painful polyneuropathy Tension-type headache	Initial: venlafaxine SA 37.5 mg PO daily Titrate: by no more than 75 mg/day q4 days Maximum dose: 225 mg/day	Higher doses needed to achieve SNRI effect Dose adjustments with renal/hepatic impairment Hypertension Hyponatremia QTc prolongation Increased bleeding risk

¹FDA-approved indication(s).

Data from References 64, 95, and 96.

TCAs exert their effects through inhibition of serotonin and norepinephrine reuptake that enhances the descending inhibitory pain pathway.⁶⁸ Regardless of whether a patient has depression or not, TCAs provide analgesic effects.⁶⁸ In addition to activity on serotonin and norepinephrine, TCAs also interact and inhibit acetylcholine muscarinic receptors, alpha-adrenergic receptors, histamine-1 receptors, and voltage-gated sodium channels, all of which contribute to their many side effects.^{97,98} Notably, TCAs can be divided into 2 different subgroups — tertiary amines (eg, amitriptyline and imipramine) and secondary amines (eg, nortriptyline and desipramine) with the tertiary amines being metabolized to secondary amines. Secondary amines interact with fewer receptors associated with adverse effects and provide similar analgesic efficacy.⁷¹

The major downfall with TCAs is their adverse effect profile. There are numerous cardiovascular adverse effects associated with TCAs including slowed cardiac conduction, QTc prolongation, arrhythmias, tachycardia, and orthostatic hypotension. Doses of TCAs in excess of 100 mg/day have been associated with sudden

cardiac death.⁹⁹ There are varying recommendations regarding electrocardiogram monitoring with TCAs but may be appropriate in patients ≥ 40 –50 years of age prior to starting and periodically during continued use.^{71,99} Anticholinergic effects are another major issue with TCAs and often preclude their use in patients with benign prostatic hypertrophy, glaucoma, or cognitive impairment. Sedative effects, owing to their inhibition of histamine receptors, may be unwanted in some patients, though desired in patients with insomnia; thus, TCAs are typically given at bedtime.

Duloxetine, venlafaxine, and [milnacipran](#) are serotonin norepinephrine reuptake inhibitors (SNRIs) that are either FDA-approved or have evidence to support their use in various chronic pain syndromes. Similar to TCAs, SNRIs inhibit the reuptake of serotonin and norepinephrine and modulate the descending pain pathway. Though a mental health diagnosis is not needed for analgesic benefit, SNRIs may be particularly useful in those with mental health comorbidities as doses used for pain are frequently similar to those used for mental health conditions. In addition to MDD and generalized anxiety disorder (GAD), duloxetine is FDA-approved for fibromyalgia, chronic musculoskeletal pain (low back pain and osteoarthritis), and diabetic peripheral neuropathic pain. The American College of Physicians' guideline for low back pain recommends duloxetine as a second-line medication for those that fail nonpharmacological approaches and NSAIDs.¹⁰⁰ Venlafaxine is not FDA-approved for any pain diagnoses; however, there is evidence supporting the use of venlafaxine for neuropathic pain, low back pain, fibromyalgia, migraine prophylaxis, and tension-type headache prophylaxis.^{101–105} Duloxetine and venlafaxine are considered first-line options for neuropathic pain according to several neuropathic pain guidelines.^{64–66,73} [Milnacipran](#) is FDA approved for fibromyalgia syndrome.¹⁰⁶

More likely side effects of SNRIs include nausea, somnolence, dry mouth, anorexia, erectile dysfunction, and constipation. Seizures, hyponatremia, and worsening of acute angle closure glaucoma may also occur. Because SNRIs impact norepinephrine, hypertension may occur. Therefore, it is important to ensure blood pressure control prior to initiation and monitor it during therapy. In addition, venlafaxine has been associated with QTc prolongation, so caution is advised in those with cardiovascular disease or risk factors for QTc prolongation.¹⁰⁷ There are no agreed upon recommendations for QTc monitoring with venlafaxine. All SNRIs have liver and renal considerations; however, the specific criteria vary amongst the different SNRIs. Furthermore, SNRIs interfere with platelet aggregation and increase risk for bleeding, particularly when combined with NSAIDs, anticoagulants, or corticosteroids. This risk of gastrointestinal bleeding can be reduced with concomitant proton pump inhibitors use.^{108,109}

Skeletal Muscle Relaxants

6 7 8 Skeletal Muscle Relaxants (SMRs) are comprised of antispasmodic and antispasticity medications ([Table 77-9](#)).^{110–114} A few medications have properties of both categories (diazepam and tizanidine). Spasticity and spasms have several differences including etiology, symptoms, and causes.¹¹⁵

Skeletal Muscle Relaxants

Medication	Role	Mechanism of Action	Dosing	Notes
Baclofen	Antispasticity	Related to GABA, works at spinal cord, inhibits polysynaptic and monosynaptic reflexes	Initial: 5 mg PO TIME Titrate: q3 days to effect Maximum: 80 mg/day	Withdrawal syndrome (hallucinations, seizures) Respiratory depression Requires renal dose adjustment
Carisoprodol	Antispasmodic/antispasticity	Centrally acting, changing interneuronal activity in descending reticular formation and spinal cord Meprobamate (primary metabolite) leads to barbiturate effects at GABA _A	250-300 mg 4 times daily	Meprobamate (a barbiturate) is primary metabolite and has abuse potential Schedule IV controlled substance Withdrawal syndrome Respiratory depression with opioids, benzodiazepines, or barbiturates Metabolized by CYP2C19 which has genetic variabilities
Chlorzoxazone	Antispasmodic	Works in spinal cord and subcortical area of brain by inhibiting multisynaptic reflex arcs	Initial: 250-500 mg 3-4 times daily Maximum dose: 750 mg 3-4 times daily	Rare hepatotoxicity Urine discoloration Respiratory depression when combined with opioids, benzodiazepines, or barbiturates
Cyclobenzaprine	Antispasmodic	Structurally related to TCAs, sedative effects, works at brainstem level, decreases excitability of alpha and gamma motor neurons	Initial: 5 mg PO TID Titrate: increase to 7.5-10 mg TID × 2-3 weeks Elderly: 5 mg dose with less frequent doses	Anticholinergic effects Avoid in elderly Caution in patients with cardiac conduction/arrhythmias Avoid closed angle glaucoma Hepatic dose adjustments
Dantrolene	Antispasticity	Inhibits calcium release from sarcoplasmic reticulum	Initial: 25 mg PO daily × 1 week Titrate dose: 25 mg PO TID × 7 days 50 mg PO TID × 7 days 100 mg PO TIME Maximum dose: 400 mg/day	Black box warning — hepatitis (dose-dependent) Discontinue at 45 days if no benefit
Diazepam	Antispasmodic/antispasticity	Postsynaptic inhibition of GABA neurons in spinal cord	Adults: 2-10 mg 3-4 times daily	Long half-life Avoid in elderly and renal/hepatic impairment Withdrawal with abrupt discontinuation

Medication	Role	Mechanism of Action	Dosing	Notes
Methocarbamol	Antispasmodic	Unknown, sedative properties	Initial: 1,500 mg PO 4 times daily × 2-3 day Then: 750-1,000 mg PO 4 times daily	Urine discoloration Respiratory depression with opioids, benzodiazepines, or barbiturates
Metaxalone	Antispasmodic	Unknown, sedative properties	800 mg PO 3-4 times daily	Respiratory depression when used with opioids, benzodiazepines, or barbiturates Contraindicated in severe liver/renal impairment
Orphenadrine	Antispasmodic	Unknown, suspect analgesic and anticholinergic effects, H ₁ receptor antagonist, NMDA receptor antagonist	100 mg PO BID	Anticholinergic effects Rare aplastic anemia
Tizanidine	Antispasmodic/antispasticity	Centrally acting α -2 agonist, inhibits presynaptic motor neurons, decreases polysynaptic reflex and abnormal contraction of opposing muscle groups	Initial: 4 mg Titrate by 2-4 mg q6-8h Maximum: 36 mg/day	Hypotension Hepatotoxicity Tablets and capsules not bioequivalent Withdrawal syndrome with abrupt discontinuation

Data from References 95 and 115.

Spasticity involves an upper motor neuron disorder.¹¹⁵ Symptoms include stiffness, hypertonicity, and hyperreflexia.¹¹⁵ Causes of spasticity include multiple sclerosis, cerebral palsy, spinal cord injury, traumatic brain injury, and post-stroke syndrome.¹¹⁵ Medications used for spasticity include baclofen, dantrolene, diazepam, and tizanidine.

Baclofen is similar in structure to GABA and binds to GABA_B receptors. These receptors are coupled to Ca²⁺ and K⁺ channels located pre- and post-synaptically. Essentially this leads to reduction in the release of excitatory glutamate and increases presynaptic inhibition. Additionally, baclofen may reduce the release of substance P. Sedation, dizziness, weakness, nausea are possible side effects. The most concerning side effect of baclofen is the risk of hallucinations or seizures from withdrawal with abrupt discontinuation. Therefore, baclofen must be tapered slowly if therapy is no longer going to be continued.¹¹⁵ Baclofen also requires dose adjustment for decreased renal function.¹¹⁶

Dantrolene has a limited role in treating spasticity due to its adverse effects as its more typical role is in the treatment of neuroleptic malignant syndrome or malignant hyperthermia. It has a black box warning for fatal or nonfatal hepatitis that has occurred at lower doses but is more likely to occur with higher doses. It is recommended that if no benefit is seen at 45 days the medication be discontinued. Dantrolene works by inhibiting the ryanodine channel that leads to decreased release of Ca²⁺ from the sarcoplasmic reticulum.¹¹⁵

Diazepam is not often used for non-cancer pain because of its sedative side effects and potential for abuse. The mechanism of action is binding to GABA_A resulting in increased chloride conductance which subsequently leads to presynaptic inhibition of the spinal cord. Abrupt discontinuation of diazepam can lead to a withdrawal syndrome, most concerning of which is seizures. Diazepam has a long half-life (20–50 hours for parent and up to 100 for active metabolites) which is problematic especially for the elderly. Other groups to avoid the use of diazepam include those with renal or hepatic impairment.¹¹⁵

