Chapter 79: Pain Management

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CHAPTER SUMMARY FROM THE PHARMACOTHERAPY HANDBOOK

For the Chapter in the Schwinghammer Handbook, please go to Chapter 57, Pain Management.

KEY CONCEPTS

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1. Understanding the pathogenesis of pain should guide treatment and patient education.
2. Whenever possible ask patients if they have 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. A multidisciplinary approach that includes incorporation of nonpharmacologic strategies for pain management should be undertaken.
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 based on the patient's needs.
8. Patients taking analgesics should be monitored for response (analgesia, functionality, quality-of-life) and medication adverse 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 who have failed nonpharmacologic and nonopioid treatment only when the anticipated benefits are expected to outweigh the risks.
11. Use risk mitigation strategies such as informed consent/patient agreements, urine toxicology monitoring, opioid overdose education and naloxone distribution (OEND), and prescription drug monitoring programs (PDMP) checks when necessary.

BEYOND THE BOOK

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Watch the following videos on YouTube to learn more about this topic:

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

URL: https://tinyurl.com/yxjyltp6

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

URL: https://tinyurl.com/y2nbtbb2

The mystery of chronic pain—Elliot Krane

URL: https://www.ted.com/talks/elliot_krane_the_mystery_of_chronic_pain?language=en

INTRODUCTION

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

—Primo Levi[1]

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 why 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 pain management. Therefore, understanding its pathophysiology and maintaining a thorough understanding of both nonpharmacologic and pharmacologic treatment modalities are important factors in addressing pain control.

EPIDEMIOLOGY

Data collected by the National Health Interview Survey suggest that greater than 50 million persons in the United States live with chronic pain.[5] Of whom, 7.5% report "high impact pain," which is considered chronic pain that limits life or work activities on most days or every day.[5] In 1 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

Pain pathophysiology involves complex interactions between neural and immune networks within the peripheral and central nervous system (CNS) in response to afferent sensory stimuli that produce 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

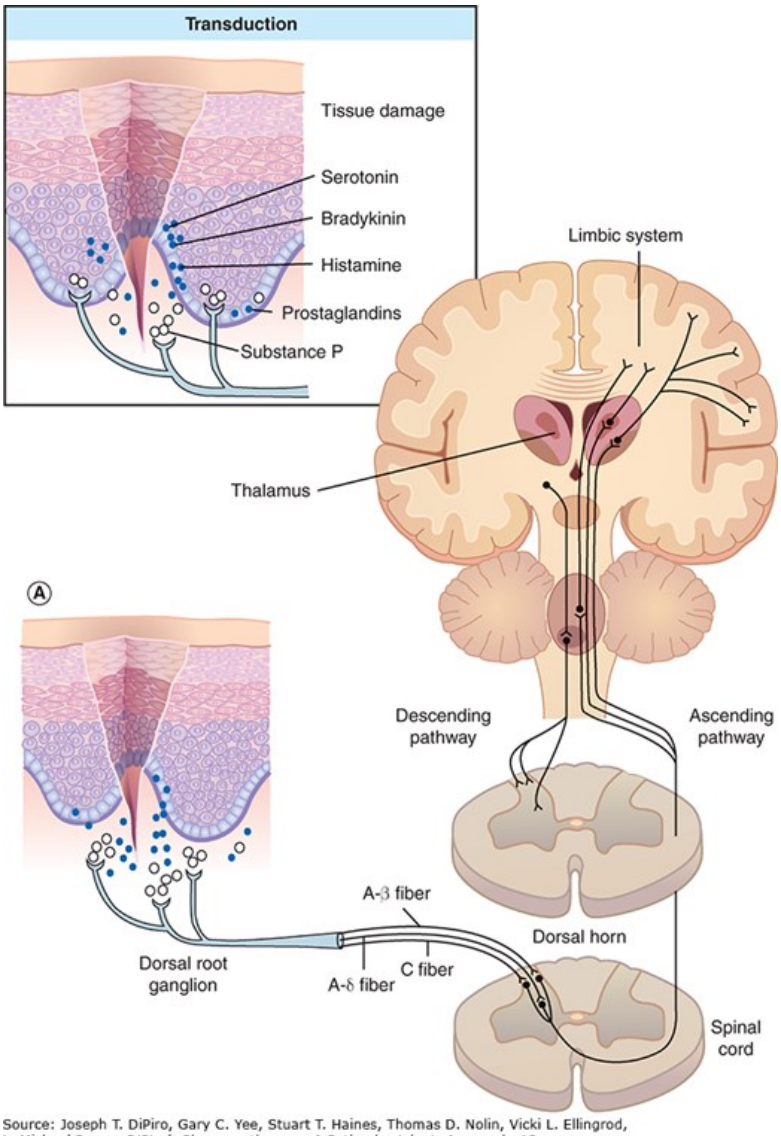
neurotransmission circuit via a number of steps known as transduction, conduction, transmission, modulation, and perception.[8]