Similar to diazepam, tizanidine has both antispasticity and antispasmodic uses. Tizanidine is an α ₂-agonist that works centrally. Pre-synaptically, tizanidine inhibits the release of excitatory neurotransmitters that leads to a reduction in postsynaptic activation of the upper motor neuron. In addition, tizanidine leads to the potentiation of glycine. Not surprisingly, because of its α ₂-agonist activity, hypotension can occur. Other significant issues with tizanidine include sedation and elevation in hepatic enzymes requiring periodic monitoring. Tizanidine is metabolized by CYP1A2 and is contraindicated in combination with ciprofloxacin or fluvoxamine.^{115,117}

Spasms are involuntary contractions of the muscle^{115,117} and antispasmodics treat musculoskeletal conditions and symptoms like jerks, twitches, and cramps.¹¹⁵ Associated causes include musculoskeletal pain, fibromyalgia, mechanical low back pain, sciatica, disc herniation, and myofascial pain.¹¹⁵ According to the American College of Physicians low back pain guideline, NSAIDs or SMRs are recommended as pharmacologic treatment for patients with acute or subacute low back pain.¹⁰⁰ While studies suggest SMRs are associated with a small increase in pain relief, there is no evidence to support improvement in function with SMRs.¹⁰⁰ Importantly, SMRs should be used short-term. If used long-term, SMRs may increase risk for adverse effects and polypharmacy, particularly in the elderly population

as many appear on the Beer's List of Potentially Inappropriate Medications for Use in the Elderly from the American Geriatrics Society.¹¹⁸⁻¹²⁰ Antispasmodics include carisoprodol, chlorzoxazone, cyclobenzaprine, diazepam, metaxalone, methocarbamol, [orphenadrine](#), and tizanidine.

Carisoprodol is a Schedule IV controlled substance and is metabolized via CYP2C19 to meprobamate, a barbiturate. Because of its barbiturate activity, carisoprodol has the potential for dependence and abuse. It is centrally acting and changes interneuronal activity in the descending reticular formation and spinal cord. Meprobamate has activity at GABA_A receptors and withdrawal can occur with abrupt discontinuation. Furthermore, respiratory depression can occur when combined with opioids, benzodiazepines, or barbiturates.^{115,117}

Chlorzoxazone blocks multisynaptic reflex arcs in the spinal cord and subcortical area of the brain. Sedation is a common side effect of chlorzoxazone and rare adverse effects include hepatotoxicity or GI bleeding. If used chronically, hepatic transaminase monitoring is recommended. Red/orange urine discoloration may occur and respiratory depression may occur when combined with opioids, benzodiazepines, or barbiturates.^{115,117}

Structurally, cyclobenzaprine is similar to the TCAs. It is thought to exert its effects through decreasing the excitability of alpha and gamma motor neurons while also leading to CNS depression through the brain stem. Anticholinergic side effects are common and should be used with caution in those with cardiac arrhythmias or conduction disturbances. Cyclobenzaprine should be avoided in those with acute narrow angle glaucoma. With mild hepatic impairment, dose adjustments are recommended and cyclobenzaprine should be avoided in those with moderate to severe hepatic impairment.^{115,117}

The mechanism of action of metaxalone is unclear as it has no activity on skeletal muscle or nerve fibers. Thus, it is suspected that its effects are primarily due to CNS depression. Metaxalone is metabolized through multiple CYP enzymes including CYP1A2, CYP2D6, CYP2E1, and CYP3A4. In those with severe renal or hepatic impairment, metaxalone should not be used. Rare side effects of metaxalone include leukopenia, hemolytic anemia, or hepatic transaminase elevation. Again, respiratory depression can occur when it is used with opioids, benzodiazepines, or barbiturates.^{115,117}

Similar to metaxalone, the mechanism of action of methocarbamol is unknown and suspected to be associated with its sedative properties. Respiratory depression can occur when used concomitantly with other medications. Urine discoloration (brown, green, black) is also possible.^{115,117}

[Orphenadrine](#) is structurally related to [diphenhydramine](#) and possesses comparatively higher anticholinergic effects. Yet again, the mechanism of action is not completely elucidated and conjectured due to its sedative and anticholinergic effects. [Orphenadrine](#) also inhibits histamine-1 receptors and NMDA receptors. With [orphenadrine](#), GI irritation may occur and there is rare incidence of aplastic anemia. It should be avoided in those with glaucoma, myasthenia gravis, or cardiospasm. Because of the anticholinergic effects, it should be avoided in the elderly. It has a relatively long half-life ranging from 13 to 20 hours. Its CNS depressant effects are magnified when used with other CNS depressants.^{115,117}

Topicals

6 7 8 9 The advantages of topicals include addressing local symptoms while minimizing systemic exposure and risk for adverse effects ([Table 77-10](#)).^{121,122}

According to the NICE osteoarthritis guidelines, topical NSAIDs should be considered for knee or hand OA before a trial of oral NSAIDs.¹²³ The American College of Rheumatology (ACR) guidelines for hand, hip, and knee OA also recommend topical NSAIDs including [trolamine](#) salicylate as a pharmacologic option. Furthermore, ACR recommends topical NSAIDs over oral NSAIDs in those ≥75 years of age.⁵⁷ Additionally, topical capsaicin may be considered as an adjunct to core treatments for hand and knee osteoarthritis according to the NICE guidelines while ACR recommend capsaicin as a pharmacologic option alone or in combination.⁵⁷ Capsaicin appears in several neuropathic pain guidelines though in different places as either second-line, third-line, or fourth-line for peripheral neuropathic pain.^{52,64,65,73} Capsaicin activates transient receptor potential vanilloid 1 (TRPV1) channels. There are various over-the-counter (OTC) and prescription strength products available. It is important to note that burning may occur with initial application and that this decreases over time with repeated, scheduled use. Capsaicin is not recommended for as-needed use as repeated application is needed to desensitize C-fibers. The capsaicin 8% patch is FDA-approved for PHN and is to be administered under the direct supervision of a physician. There are specific administration directions in the packaging information including pretreatment of the area with topical anesthetic. Topical medications should not be applied to open skin. The NICE guidelines recommend against the use of rubefacients for osteoarthritis.¹²³ [Lidocaine](#) is also used topically and works by inhibiting voltage-gated sodium channels. For PHN, one guideline places [lidocaine](#) as first-line option and may even be preferred over other first-line options in the elderly when CNS adverse effects are a concern.⁵² Other guidelines list topical [lidocaine](#) as second-line or fourth-line options for neuropathic pain.^{64,65}

Topical Analgesics

Medication	Uses	Mechanism of Action	Dosing	Notes		
Capsaicin cream (various)	Temporary relief of minor aches and pains of muscles and joints Localized neuropathic pain	Transient receptor potential vanilloid 1 (TRPV1) receptor agonist	Apply 3-4 times daily	Continue scheduled use for 2-4 weeks for best results		
Capsaicin 8% patch (Qutenza)	PHN	Transient receptor potential vanilloid 1 (TRPV1) receptor agonist	Apply 1-4 patches to affected area for 60 min Repeat no more frequently than q3 months Max: 4 patches	Administer under supervision of physician Specific administration directions in packaging information Apply topical anesthetic before applying Monitor blood pressure due to transient increase in blood pressure during application		
Diclofenac 1% gel (Voltaren)	Pain of osteoarthritis of joints amenable to topical treatment (knees, hands)	Nonsteroid anti-inflammatory drugs (NSAIDs)	Lower extremities: 4 g QID, max 16 g/day Upper extremities: 2 g QID, max 8 g/day Total dose maximum: 32 g/day	Same black box warnings as PO NSAIDs despite low systemic bioavailability (6% of systemic exposure from oral diclofenac) Use dosing card to measure amount		
Diclofenac epolamine 1.3% patch (Flector)	Topical treatment of acute pain due to minor strains, sprains, and contusions	NSAIDs	1 patch to most painful area BID	Systemic effects were <1% after 4 days of repeated dosing		
Diclofenac topical solution (Pennsaid)	Pain from osteoarthritis of the knee	NSAIDs	1.5%: 40 drops to each affected knee 4 times daily. Apply 10 drops at a time 2%: 2 pumps (40 mg) on each painful knee BID	Same black box warnings as PO NSAIDs		
Lidocaine gel/ointment/patch (various)	Neuropathic pain	Sodium channel blocker	Cream/ointment: Apply to affected area 3 times daily Patch: apply 1 patch to affected area up to 12 h	Apply to intact skin only		
Lidocaine 5% patch (Lidoderm)	PHN	Sodium channel blocker	Apply 1-3 patches to site of pain for 12 h Maximum: 3 patches	May cut lidocaine patches Apply to intact skin only Severe hepatic impairment increases risk of side effects		
Menthol/methyl salicylate (various)	Minor aches and pains of muscles and joints (simple backache, arthritis, strains, bruises, sprains)	Rubefacient	Apply topically 3-4 times a day to affected area		Do not apply to damaged skin	
Trolamine salicylate cream 10% (various)	Aches and pains of muscles and joints (arthritis, simple backache, bruises, sprains, strains)	Rubefacient	Apply topically 3-4 times a day to affected area	Do not apply to damaged skin		

Data from Reference 95.

In the management of cancer pain, radiopharmaceuticals (eg, [strontium-89](#) or samarium), corticosteroids, [denosumab](#), and certain bisphosphonates are useful co-analgesics in treating bone pain.⁴⁷ Although antihistamines and amphetamines have been used as co-analgesics, they have demonstrated only limited efficacy.

Emerging Agents

Two agents have received widespread attention recently for their potential analgesic benefit, namely cannabis and ketamine. Medical cannabis has been studied primarily in neuropathic pain conditions with equivocal results. Route of administration, dose, and monitoring recommendations are still unclear. More importantly, research on the specific cannabinoids and terpenes present in many of the *cannabis* strains is required considering the widely variable pharmacologic profiles of these substances.^{124,125} The non-psychoactive cannabinoid, *cannabidiol* (CBD) may have a significant role in the treatment of chronic pain, although its utility in the absence of delta-9-tetrahydrocannabinol (THC) is unclear.¹²⁶

Ketamine, a non-competitive *N*-methyl-D-aspartate glutamate receptor antagonist, is typically used for procedural sedation and for induction of anesthesia. Given its potent glutamate antagonism, its use has gained popularity among pain specialists for maladaptive pain syndromes, such as Complex Regional Pain Syndrome (CRPS). Guidelines for the use of ketamine as an adjunct analgesic in acute pain are available, but appropriate dose, duration, and patient selection for chronic pain are still unclear.¹²⁷ Use of this agent should be supervised by clinicians experienced in its use.

Opioid Agents

7 8 9 10 1 9 10 11 Opioids are often the next step in the management of acute pain and cancer-related chronic pain. This medication class may also be an effective treatment option in the management of chronic noncancer pain; however, this continues to be increasingly controversial. When a trial of opioids is warranted, it should follow a complete assessment of the pain complaint, an assessment of the patient's functionality goals, and risk factors for opioid misuse, abuse, diversion, or overdose.⁴⁹

Opioid choice should be based on patient acceptance, analgesic effectiveness, as well as pharmacokinetic, pharmacodynamic, and side-effect profiles with the attributes provided in [Tables 77-11](#) and [77-12](#).^{47,95}

Opioid Analgesics

Class and Generic Name (Brand Name)	Chemical Source	Metabolic Pathway/Metabolites	Route ^a	Equianalgesic Dose in Adults (mg)	Approximate Onset (min)/Half-Life (h) ^b
Phenanthrenes (morphine-like agonists)					
Morphine (Embeda ^j , Arymo ER ^j , MorphaBond ^j)	Naturally occurring	Phase II via glucuronidation/M3G ^j (inactive) and M6G ^j (active)	IM/IV	10	10-20/2
			PO	25-30	
Hydromorphone (Dilaudid, Exalgo, various)	Semisynthetic	Phase II via glucuronidation/H3G (active) ^m , H6G ⁿ	IM/IV	1.5	10-20/2-3
			PO	7.5	
Oxymorphone (Numorphan, Opana)	Semisynthetic	Phase II via glucuronidation/O3G (inactive) ^o	IM/IV ^a	1	10-20/2-3
			PO	10	
Levorphanol (various)	Semisynthetic	Phase II via glucuronidation/levorphanol-3-glucuronide (inactive)	PO	Variable	10-20/12-16
Codeine (various)	Naturally occurring	CYP2D6/morphine (active), Phase II glucuronidation/codeine-6-glucuronide (unknown), CYP3A4/norcodeine (inactive)	PO	15-30 ^c	10-30/3
Hydrocodone (available as combination, single entity extended release—Hysingla ER ^j , Zohydro ER, Vantrela ^j)	Semisynthetic	CYP3A4/norhydrocodone (inactive); CYP2D6/hydromorphone (active)	PO	5-10 ^c	30-60/4
Oxycodone (OxyContin ^j , Xtampza ^j , RoxyBond ^j Troxyco ER ^j [oxycodone & acetaminophen])	Semisynthetic	CYP3A4/noroxycodone (active), CYP2D6/oxymorphone (active)	PO	15-30 ^d	30-60/2-3
Phenylpiperidines (meperidine-like agonists)					
Meperidine (Demerol, various)	Synthetic	Phase II hydrolysis/meperidinic acid, CYP2B6, CYP3A4, & CYP2C19/norcodeine	IM / IV	75	10-20/3-5
			PO	300 ^d ; not recommended	
Fentanyl (Sublimaze, Duragesic, Lazanda, Abstral, Fentora, Subsys, OTFC, various)	Synthetic	CYP3A4/norfentanyl (inactive)	IM / IV	0.125 ^e	7-15/3-4
			Transdermal, Buccal, transmucosal, sublingual, nasal, nebulized	Variable ^f	
				Variable ^f	
Diphenylheptanes (methadone-like agonists)					

Class and Generic Name (Brand Name)	Chemical Source	Metabolic Pathway/Metabolites	Route ^a	Equianalgesic Dose in Adults (mg)	Approximate Onset (min)/Half-Life (h) ^b
Methadone (Dolophine, various)	Synthetic	CYP3A4, CYP2B6, CYP2C19, CYP2C9, CYP2D6/EDDP (inactive) ^p	IM / IV	Variable ^g (acute)	
			PO	Variable ^g (acute)	30-60/12-190
Phenylpropanolamines					
Tramadol (Ultram, Rybix, Ryzolt, ConZip, various)	Synthetic	CYP3A4/nortramadol (inactive), CYP2D6/ <i>O</i> -desmethylnortramadol (active)	PO	50-100 ^{c,h,i}	<60/5-7
Tapentadol (Nucynta)	Synthetic	Phase II glucuronidation/tapentadol-o-glucuronide (inactive), CYP2C9 and CYP2C19/ <i>N</i> -desmethylnortramadol (inactive), CYP2D6/hydroxytapentadol	PO	50-10 ^{c,h,i}	Within 60/4
Agonist-antagonist derivatives					
Pentazocine (Talwin, various)	Synthetic	Liver/Alcoholic and carboxylic acid derivatives (inactive), pentazocine glucuronide (inactive)	IM	Not recommended	
			PO	50 ^c	15-30/2-3
Butorphanol (Stadol, various)	Synthetic	CYP3A4/hydroxybutorphanol (active), norbutorphanol (inactive)	IM/IV	2	10-20/3-4
			Intranasal	1 ^c (one spray)	
Nalbuphine (Nubain, various)	Synthetic	CYP3A4 CYP2C19/nornalbuphine, 6-ketonalbuphine	IM / IV	10	<15/5
Buprenorphine (Buprenex, Butrans, Suboxone, Belbuca, Subutex, various)	Synthetic	CYP3A4/norbuprenorphine (active)	IM/IV	0.3	10-20/2-3
			Transdermal	Variable	
			Sublingual	Variable	

IM, intramuscular; IV, intravenous; PO, oral.

^aThe IM route should be avoided whenever possible — produces significant pain with administration and rate and extent of absorption is highly variable. If IV route is unavailable then administer subcutaneously (SC).

^bER/LA formulations may vary greatly in terms of onset and duration of analgesia. The reader should consult individual prescribing labels.

^cStarting dose only (equianalgesia not shown).

^dStarting doses lower (oxycodone 5–10 mg, meperidine 50–150 mg).

^eEquivalent PO morphine dose = variable.

^fFor breakthrough pain only. Equianalgesic dose conversion should be avoided for Transmucosal Immediate Release Fentanyl (TIRF) products.

^gThe equianalgesic dose of methadone when compared with other opioids will decrease progressively the higher the previous opioid dose. Caution should be exercised when initiating in opioid naïve patients.

^hFirst day of dosing may administer second dose 1 hour after first dose.

ⁱOnset of action may differ for long-acting formulations. Ceiling dose recommendations exist and may differ from immediate release dosing recommendations.

^jFDA approved as abuse-deterrent formulation.

^kMorphine-3-glucuronide (accumulates in renal failure).

^lMorphine-6-glucuronide (accumulates in renal failure).

^mHydromorphone-3-glucuronide (accumulates in renal failure).

ⁿHydromorphone-6-glucuronide.

^oOxymorphone-3-glucuronide.

^p2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidene (EDDP).

Data from References 95, 47, and individual product package inserts.

Agent(s)	Doses (Use Lowest Effective Dose, Titrate Up or Down Based on Patient Response, Opioid-Tolerant Patients May Need Dose Modification)	Notes
NSAIDs/acetaminophen/aspirin	Use lowest effective dose for the shortest duration possible	Used in mild-to-moderate pain
		May use in conjunction with opioid agents to decrease doses of each
		Regular alcohol use and of acetaminophen may result in liver toxicity
		Care must be exercised to avoid overdose when combination products containing these agents are used
		Underlying renal impairment, hypovolemia, and CHF may predispose to nephrotoxicity
Morphine	PO 5-30 mg every 4 h ^a	Drug of choice in severe pain
	IM 5-20 mg every 4 h ^a	Use immediate-release product with SR product to control breakthrough pain in cancer patients
	IV 5-15 mg every 4 h ^a	Typical patient controlled analgesia IV dose is 1 mg with a 10-min lock-out interval
	SR 15-30 mg every 12 h (may need to be every 8 h in some patients)	Every 24-h products available
	Rectal 10-20 mg every 4 h ^a	
Hydromorphone	PO 2-4 mg every 4-6 h ^a	Use in severe pain
	XR 8 mg to 64 mg every 24 h	More potent than morphine; otherwise, no advantages
	IM 1-2 mg every 4-6 h ^a	
	IV 0.5-2 mg every 4 h ^a	Typical patient-controlled analgesia IV dose is 0.2 mg with a 10-min lock-out interval
	Rectal 3 mg every 6-8 h ^a	Every 24-h product (Exalgo) available
Oxymorphone	IM 1-1.5 mg every 4-6 h ^a	Use in severe pain
	IV 0.5 mg every 4-6 h ^a	No advantages over morphine
	PO immediate-release 5-10 mg every 4-6 h ^a	Use immediate-release product with controlled-release product to control breakthrough pain in cancer or chronic pain patients
	PO extended-release 5-10 mg every 12 h ^a	Manufacturer recommends 5 mg every 12 h in opioid-naïve patients
		Take ER on empty stomach
Levorphanol	PO 2-3 mg every 6-8 h ^a (Levo-Dromoran)	Use in severe pain
	PO 2 mg every 3-6 h ^a (Levorphanol Tartrate)	Extended half-life useful in cancer patients
	IM 1-2 mg every 6-8 h ^a	In chronic pain, wait 3 days between dosage adjustments
	IV 1 mg every 3-6 h ^a	