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. 79-1).[8-10]

FIGURE 79-1

Schematic representation of nociceptive pain. *(Reprinted from Pasero C, 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, MO: Mosby; 2011:1–12.)*



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

Conduction

Nociceptor activation leads to the conversion of a chemical signal into an electrical signal through 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 neo- and paleospinothalamic 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, and 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.[14-16] Like exogenous opioids, endogenous peptides bind to opioid receptor sites and modulate the transmission of pain impulses.[14] Other receptor types, such as the glutamate receptor, also can influence this system. Blockade of one such receptor, *N*-methyl-D-aspartate (NMDA), may increase the mu (μ)-receptors' responsiveness to opiates.[17]

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, cognitive and behavioral functions can modify pain; thus, relaxation, distraction, meditation, and guided mental imagery may strongly influence pain perception and decrease pain.[18,19] In contrast, conditions such as depression or anxiety often worsen pain.[20]

Impact of Immune System on Pain Signaling

A two-way communication exists between neurons and immune cells within the CNS, especially astrocytes and microglia which are the equivalent of a macrophage within the CNS.[17,21] Their activation within the CNS in response to peripheral and central nerve injury leads to a complex cascade of events 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.[22]

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.[17] Maladaptive pain can be neuropathic, 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.[23] 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.[14,17] 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.[24] 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).[13,25,26] 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 the assessment and treatment of pain to classify or subdivide the presenting symptoms by the 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 also increases one's risk for the development of chronic pain syndromes.[27] Acute pain is typically short in duration, lasting less than 30 days and 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.[28]

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 79-1).[28,29] 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.[30]

TABLE 79-1

Characteristics of Acute and Chronic Pain

Characteristics	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 28 and 29.

Cancer Pain

1 2 4 Pain associated with potentially life-threatening conditions is often called malignant pain or cancer pain.[32] 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, anticancer, radiation, and surgical incisions), or as a result of diagnostic procedures (eg, biopsy).[32] 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).[33] 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. Additional information about cancer pain can be found in Chapter 150, "Supportive Care."

CLINICAL PRESENTATION

2 4 A patient-oriented approach is essential, and symptom assessment methods for pain should not differ from those used in other conditions.[34] Therefore, a comprehensive history and physical examination is imperative to evaluate underlying diseases and possible other contributing factors.[28] 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.[28] A baseline characterization of pain should be obtained using a symptom assessment mnemonic (eg, OLDCARTS, SOCRATES, SCHOLAR-MAC, or PQRST).[31] Ongoing assessment should occur using a consistent and validated method (ie, Wong Baker Faces Scale, Brief Pain Inventory, Numeric Rating Scale, or Pain-Enjoyment-General Activity Scale).[35]

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, or 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 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, similar to acute pain.

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 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 28.

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 medication use when possible, improve the patient's quality of life, and minimize the adverse effects of analgesics.[33]

Nonpharmacologic Therapy

2 3 5 The use of nonpharmacologic therapies 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 79-2).[36-39] There are numerous complementary and integrative approaches with evidence in pain treatment that include acupuncture, Tai chi, yoga, mindfulness, meditation, relaxation, and biofeedback.[40,41] Complementary and integrative approaches to the treatment of chronic pain are outlined in Table 79-3.[40]

TABLE 79-2

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
- Cognitive behavioral therapy for chronic pain
- Multidisciplinary rehabilitation programs

Data from References 38, 41, and 42.