Agent(s)	Doses (Use Lowest Effective Dose, Titrate Up or Down Based on Patient Response, Opioid-Tolerant Patients May Need Dose Modification)	Notes
Codeine	PO 15-60 mg every 4-6 h ^a	Use in mild-to-moderate pain
	IM 15-60 mg every 4-6 h ^a	Weak analgesic; analgesic prodrug
Hydrocodone	PO 5-10 mg every 4-6 h ^a	Use in moderate/severe pain
Oxycodone	PO 5-15 mg every 4-6 h ^a	Use in moderate/severe pain
	Controlled release 10-20 mg every 12 h	
		Use immediate-release product with controlled-release product to control breakthrough pain in cancer or chronic pain patients
		CR reformulated to deter abuse
Meperidine	IM 50-150 mg every 3-4 h ^a	Use in severe pain
	IV 5-10 mg every 5 min prn ^a	Oral not recommended
		Do not use in renal failure
		May precipitate tremors, myoclonus, and seizures
		Monoamine oxidase inhibitors can induce hyperpyrexia and/or seizures or opioid overdose symptoms
Fentanyl	IV 25-50 mcg/h	Used in severe pain
	IM 50-100 mcg every 1-2 h ^a	Do not use transdermal in acute pain
	Transdermal 25 mcg/h every 72 h	Transmucosal for breakthrough cancer pain in patients already receiving or tolerant to opioids
	Transmucosal (Actiq / OTFC Lozenge and Onsolis buccal film) 200 mcg may repeat × 1, 30 min after first dose is started, then titrate	Always start with lowest dose despite daily opioid intake; product-specific titration recommendations exist
	Transmucosal (Fentora Buccal Tablet) 100 mcg, may repeat × 1, 30 min after first dose is started, then titrate	
	Intranasal (Lazanda Spray) 100 mcg (one spray) in one nostril. Wait 2 h prior to redosing	
	Sublingual (Subsys Spray) 100 mcg (1 spray). Wait 4 h prior to redosing	
	Sublingual (Abstral Tablet) 100 mcg tablets placed sublingually. Must wait 2 h prior to redosing	
Methadone	PO 2.5-10 mg every 8-12 h ^a	Effective in severe chronic pain
	IM 2.5-10 mg every 8-12 h ^a	
		Some chronic pain patients can be dosed every 12 h

Agent(s)	Doses (Use Lowest Effective Dose, Titrate Up or Down Based on Patient Response, Opioid-Tolerant Patients May Need Dose Modification)	Notes
		Equianalgesic dose of methadone when compared with other opioids will decrease progressively the higher the previous opioid dose. Avoid dose titrations more frequently than weekly in chronic pain maintenance
Pentazocine	PO 50-100 mg every 3-4 h ^b (max. 600 mg daily, for those 50 mg tablet containing 0.5 mg of naloxone)	Second-line agent for moderate-to-severe pain; may precipitate withdrawal in opiate-dependent patients; parenteral doses not recommended
	PO 25 mg every 4 h ^b (max. 150 mg daily, for those 25 mg tablet containing 325 mg of acetaminophen)	
Butorphanol	IM 1-4 mg every 3-4 h ^b	Second-line agent for moderate-to-severe pain
	IV 0.5-2 mg every 3-4 h ^b	May precipitate withdrawal in opiate-dependent patients
	Intranasal 1 mg (1 spray) every 3-4 h ^b	
	If inadequate relief after initial spray, may repeat in other nostril × 1 in 60-90 min	
	Max. 2 sprays (one per nostril) every 3-4 h ^b	
Nalbuphine	IM/IV 10 mg every 3-6 h ^b (max. 20 mg dose, 160 mg daily)	Second-line agent for moderate-to-severe pain; may precipitate withdrawal in opiate-dependent patients
		Used frequently in low doses to treat / prevent opioid-induced pruritus
Buprenorphine	IM 0.3 mg every 6 h ^b	Second-line agent for moderate-to-severe pain
	Slow IV 0.3 mg every 6 h ^b	May precipitate withdrawal in opiate-dependent patients
		Transdermal delivery systems (5, 7.5, 10, 15, 20 micrograms/hour) available for every 7 day administration. Detailed manufacturer dosing conversion recommendations exist
	May repeat × 1, 30-60 min after initial dose	Naloxone may not be effective in reversing respiratory depression
Naloxone	IV / IM 0.4-2 mg	When reversing opiate side effects in patients needing analgesia, dilute and titrate (0.1-0.2 mg every 2-3 min) so as not to reverse analgesia
Tramadol	PO 50-100 mg every 4-6 h ^a	Maximum dose for nonextended-release, 400 mg/24 h; maximum for extended release, 300 mg/24 h
	If rapid onset not required, start 25 mg/day and titrate over several days	Decrease dose in patient with renal impairment and in the elderly
	Extended release PO 100 mg every 24 h	
Tapentadol	PO 50-100 mg every 4-6 h ^a	First day of therapy may administer second dose after the first within 1 h maximum dose first day 700 mg, max. dose thereafter 600 mg (maximum dose for CR 500 mg)

HCL, hydrochloride; IM, intramuscular; IV, intravenous; NSAID, nonsteroidal anti-inflammatory drug; PO, oral; prn, as needed; SR, sustained release.

^aMay start with an around-the-clock regimen and switch to prn if/when the painful signal subsides or is episodic.

^bMay reach a ceiling analgesic effect.

Data from References 47, 95, and 131.

The pharmacologic activity of opioids depends on their affinity for and action at one or more central and peripheral opiate receptors. These g-protein coupled receptors include mu (MOR), kappa (KOR), delta (DOR), and nocepin (OLR-1), which have variable physiologic effects. Therapeutic activities and side effects for this medication class range from those exhibited by the MOR agonists (eg, morphine) to those seen with the nonselective antagonists (eg, naloxone). Partial MOR agonists (eg, buprenorphine) and mixed MOR antagonists / KOR agonists (eg, [nalbuphine](#)) compete with agonists for opiate receptor sites and, depending on the inherent agonist and antagonist properties, may precipitate opioid withdrawal and pain crisis if initiated in an MOR agonist tolerant patient.¹²⁸ Efficacy and side effects also may further differ among opioid agents because of receptor subtype variability and may explain why some patients respond differently to certain opioids, specifically MOR agonists.¹²⁹ Opioid antagonists may act centrally (eg, naloxone or [naltrexone](#)) or be limited to peripheral action only (eg, [naloxegol](#), [methylnaltrexone](#), or [naldemedine](#)) (Table 77-13).^{95,130}

TABLE 77-13

Central and Peripheral Opioid Antagonists

Generic Name (Brand Name)	Activity	Role	Route	Dose in Adults (mg)	Special Considerations
Naloxone (Narcan, various) Methylnaltrexone (Relistor) Naltrexone (ReVia, Vivitrol) Alvimopan (Entereg) Naloxegol (Movantik)	Systemic Peripheral Systemic Peripheral Peripheral	Opioid reversal Cancer and CNMP ^a OIC ^b AUD, ^c OLD ^d Postoperative ileus CNMP, OIC	IV, IM, IN SC (both), PO (CNMP) PO, IM PO PO	0.4-2 ^e Variable 12 mg Qday-Q12 (PO) 380 mg q4weeks (IM) 12 mg PO 30 min-5h before surgery then 12 mg PO BID starting day after surgery for maximum of 7 days 12.5-25mg QD 1 hour before, 2 hours after a meal	Onset 1-2 (IV), 2-5 (IM) Half-life 0.5-1.3 Renal dose adjustments Opioid free for 7-10 days before initiation Limited to 15 doses Renal dose adjustments Avoid with moderate 3A4 inhibitors
Naldemedine (Symproic)	Peripheral	CNMP, OIC	PO	0.2 mg daily	Avoid with severe hepatic impairment

^aChronic nonmalignant pain end period.

^bOpioid-induced constipation end period.

^cAlcohol use disorder end period.

^dOpioid use disorder end period.

^eStarting doses to be used in cases of opioid overdose end period.

Data from individual package inserts.

The effects of the opioid analgesics are relatively selective, and at normal therapeutic concentrations, do not affect other sensory modalities.^{9,128} While sensations of touch and proprioception are preserved, undesirable side effects may increase as the dose is escalated (Table 77-14).^{9,128} Frequently, when opioids are administered, pain is not eliminated, but its unpleasantness is decreased. Patients report that although their pain is still present, it no longer bothers them.

TABLE 77-14

Major Adverse Effects of the Opioid Analgesics

Effect	Manifestation
Mood changes	Dysphoria, euphoria
Somnolence	Sedation, inability to concentrate
Stimulation of chemoreceptor trigger zone	Nausea, vomiting
Respiratory depression	Decreased respiratory rate, periodic breathing, oxygen desaturation
Decreased gastrointestinal motility	Constipation
Increase in sphincter tone	Biliary spasm, urinary retention (varies among agents)
Histamine release	Urticaria, pruritus, rarely exacerbation of asthma due to bronchospasm (varies among agents)
Tolerance	Larger doses for same effect
Dependence	Withdrawal symptoms upon abrupt discontinuation
Addiction	Genetic predisposition leads to loss of control of drug use, continued use despite harm, compulsion to use, cravings
Hypogonadism	Fatigue, depression, loss of analgesia, sexual dysfunction, amenorrhea (women)
Sleep	Disrupts sleep–wake cycle, causes dose-dependent rapid eye movement (REM) suppression

Data from References [47](#) and [95](#).

8 9 Opioids share related pharmacologic attributes and exert a profound effect on the CNS and GI tract. Mood changes, sedation, nausea, vomiting, decreased GI motility, constipation, respiratory depression, dependence, pruritus, and tolerance are evident in varying degrees with all agents.¹²⁸ Tolerance to side effects (except to constipation) often develops over time. Some differences exist between the opioids in regards to incidence of side effects, which may assist in selection of the most appropriate agent.

7 8 9 The route of administration depends on individual patient needs, with the oral route being preferred. However, the onset of analgesic effect for oral medications is approximately 45 minutes, and the peak effect usually occurs 1 to 2 hours after administration.^{9,47} This delay must be considered when immediate relief is needed in the management of acute pain (ie, postsurgical or cancer breakthrough). Therefore, in some scenarios, such as acute severe pain (eg, pain crisis) or when the patient is unable to take oral medications, alternative routes of therapy, such as intravenous (IV) administration, may be preferred.³¹ The relative potency, defined by the equianalgesic dose, of opioids differs greatly ([Table 77-11](#)). Equianalgesic dose tables are often based on single-dose studies without regard for patient variability and should be used only as a guide, with further dose titration frequently required.^{47,131}

Although true opioid allergies are rare, [Table 77-11](#) can also be used when treating a patient who has a documented hypersensitivity to opioids. Differing chemical classes of opioids may theoretically provide some reduction in cross reactivity when hypersensitivity is of concern. Most reactions, such as pruritus or rash, are either related to associated histamine release from cutaneous mast cells or activation of central MOR receptors and not a true allergic or immunoglobulin-E (IgE) or T-cell response.^{132–134} Although caution is always advised, a decrease in potential cross-sensitivity is thought to exist when moving from one opioid structural class to another.¹³³ The classes are phenanthrenes (morphine-like agonists), phenylpiperidines (fentanyl-like agonists), and diphenylheptanes (methadone-like agonists). When considering cross-sensitivity, the mixed agonist–antagonist and partial agonist class acts much like the morphine-like agonists.¹³⁴

8 9 9 In the initial stages of acute pain, analgesics should be given around the clock. This should commence after administering a typical starting dose and titrating up or down, depending on the patient's degree of pain and demonstrated side effects (eg, sedation). As-needed schedules may produce wide swings in analgesic plasma concentrations resulting in alternating states of uncontrolled pain and sedation. This may initiate a vicious cycle where increasing amounts of pain medications are needed for relief. As the pain subsides and the need for medication decreases, as-needed schedules may be appropriate, which may also be useful in patients who present with pain that is intermittent or sporadic in nature. When opioids are used in the management of persistent chronic pain, around-the-clock administration schedules should be utilized. As-needed opioids should be used in conjunction with around-the-clock regimens for times when patients experience breakthrough pain, which is a brief, transitory, exacerbation of moderate-to-severe pain typically occurring in patients with underlying persistent pain that may otherwise be controlled.

7 Continuous IV infusion of opioids should be reserved for opioid-tolerant patients.^{135,136} An alternative method is patient-controlled analgesia (PCA), which is a technique by which patients can self-administer a preset dose of an IV opioid via a pump electronically interfaced with a timing device. Compared with traditional as-

needed opioid dosing, PCA yields better pain control, improved patient satisfaction, and relatively few differences in side effects.^{135,137}

Administration of opioids directly into the CNS (eg, epidural and intrathecal/subarachnoid routes) may also be used by anesthesiology pain consult services in the control of acute, chronic noncancer, and cancer pain; and is useful in more difficult to control pain states (Table 77-15).^{138,139}

TABLE 77-15

Intraspinal Opioids

Agent	Single Dose (mg)	Onset of Pain Relief (min)	Duration of Pain Relief (h)	Continual Infusion Dose (mg/h)
Epidural route				
Morphine	1-6	30	6-24	0.1-1
Hydromorphone	0.8-1.5	5-8	4-8	0.1-0.3
Fentanyl	0.025-0.1	5	2-8	0.025-0.1
Sufentanil	0.01-0.06	5	2-4	0.01-0.05
Subarachnoid route				
Morphine	0.1-0.3	15	8-34	–
Fentanyl	0.005-0.025	5	3-6	–

Doses above should not be interpreted as equianalgesic doses for conversion to or from the specific opioid or route of administration.

Data from References 47, 95, and 139.

8 Due to reports of respiratory depression, pruritus, nausea, vomiting, urinary retention, and hypotension, these methods of analgesia require careful monitoring and are best used by experienced practitioners. Respiratory depression is of concern and can occur within minutes with intrathecal fentanyl or manifest as late as 19 hours after a single dose of intrathecal morphine. Guidelines mandate respiratory monitoring for at least 24 hours after a single dose of intrathecal or epidural morphine with standing orders for naloxone (opioid antagonist) for full or partial reversal.^{135,136} Analgesia and side effects are evident at even lower doses when opioids are administered intrathecally instead of epidurally. This form of analgesia is often administered as a continuous-infusion and/or on a patient-controlled basis. When given simultaneously with intrathecal or epidural local anesthetics such as bupivacaine, opioid analgesics have been proven relatively safe and effective. All agents administered directly into the CNS should be preservative free.

Morphine and Congeners

6 10 Despite the availability of several newer agents, morphine remains the prototype opiate analgesic. As new opioid and nonopioid compounds are developed, their efficacy and side-effect profiles are typically compared against morphine as the standard. Using equianalgesic tables, clinicians often refer to “oral morphine equivalents” when describing efficacy or risk of harms of other opioids.^{36,131} Many clinicians consider morphine the first-line agent when treating moderate-to-severe pain due to its relative low cost, broad clinical experience, and abundant dosage forms/strengths.

Side effects can be numerous, particularly when morphine is first initiated or when doses are significantly increased. Morphine causes nausea and vomiting through direct stimulation of the chemoreceptor trigger zone, decreased peristalsis, and a vestibular mechanism.¹²⁸ Opioid-induced nausea typically subsides over time with continued dosing, although this side-effect may be incredibly troublesome to patients, especially following surgery.¹⁴⁰ As doses of morphine are increased, the respiratory center becomes less responsive to carbon dioxide, causing progressive respiratory depression.⁹ This effect is more pronounced with concurrent administration with other respiratory depressants.¹⁴¹ Respiratory depression often manifests as a decrease in respiratory rate (although minute volume and tidal exchange also are affected).¹²⁸ More recently, end-tidal capnography has become commonplace as a means to monitor opioid-induced respiratory depression, especially in those at increased risk.¹⁴²

10 11 Opioid-induced respiratory depression can be rapidly reversed by the opioid antagonist, naloxone.¹²⁸ In patients with underlying pulmonary dysfunction or sleep-disordered breathing, caution must be exercised when opioids are used, as these patients are already using compensatory breathing mechanisms and are at risk for further respiratory compromise.¹⁴³ Caution is also urged when combining opiate analgesics with alcohol or other CNS depressants (ie, benzodiazepines, SMRs, and sleep hypnotics), because this combination is potentially harmful and possibly lethal.³⁶

Therapeutic doses of morphine have minimal effects on blood pressure, cardiac rate, or cardiac rhythm when patients are supine; however, morphine does produce venous and arteriolar vessel dilation, potentially resulting in orthostatic hypotension, and hypovolemic patients may be more susceptible to morphine-induced

cardiovascular changes (eg, decreases in blood pressure).⁹ Because morphine prompts a decrease in myocardial oxygen demand in ischemic cardiac patients, it is often used to treat pain associated with myocardial infarction, although this practice has been called into question due to the potential for increased mortality.¹⁴⁴

Morphine decreases the propulsive contractions of the GI tract resulting in constipation. Morphine-induced spasms of the sphincter of Oddi have also been observed; however, the clinical significance of this is unclear. Urinary retention is another significant side effect of morphine and should be routinely assessed. Morphine-induced histamine release often manifests as pruritus, and may even exacerbate bronchospasm in patients with a history of asthma.⁴⁷ Therapeutic doses of morphine are not contraindicated in head injury, but drug-induced respiratory depression can increase intracranial pressure. Thus, caution is advised in head trauma patients who are not mechanically-ventilated because morphine may increase intracranial pressures and cloud the neurologic examination results.¹²⁸

Morphine is metabolized to two major metabolites, morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G). Whereas M6G contributes to analgesia, M3G may contribute to unwanted neurologic side effects. The metabolites are renally cleared and can accumulate in patients with renal impairment, contributing to greater side effects.¹²⁸ Most clinicians recommend avoiding morphine in renally compromised patients (ie, creatinine clearance ≤ 30 mL/minute [0.50 mL/s]). Morphine also inhibits the release of gonadotropin-releasing hormone from the hypothalamus, thus decreasing plasma testosterone and cortisol (opioid-induced hypogonadism), whereas male patients may present with symptoms of erectile dysfunction, decreased libido, and decreased analgesic efficacy. Women may experience alopecia, amenorrhea, and depressed mood, as well as decreased analgesic efficacy. Recommendations for clinical replacement of these hormones in patients using chronic opioid therapy are not well defined.¹⁴⁵ While the clinical meaning has not clearly been elucidated, morphine and other opioids, depending on the situation being used, may either enhance or inhibit the immune system.^{47,128}

Hydromorphone is more potent than morphine, but its overall pharmacologic profile is similar. Some clinicians believe hydromorphone is associated with fewer side effects, especially pruritus, compared with other opioids. However, the research is limited and does not conclusively demonstrate this difference. Oxycodone can be administered orally and by injection. Although extended-release and immediate-release oral products are available, it offers no pharmacologic advantage over morphine. Patients must be counseled to take the extended-release oxycodone without food as high fat meals may greatly increase absorption, resulting in an increased risk of toxicity. Levorphanol has an extended half-life and purported NMDA glutamate receptor activity, but its overall therapeutic effects are similar to the other agents in this class and cost is frequently a barrier to its use.^{146,147}

Codeine is a commonly used opioid for the treatment of mild-to-moderate pain. It often is combined with other analgesic products (eg, acetaminophen). Unfortunately, it has the propensity to produce the same side effects as morphine. Due to the risk of toxicity in patients with rapid metabolizer phenotypes, the FDA recommends against codeine's use in children and breastfeeding mothers.¹⁴⁸ Hydrocodone is perhaps the most commonly prescribed opiate in the United States and is available orally as immediate-release combined with nonopioid analgesics, as well as extended-release formulations. Its pharmacologic properties are similar to those of morphine. Oxycodone is a useful oral analgesic for moderate-to-severe pain. This is especially true when the product is used in combination with nonopioids. Although oxycodone shares basic morphine characteristics, the availability of an immediate-release and controlled-release oral dosage form also makes it very useful in chronic pain as well as cancer pain.