TABLE 79-3

Complementary and Integrative Approaches for Chronic Pain

Intervention	Description	Evidence	Safety
Tai Chi	• Low impact • Mind body exercise • Started in China as a martial art • Slow mindful movement with attention to breathing and relaxation	• Osteoarthritis • Chronic low back pain (CLBP) • Fibromyalgia	Minor musculoskeletal aches and pains
Yoga	• From India • Blend of meditation, breathing, and physical postures	• Osteoarthritis • Rheumatoid Arthritis • Kyphosis • Fibromyalgia • Low back pain (LBP) • Neck pain	• Similar to musculoskeletal pain associated with physical therapy (PT) • 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	*Acute:* • Post-surgical pain (reduces opioid dose) • Migraine • Acute/subacute LBP	• Low risk for adverse effects • Minor: itching, relaxation, tired • Rare:

		• Ankle sprain *Chronic:* • CLBP • Osteoarthritis (knee, hip, general) • Temporomandibular disorder (TMD) • Headache • Migraine • Neck pain • Shoulder pain • Peripheral neuropathy (diabetic, HIV, Bell's palsy, Carpal Tunnel Syndrome [CTS]) Fibromyalgia	pneumothorax, infections (associated with poor training)
Massage	Soft tissue manipulation	*Acute:* • Postoperative pain *Chronic:* • CLBP • Neck and shoulder pain • Osteoarthritis • Heel pain • Epicondylitis Fibromyalgia	Low risk for adverse effects
Mindfulness, meditation, and relaxation	• A variety of mind-body practices to capitalize on body's own calming response through reducing blood pressure and slower breathing. • 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	*Acute:* • Burn patients (music therapy) • Acute/procedural pain (music therapy, hypnosis, guided imagery) *Chronic:* • LBP (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,	Rare adverse reactions (psychiatric patients, epilepsy, hx of trauma)

		guided imagery) • Rheumatoid arthritis (PCST, guided imagery) • Diabetic neuropathy (mindfulness/meditation) • TMD (relaxation)	
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 • 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 • CTS • TMD	• Musculoskeletal aches and pains • Uncommon serious adverse reactions (cervical artery dissection, stroke, neck injury)

Data from References 38, 40 and 48-51.

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.[43] Psychological techniques (eg, cognitive-behavioral therapy, relaxation training, mindfulness-based stress reduction) are effective in reducing pain-related disability and improving global functioning in patients with numerous types of chronic pain.[40,44] Multidisciplinary rehabilitation programs with both psychological and physical components improve pain, function, and disability.[39,42]

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).[39,45] Transcutaneous electrical nerve stimulation (TENS) may reduce pain by enhancing natural descending inhibitory pathways within the CNS. 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.[46] Although data are conflicting on the efficacy of TENS, with its low risk for adverse effects, it remains a practical option.[45,47]

Pharmacologic Therapy

Appropriate Patient Selection

6 7 8 9 Pharmacologic treatment is often considered the cornerstone of pain management. The potential for benefit with each pharmacologic option, as well as the risk of adverse effects, must be assessed at baseline and periodically 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 at baseline and periodically.

Patient Selection Considerations in Acute or Cancer Pain

9 10 11 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).[52] 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 and specifics regarding its treatment are included in Chapter 150, "Supportive Care." 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 79-4.[53]

TABLE 79-4

Steps for Equianalgesic Opioid Calculation

Step 1. Use the equianalgesic dose chart in Table 79-5 for a first estimate of the dose of the new medication that is equianalgesic to the old medication.

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 79-5 for that opioid and route, converting the dose into equianalgesic dose units. Add the equianalgesic dose units for all medications 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 medication by multiplying the sum obtained in Step 3 by the equianalgesic dose for the new medication and route.