Meperidine and Congeners (Phenylpiperidines)

The prototype phenylpiperidine, meperidine, has a pharmacologic profile comparable with that of morphine; however, it is not as potent and has a shorter analgesic duration. Meperidine offers no analgesic advantage over morphine, has greater toxicity (CNS hyperirritability caused by its renally eliminated metabolite normeperidine), and should be limited in use, especially in elderly patients, those with renal dysfunction, or for prolonged treatment durations.^{47,149} In particular, avoid long-term usage and use in patients at greatest risk for toxicity (eg, elderly patients and those with renal dysfunction).¹⁴⁹

Fentanyl is a synthetic opioid structurally related to meperidine that is used often in anesthesiology as an adjunct to general anesthesia. This agent is significantly more potent and faster acting than meperidine. It can be administered parenterally, transmucosally, sublingually, intranasally, and transdermally.^{9,128}

Methadone and Congeners

Methadone is a useful analgesic due to its oral efficacy, extended duration of action, and low cost. Properties unique to methadone, compared with other opioids, include the s-isomer's ability to antagonize NMDA receptors, agonist effects at the kappa and delta opioid receptor, as well as the blockade of serotonin and norepinephrine reuptake.^{128,150} These properties may prove useful in the treatment of neuropathic and chronic pain. However, few trials have thoroughly evaluated methadone's risks versus benefits.^{150,151} Epidemiologic studies suggest a growing number of methadone-related deaths, and cardiac arrhythmias have been associated with this medication, particularly at higher doses or when used concurrently with other agents that prolong QTc intervals.¹⁴¹ Recommendations exist for specific echocardiogram monitoring for methadone; however, concerns exist regarding their applicability.¹⁵⁰ The equianalgesic dose of methadone may decrease with higher doses of the comparator opioid, complicating conversions from other opioids to methadone. Methadone should not be titrated more frequently than every 5 to 7 days due to its unpredictable potency and variable half-life.¹⁵⁰

Opioid Agonist–Antagonist Derivatives

This analgesic class produces analgesia and has the potential for less respiratory depression than opioid agonists as they exert their analgesic activity via the KOR and either block or act as partial agonists at the MOR.¹²⁸ Agents in this class are considered to have a lower abuse potential than morphine, but psychotomimetic responses (eg, hallucinations and dysphoria), limited analgesic effect, and a potential to initiate withdrawal in opioid-dependent populations have precluded their

widespread clinical use. Both butorphanol and [nalbuphine](#) are available parenterally, with butorphanol also available as an intra-nasal spray. [Nalbuphine](#) is gaining popularity as a treatment for MOR agonist-associated pruritus.¹⁵²

Buprenorphine is a pharmacologically complex opioid, which exhibits KOR antagonism, and several MOR-related actions, including partial agonism. Buprenorphine also displays agonist properties at the opioid receptor-like 1 (ORL-1) receptor which may have clinical ramifications in prevention of tolerance, euphoria / reward, and hyperalgesia.¹⁵³ Buprenorphine is available as a sublingual tablet, a buccal film, a once-weekly transdermal patch, or in combination with naloxone as a sublingual film or sublingual tablet. When buprenorphine, with or without naloxone, is prescribed for opioid use disorder, a special DEA license is required by the prescriber.¹⁵⁴

Central-Acting Opioids

Tramadol and tapentadol are the only centrally acting analgesics currently available in the United States. Tramadol binds to MOR receptors and inhibits serotonin, and to a lesser extent, norepinephrine reuptake.¹⁵⁵ Tapentadol also binds the MOR receptor, but inhibits largely norepinephrine reuptake. Tramadol is indicated for the relief of moderate to moderately severe pain, while tapentadol is indicated for moderate-to-severe acute pain and diabetic peripheral neuropathy.

Both tramadol and tapentadol have side-effect profiles similar to that of the previously mentioned opioid analgesics (eg, dizziness, nausea, somnolence, and constipation). Tapentadol has not been systematically evaluated in patients with seizures, and it should be used with caution in these patients. Seizure risk, as well as risk of hypoglycemia and hyponatremia, may be elevated in patients taking tramadol.^{155,156} Tramadol may have a place in treating patients with chronic pain, especially neuropathic pain, while tapentadol may be useful in the management of acute pain and the controlled release product may have a role in chronic pain treatment (eg, diabetes-related nerve pain).^{157,158}

Opioid Antagonists

11 The opioid antagonist naloxone binds competitively to opioid receptors but does not produce an analgesic or opioid side-effect response. Therefore, it is used most often to reverse the toxic effects of agonist- and agonist-antagonist-derived opioids. Other opioid antagonists exist, including [naltrexone](#), [naloxegol](#), [naldemedine](#), and [methylnaltrexone](#). [Naltrexone](#)'s use is primarily limited to addiction medicine, while [naloxegol](#), [naldemedine](#), and [methylnaltrexone](#) are peripherally-acting only and used for opioid-induced constipation.¹³⁰

11 With the growing prevalence of illicit (heroin and fentanyl analogs) opioid abuse-related overdoses, pharmacists are increasingly being called upon to assist in the prevention of these deaths. Many states have legislation in place that allows pharmacists to provide expanded access to naloxone for those themselves or have a family member at risk for an opioid overdose. Naloxone may be administered intranasally, intravenously, or intramuscularly.¹⁵⁹ Further discussion of naloxone education, administration, and monitoring is provided in [Chapter 82](#), "Substance-Related Disorders: Overview and Depressants, Stimulants, and Hallucinogens."

Tolerance, Hyperalgesia, Physical Dependence, and Opioid Use Disorder

1 2 3 4 11 A barrier that consistently causes clinicians to misjudge and mistreat pain is the misunderstanding of opioid tolerance, hyperalgesia, physical dependence, and addiction. Tolerance is the reduction of drug effect over time as a result of exposure to the drug.¹²⁸ It develops at different rates and with great patient variability. However, with stable disease, opioid doses may stabilize over time. Hyperalgesia is an increased sensitivity to pain. Opioids have been implicated in contributing to this phenomenon and can be seen with rapid opioid escalation or high-dose administration.¹⁶⁰ The mechanism or true clinical impact of this phenomenon is not currently understood.

Opioid physical dependence is characterized by an abstinence syndrome following administration of an antagonist drug or abrupt dose reduction or discontinuation of an opioid.^{128,129} Clinicians must understand that physical dependence and tolerance are not equivalent to addiction; and with chronic opioid use, physical dependence is expected.¹²⁹

Many definitions and classifications exist to describe the biopsychosocial phenomenon of addiction. The American Society of Addiction Medicine (ASAM) defines addiction as a "primary, chronic disease of brain reward, motivation, memory and related circuitry" leading to biological, psychological, social, and spiritual manifestations.¹⁶¹ Addiction is characterized by cravings, resulting in an inability to abstain from continued drug use despite harm and impairment in behavioral control. Individually, these behaviors are often described as aberrant, although patients may display aberrant behaviors (eg, medication-related behaviors that are inconsistent with strict adherence to the prescribed treatment) that are not a result of an underlying addiction.⁷ A baseline assessment and ongoing evaluation of these behaviors and an individual's risk of misuse, abuse, and addiction is critical to mitigate risks of chronic opioid therapy and to balance effective pain management and patient safety.^{161,162} Higher risk for opioid misuse or abuse is associated with personal substance abuse, misuse, addiction, or diversion history, a significant family history of substance abuse, and underlying psychiatric diagnoses. Modifications to the treatment plan, which should be stratified based on patient risk, include baseline and random drug screens, patient-provider treatment agreements, pill counts, a smaller prescription supply, and regular assessment of aberrant behaviors. Combining these approaches with regular and ongoing assessments of pain and functionality may result in improved outcomes.

Multimodal Therapy

4 5 6 Commonly, multimodal therapy may be employed to optimize either acute or chronic pain management. Multimodal therapy is the concomitant use of different therapeutic interventions with the intent of obtaining additive therapeutic effects. Multimodal analgesia, one type of multimodal therapy, includes combining medications from different analgesic classes (eg, combination therapy with opioids and nonopioids or co-analgesics).^{9,129} This often results in analgesia

superior to that produced by either agent alone. Multimodal analgesia may also permit the use of lower doses and provide a more favorable side-effect profile, for example when NSAIDs are prescribed with opioids yielding an “opioid sparing” effect.

Regional Analgesia

7 **9** Regional analgesia with properly administered local anesthetics can provide relief of both acute and chronic pain (Table 77-16).^{139,163,164} These agents can be positioned by injection (eg, in joints, in the epidural or intrathecal space, along nerve roots, or in a nerve plexus) or topically. **Lidocaine** in the form of a patch has proven effective in treating focal neuropathic pain.⁶⁴ Regional nerve blocks with local anesthetics may effectively relieve pain. Although rare, elevated plasma concentrations of local anesthetics can cause CNS excitation and depression, including dizziness, tinnitus, drowsiness, disorientation, muscle twitching, seizures, and respiratory arrest.¹⁶³ This syndrome is called LAST (local anesthetic systemic toxicity).¹⁶⁵ Cardiovascular adverse effects include myocardial depression, hypotension, decreased cardiac output, heart block, bradycardia, arrhythmias, and cardiac arrest. Disadvantages of such methods include the need for skillful technical application, need for frequent administration, and highly specialized follow-up procedures.

TABLE 77-16
Local Anesthetics^a

Agent (Brand Name)	Onset (min)	Duration (h)
Esters		
Procaine (Novocain, various)	2-5	0.25-1
Chloroprocaine (Nesacaine, various)	6-12	0.5
Tetracaine (Pontocaine)	≤15	2-3
Amides		
Mepivacaine (Polocaine, various)	3-5	0.75-1.5
Bupivacaine (Marcaine, various)	5	2-4
Bupivacaine liposomal (Exparel—wound infiltration only)	variable	24 local
		96 systemic
Lidocaine (Xylocaine, various)	<2	0.5-1
Prilocaine (Citanest)	<2	1-2
Ropivacaine ^b (Naropin)	10-30	0.5-6

^aUnless otherwise indicated, values are for infiltrative anesthesia.

^bEpidural administration.

Data from Reference 95.

SPECIAL POPULATIONS

6 **9** The elderly and the young are at a higher risk for under-treatment because of potential inability to communicate or rate their pain. It is in these cases that parent or caregiver input becomes paramount to identify changes in behavior, which might suggest pain (eg, fussy, inconsolable, changes in eating patterns, crying out, or agitation). When patients cannot verbalize their pain (eg, coma), monitoring behaviors (eg, agitation) and physiologic signs and symptoms (eg, heart rate) is appropriate. Validated pain assessment tools are available to assist the clinician in approaching patients who are unable to readily communicate the severity of their pain.