Step 5. Modify the initial estimate based on the clinical situation and the specific medications involved. Factors that enter into this process include the following:

a. Effective analgesia, intolerable adverse effects: calculate the dose of the new opioid as outlined in Steps 1 to 4. Reduce target dose by 25% to 50% to account for lack of cross-tolerance between various opioids.

b. Ineffective analgesia, no intolerable adverse effects: calculate the dose of the new opioid as outlined in Steps 1 to 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%-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 5-6 half-lives).

Step 6. Should PRN dosing of an immediate release medication be necessary for breakthrough 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 the patient frequently following opioid rotation (48-72 hours following dose change).

Data from Reference 53.

TABLE 79-5

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 (numerous)	Naturally occurring	Phase II via glucuronidation/M3G[c] (inactive) and M6G[d] (active)	IM/IV	10	10-20/2

			PO	25	30-40/2
Hydromorphone (Dilaudid, Exalgo, various)	Semisynthetic	Phase II via glucuronidation/H3G (active)[e], H6G[f]	IM/IV	1.5	10-20/2-3
			PO	7.5	
Oxymorphone (Numorphan, Opana)	Semisynthetic	Phase II via glucuronidation/O3G (inactive)[g]	IM/IV	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[h]	10-30/3
Hydrocodone (available as combination, single entity extended release—Hysingla ER[i], Zohydro ER)	Semisynthetic	CYP3A4/norhydrocodone (inactive); CYP2D6/hydromorphone (active)	PO	5-10[h]	30-60/4
Oxycodone (OxyContin, Xtampza)[i]	Semisynthetic	CYP3A4/noroxycodone (active), CYP2D6/oxymorphone (active)	PO	15-30[j]	30-60/2-3
Phenylpiperidines (meperidine-like agonists)					
Meperidine (Demerol, various)	Synthetic	Phase II hydrolysis/meperidinic acid, CYP2B6, CYP3A4, & CYP2C19/normeperidine	IM/IV	75	10-20/3-5
			PO	300[j]; not recommended	
Fentanyl (Sublimaze, Duragesic, Lazanda, Abstral, Fentora, Subsys, OTFC, various)	Synthetic	CYP3A4/norfentanyl (inactive)	IM/IV	0.125[k]	7-15/3-4
			Transdermal, Buccal, transmucosal, sublingual, nasal, nebulized	Variable[l]	
Sufentanil (Sufenta, Dsuvia, various)	Synthetic	CYP3A4/norsufentanil (inactive)	IV/SL	0.030 (SL only)	30/2.5
Diphenylheptanes (methadone-like agonists)					

Methadone (Dolophine, various)	Synthetic	CYP3A4, CYP2B6, CYP2C19, CYP2C9, CYP2D6/EDDP (inactive)[m]	IM/IV	Variable[n] (acute)	
			PO	Variable[n] (acute)	30-60/12-190
Centrally Acting Agents					
Tramadol (Ultram, ConZip, various)	Synthetic	CYP3A4/nortramadol (inactive), CYP2D6/*O*-desmethyltramadol (active)	PO	50-100[g,o,p]	<60/5-7
Tapentadol (Nucynta)	Synthetic	Phase II glucuronidation/tapentadol-o-glucuronide (inactive), CYP2C9 and CYP2C19/*N*-desmethyltapentadol (inactive), CYP2D6/hydroxytapentadol	PO	50-10[h,o,p]	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[h]	15-30/2-3
Butorphanol (Stadol, various)	Synthetic	CYP3A4/hydroxybutorphanol (active), norbutorphanol (inactive)	IM/IV	2	10-20/3-4
			Intranasal	1[h] (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	

[a]The 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).

[b]ER/LA formulations may vary greatly in terms of onset and duration of analgesia. The reader should consult individual prescribing labels.

[c]Morphine-3-glucuronide (accumulates in renal failure).

[d]Morphine-6-glucuronide (accumulates in renal failure).

[e]Hydromorphone-3-glucuronide (accumulates in renal failure).

[f]Hydromorphone-6-glucuronide.

[g]Oxymorphone-3-glucuronide.

[h]Starting dose only (equianalgesia not shown).