In addition, those living with chronic, debilitating, and life-threatening illnesses need specialized pain control and care that is palliative in nature.¹⁶⁴ Although care must be taken in these populations to ensure that proper individualized treatment plans follow accepted guidelines, the key concepts in pain management as outlined in this chapter are the guiding tenets in maximizing pain control.^{166,167}

PERSONALIZED PHARMACOTHERAPY

6 8 9 Recent research has illustrated genetic differences in pain transmission and response inter-individually as well as between genders, ages, and ethnicity. More interesting is the pharmacogenomic variability of analgesic response to both opioid and nonopioid analgesics. Genotyping (eg, CYP 2D6, CYP 2B6) may be useful when considering the addition of an opioid metabolized via one of these enzymes.

Codeine, oxycodone, hydrocodone, and methadone, as well as several of the SSRIs and SNRIs, are all either converted to active or inactive metabolites via one of these enzyme pathways.^{168–170} Individuals who possess a variant allele for one or more of these enzymes may have unexpected outcomes, including greater than expected toxicity or side effects or lower than expected efficacy, depending on the individual genotype and phenotype. This may be especially relevant for opioids in which much of the analgesic activity relies on conversion to an active metabolite from a relatively inactive parent (ie, codeine, tramadol). Recent data suggests high rates of variant metabolism in patients evaluated for genetic variation in CYP2C9, CYP2C19, and CYP2D6, with over 50% of patients expressing a variant in two or more genes.¹⁷¹

In some cases, genotype results may further help explain cases where patients require higher doses to achieve adequate analgesia. For example, data suggests that variants in opioid-receptor subtypes, specifically MOR-1 (OPRM1 gene), may predict efficacy and dosing requirements for some opioids such as morphine or hydromorphone.^{172,173}

Use of pharmacogenomic testing results may be beneficial in the accurate interpretation of drug screens when assessing adherence to chronic opioid therapy. For instance, a urine drug screen and confirmation result that reveals only parent drug and no expected metabolites may be explained by drug–drug interactions, CYP poor metabolizer phenotype, or diversion (pill shaving). For more information regarding specific drug gene pairs related to pharmacogenomics, the Clinical Pharmacogenomics Implementation Consortium (CPIC) provides evidence-based peer-reviewed guidelines on interpretation of these testing results (www.cpicpgx.org).

EVALUATION OF THERAPEUTIC OUTCOMES

8 Consistent monitoring for effectiveness (eg, pain relief, adequate functionality) and adverse effects (eg, sedation) is critical in optimizing therapeutic outcomes. Numerous validated scoring tools exist (eg, numeric rating scale, visual analog scale); however, the tools need to be appropriate for the type of pain being evaluated, used consistently, and with good clinical judgment.^{27,32} Pain management efficacy, any change in pain, and medication side effects (eg, opioid-induced sedation or constipation) must be assessed and reassessed on a regular basis. Frequency of reassessment should be dictated by the medication's route of administration, duration of action, various pharmacokinetic factors, or other concomitant therapies. Postoperative pain and acute exacerbation of cancer pain may need to be assessed hourly or even more frequently, whereas chronic noncancer pain may require only daily or less frequent assessment. Pain intensity assessment is vital in acute pain, whereas functionality becomes more of an issue in chronic pain. Quality of life must be assessed on a regular basis in all patients. Many advocate using the five “A’s” (analgesia, activity, aberrant drug behavior, adverse effects, affect) as key assessment measures for any patient with chronic pain.

It is important to note that often objective signs are lacking for pain evaluation. Acute pain may result in increased sympathetic tone (eg, hypertension, tachycardia, and tachypnea); however, this response is usually diminished as acute pain progresses to chronic pain. The clinician must rely on the patient's description of their pain.

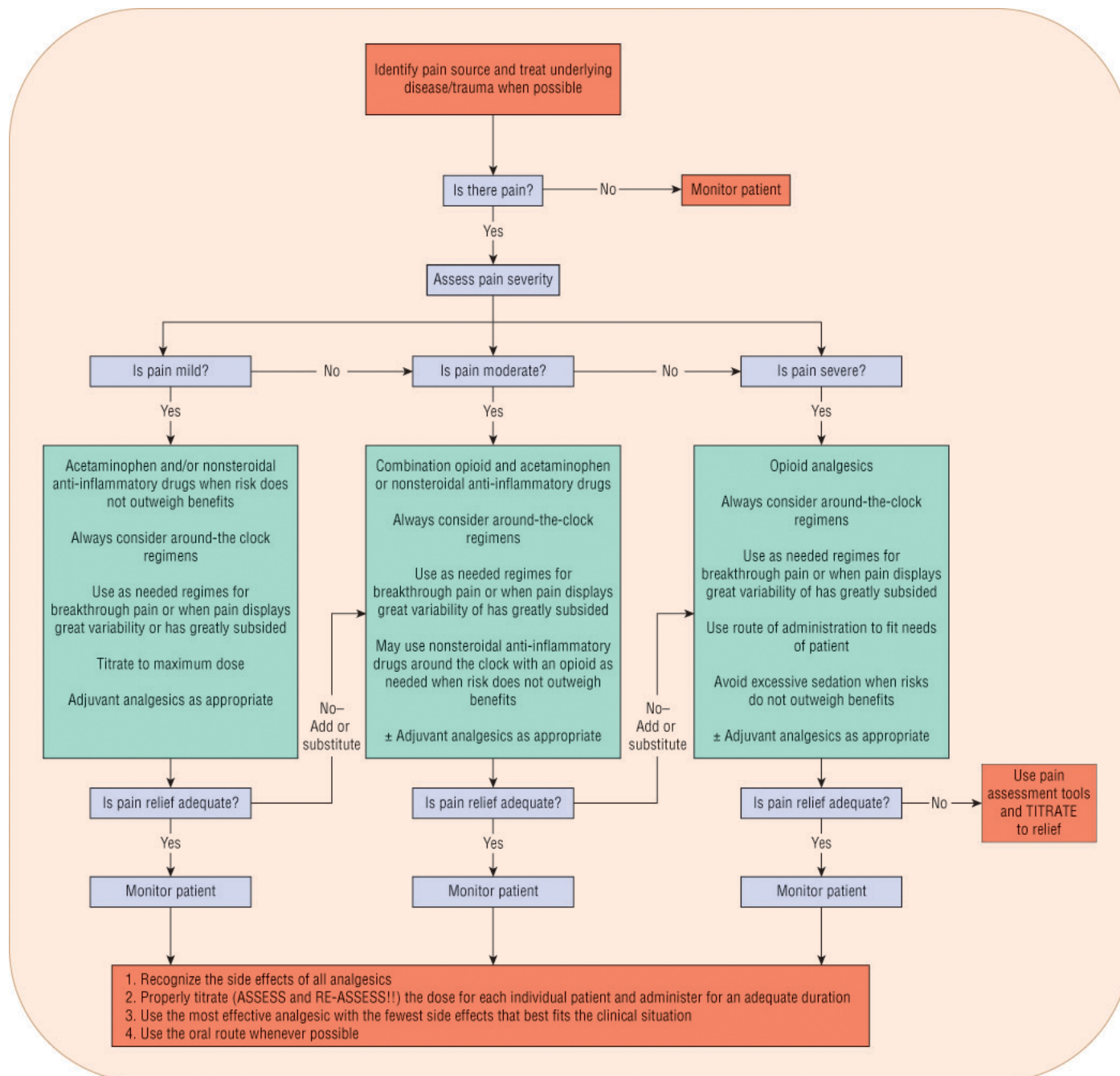
8 9 All opioids can cause constipation. The best management of constipation is prevention and patients should be counseled on the proper intake of fluids and fiber. A stimulating laxative should be added with chronic opioid use. For constipation that doesn't respond to standard bowel regimens, peripherally acting mu-opioid receptor antagonists (PAMORAs) are available for treating opioid-induced constipation. All CNS depressants (eg, alcohol, benzodiazepines) amplify CNS depression when used with opioid analgesics, and use of these combinations should be discouraged when possible. When the combinations are used, patients should be monitored closely.

CONCLUSION

Pain represents a significant source of disability as well as healthcare resource utilization. A thorough understanding of pain pathogenesis is imperative for clinicians involved in its treatment. Multidisciplinary and multimodal approaches to pain management must be considered with nonpharmacological and nonopioid modalities preferred as first-line treatments. Opioid analgesics are important analgesic alternatives and should be considered after careful patient selection. Monitoring for risk of misuse and abuse while these agents are employed is essential. Adverse effects of all pharmacologic therapy for pain require judicious anticipation and treatment (Fig. 77-3).

Figure 77-3

Algorithm for acute pain. (Data from Omnicare, Inc., *Acute Pain Pathway*).



Source: JT DiPiro, GC Yee, LM Posey, ST Haines, TD Nolin, VL Ellingrod. Pharmacotherapy: A Pathophysiologic Approach. 11th Edition. Copyright © McGraw-Hill Education. All rights reserved.

POSTCLASS ACTIVITY

Postclass Engaged Learning Activity

Use the Pharmacotherapy Casebook: [Chapter 70](#), “Chronic Pain Management: Using Opioid Medication in a Troubled Time Level II” to develop a pain-focused assessment and plan (including rationale) for this case.

ABBREVIATIONS

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COX-2	cyclooxygenase-2
GABA	γ-aminobutyric acid
M3G	morphine-3-glucuronide

M6G	morphine-6-glucuronide
NMDA	<i>N</i> -methyl-D-aspartate
NSAIDs	nonsteroidal anti-inflammatory drugs
PCA	patient-controlled analgesia
Civil servants	peripheral nervous system
TENS	transcutaneous electrical nerve stimulation
WHO	World Health Organization
PAIN	delta opioid receptor
DISEASE	kappa opioid receptor
MOR	mu-opioid receptor
CYP	cytochrome P450
CNS	central nervous system
GIVE	gastrointestinal
IV	intravenous
IM	intramuscular
IgE	immunoglobulin E
ORL-1	opioid receptor-like receptor (noceptin receptor)
ACID	American Society of Addiction Medicine
OPRM1	opioid receptor, mu-1 gene subtype

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LEARNING OBJECTIVES

LEARNING OBJECTIVES

Upon completion of this chapter, the reader will be able to:

1. Define pain.
2. Describe the epidemiology of pain.
3. Discuss nociceptive pain pathophysiology, including transduction, transmission, perception, and modulation.
4. Discuss and list examples of pain syndromes with varying etiologies.

5. Explain the patient-oriented approach to pain assessment.
6. Characterize the difference between acute and chronic pain.
7. Describe the usual doses of the nonopioids and opioids indicated for pain.
8. Discuss the pharmacology of the opioid analgesics.
9. Explain the advantages of multimodal therapy in the treatment of pain period
10. Outline the management of pain, including drug selection, dosing, monitoring, and patient education.
11. Compare and contrast the treatment of chronic noncancer pain with that of acute pain and cancer pain.
12. Discuss nonpharmacologic treatment options for acute, chronic noncancer, and cancer pain.
13. Explain why the elderly and very young are at higher risk than other populations for under-treatment of pain.
14. Explain the importance of a multidisciplinary approach to pain.

SELF-ASSESSMENT QUESTIONS

1. Which of the following is a maladaptive pain state?
 - A. Acute post-op pain
 - B. Ankle sprain
 - C. Fibromyalgia
 - D. Pain associated with an infection
2. In which phase of nociception is a noxious stimulus converted into an action potential?
 - A. Conduction
 - B. Transmission
 - C. Modulation
 - D. Perception
3. Which of the following is an excitatory neurotransmitter involved in pain transmission?
 - A. B-endorphin
 - B. γ -aminobutyric acid (GABA)
 - C. Glutamate
 - D. Norepinephrine
4. What mechanism is principally involved in the maintenance of maladaptive pain states?
 - A. Altered pain processing in the CNS
 - B. Upregulation of sodium channels in the PNS
 - C. Excessive prostaglandin synthesis
 - D. Overproduction of endorphin neuropeptides
5. Which of the following is believed to augment the descending inhibitory pathway to produce analgesia?
 - A. Cognitive behavioral therapy
 - B. Massage
 - C. Mindfulness-based stress reduction
 - D. Transcutaneous electrical nerve stimulation (TENS)

6. The dose of breakthrough pain medication (exception rapid-acting fentanyl) is generally calculated as:

- A. 5% of the total daily dose of opioids
- B. 10%–15% of the total daily dose of opioids
- C. 25%–50% of the total daily dose of opioids
- D. 50%–75% of the total daily dose of opioids

7. Which of the following options is an optimal nonopioid medication for a person with significant musculoskeletal pain and comorbid depression?

- A. Amitriptyline
- B. Duloxetine
- C. Lamotrigine
- D. Milnacipran

8. When initiating oral transmucosal fentanyl citrate (Actiq and generics), the most appropriate starting dose is:

- A. The lowest available dosage form
- B. One-half of the 24-hour morphine equivalent intake
- C. Equal to the 24-hour morphine equivalent intake
- D. Twice the 24-hour morphine equivalent intake

9. Which of the following adverse effects is considered a transient side effect of opioids?

- A. Hypogonadism
- B. Somnolence
- C. Constipation
- D. Pruritus

10. You have a patient that is currently being treated with erythromycin (potent CYP 3A4 inhibitor) for diabetic gastroparesis. She has painful diabetic peripheral neuropathy and is on numerous adjuvant analgesics with no effect. The decision has been made to place the patient on long-term opioid therapy. Which of the following opioids would you NOT recommend due to potential drug–drug interactions?

- A. Morphine
- B. Hydromorphone
- C. Oxycodone
- D. Fentanyl

11. Which of the following best describes the mechanism of action of tapentadol (Nucynta)?

- A. Mu-opioid agonist
- B. Mu-opioid agonist plus serotonin > norepinephrine reuptake inhibition
- C. Mu-opioid agonist plus norepinephrine > serotonin reuptake inhibition
- D. None of the above

12. Which of the following two analgesics are actually prodrugs requiring metabolism to their active metabolite for analgesia?

- A. Hydrocodone and hydromorphone
- B. Codeine and tramadol
- C. Tramadol and tapentadol
- D. Morphine and codeine

13. When starting methadone, titration (increase) in dosing should NOT occur more frequently than:

- A. Once a day
- B. Twice a week
- C. Weekly
- D. Monthly

14. Which of the following would be considered components of a risk mitigation strategy for monitoring misuse or abuse with opioid prescriptions?

- A. Prescription Drug Monitoring Programs
- B. Urine Drug Screening
- C. Patient-Provider Agreements
- D. All of the above

15. When converting from one opioid to another using equianalgesic dosing tables, the target drug dose should be decreased by _____ to account for lack of cross-tolerance between opioids.

- A. 10%
- B. 25%
- C. 75%
- D. 90%

SELF-ASSESSMENT QUESTION-ANSWERS

1. C. Fibromyalgia is considered a maladaptive pain state, in that it does not provide any protective function. Acute post-op pain, ankle sprain, and pain associated with infection all alert the brain that tissue damage has occurred and prompts the symptom of pain in order to protect injured tissue from further damage/insult. (See “[Pathophysiology](#)” section.)

2. A. Noxious stimuli are converted to action potentials during the *conduction* phase of nociception. Transmission refers to the spread of the action potential through the neuron. Modulation is the central nervous system's response to the nociceptive signal and serve as the “brakes” to keep pain from growing more severe than is physiologically necessary. Perception involves numerous pathways in the brain in which the body *localizes* the pain origin and mounts an *emotional* response to the pain, depending on severity. (See “[Pathophysiology](#)” section.)

3. C. In pain transmission, B-endorphins, gamma-aminobutyric acid, and norepinephrine all play either a direct or indirect inhibition role to slow primary and secondary neuron depolarization. Glutamate is the primary excitatory neurotransmitter found in vesicles in the pre-synapse. (See “[Pathophysiology](#)” section.)

4. A. While upregulation of sodium channels in the peripheral nervous system may certainly contribute to heightened pain response, altered processing in the central nervous system is primarily involved in the development of maladaptive pain states. Prostaglandins and endorphin neuropeptides will typically have an inhibitory role in nociception and pain processing. (See “[Pathophysiology](#)” section.)

5. D. Transcutaneous electrical nerve stimulation (TENS) is thought to assist the nervous system in the *modulation* of pain via the descending inhibitory pain pathway. This may be due to changes in activated neurons. Cognitive behavioral therapy, while helpful in the treatment of acute and chronic pain, focuses on coping skills, as does mindfulness-based stress reduction. Massage may impact the ascending pain pathway. (See [Table 77-3](#).)

6. B. While no clear guidelines exist to help guide breakthrough pain dosing of opioids, providing enough immediate release opioid for breakthrough pain is essential as the higher the dose received over a 24-hour period, the higher the dose of immediate release opioid that will be required. In cancer pain models, 10% to 15% has generally been proven effective as a ratio of the total daily opioid dose. (See [Table 77-4](#).)

7. B. Duloxetine is the only nonopioid antidepressant analgesic that possesses an FDA approval for the treatment of chronic musculoskeletal pain. The other choices do not possess sufficient evidence to support their use in such pain states. (See [Table 77-8](#).)

8. A. Breakthrough pain dosing opioid immediate release opioids is typically derived from a percentage of total daily opioid dose. This is not true for transmucosal immediate release fentanyl products, given their unpredictably transmucosal absorption. Therefore product prescribing information recommends starting at the lowest available dose of transmucosal fentanyl and titrating to affect. (See [Table 77-12](#).)

9. B. Opioids have numerous unique adverse effects. Patients may develop tolerance to some. Nausea and somnolence typically subside after 2 to 3 days of continued dosing. Hypogonadism, constipation, and pruritus typically continue despite ongoing therapy. (See [Table 77-14](#).)

10. **D.** Fentanyl is metabolized to norfentanyl via CYP 3A4. Morphine and hydromorphone undergo glucuronidation to morphine-3-glucuronide, morphine-6-glucuronide and hydromorphone-3-glucuronide, hydromorphone-6-glucuronide, respectively. Oxycodone largely undergoes metabolism via CYP 2D6 to its active metabolite, [oxymorphone](#). Oxycodone does undergo metabolism in part via CYP 3A4; however, this is to an inactive metabolite, noroxycodone. (See [Table 77-11](#).)
11. **C.** Tapentadol is a weak mu-opioid agonist as well as norepinephrine reuptake inhibitor. While it does possess some mild serotonin reuptake inhibition, this is of a much lesser extent when compared to tramadol or other serotonergic active drugs. (See [“Central-Acting Opioids”](#) section.)
12. **B.** The Clinical Pharmacogenomics Implementation Guidelines recommend CYP 2D6 genotyping when considering initiation of codeine or tramadol as both of these agents must be metabolized via CYP 2D6 to their active metabolites for analgesic activity. Other answers include opioids that have analgesic activity without conversion to other more active metabolites. (See [“Personalized Pharmacotherapy”](#) section.)
13. **C.** Methadone's extended and unpredictable half-life results in maximum analgesic efficacy (and risk of adverse effects) once it reaches steady state, which typically occurs in 5 to 7 days. Titration earlier than weekly may result in dose stacking and risk overdose. Monthly titration would be too long if titrating to effect for a patient with uncontrolled pain. (See [“Methadone and Cogeners”](#) section.)
14. **D.** Any opportunity to identify aberrant drug-taking behaviors or signs/symptoms of opioid use disorder should be utilized when managing opioid therapy. Additionally, pharmacists have a corresponding responsibility to ensure safe use and prevent diversion of these substances. (See [“Tolerance, Hyperalgesia, Physical Dependence, and Opioid Use Disorder”](#) section.)
15. **B.** While most of the opioids used clinically are mu-opioid agonists, several subtypes of mu-opioid receptor exist, resulting in potential differences in the cross-tolerance to different opioids. To ensure patient safety, target opioid dose should be empirically reduced by 25% to 50% to account for this lack of cross-tolerance and to prevent possible oversedation or overdose. (See [Table 77-4](#).)

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