[i]FDA approved as unhealthy use deterrent formulation.

[j]Starting doses lower (oxycodone 5-10 mg, meperidine 50-150 mg).

[k]Equivalent PO morphine dose = variable.

[l]For breakthrough pain only. Equianalgesic dose conversion should be avoided for Transmucosal Immediate Release Fentanyl (TIRF) products.

[m]2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidene (EDDP).

[n]The 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.

[o]First day of dosing may administer second dose 1 hour after first dose.

[p]Onset of action may differ for long-acting formulations. Ceiling dose recommendations exist and may differ from immediate release dosing recommendations.

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

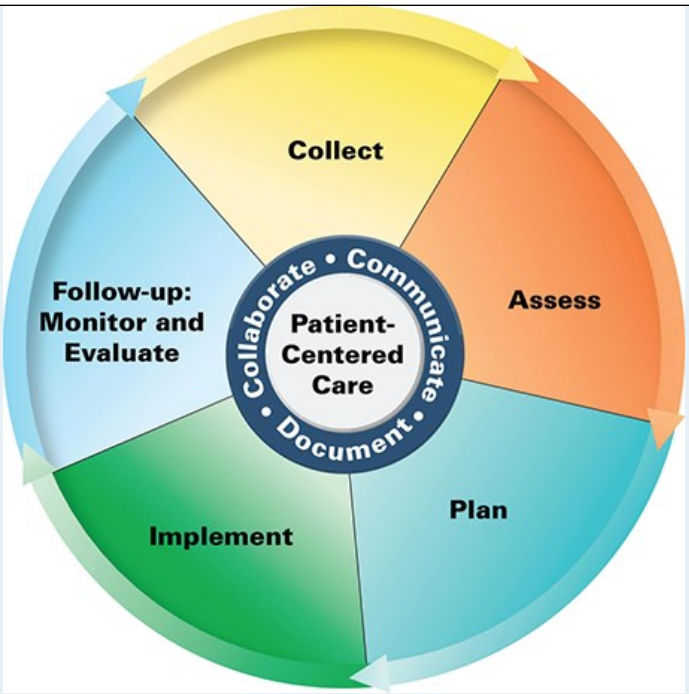
Data from References 53 and 61 and individual product package inserts.

Patient Selection Considerations in Chronic Noncancer Pain

[3,4,5,7,8,9,10,11] 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 assess improvement in the patient's function, while overall tolerability is evaluated. Although long-term opioid therapy can be effective for individual patients in carefully considered situations, limited data exist to support such practice.[37,54] Chronic opioid therapy in this setting requires careful patient selection with judicious attention to risk factors (eg, person or family history of substance use disorder, younger age, male gender, and certain co-occurring mental health conditions) to evaluate the balance between potential benefit of therapy and the potential risks in the individual patient.

PATIENT CARE PROCESS

Patient Care Process for Pain Management



Watch the video of the Patient Care Process for Pain Management.

Collect

- Patient-specific characteristics (eg, age, gender, pregnancy status, race, and ethnicity)
- Pain and symptom-specific history (eg, onset, location, duration, characteristics, aggravating factors, alleviating factors, timing, severity, and impact on activities of daily living)
- Patient history including current and past medications, nonpharmacologic trials, allergies or medication intolerance, and pertinent social history (eg, tobacco, alcohol, or other substance use)
- Family history focusing on symptoms (ie, Rheumatoid arthritis) and social behavior (ie, substance use)
- Objective data including vitals, pertinent labs, targeted physical exam, and urine toxicology results

Assess

- Presence of co-occurring mental health conditions (ie, substance use disorder, depression, anxiety, or bipolar disorder) which may guide treatment decisions
- Data from prescription drug monitoring programs (PDMP), urine toxicology results, and validated risk screening or assessment tools
- Relative or absolute contraindications to the use of opioids, acetaminophen, antidepressants, antiseizure medications, 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
- Patient willingness to engage in nonpharmacologic treatment modalities (eg, physical therapy, counseling, acupuncture, nerve blocks, or surgical interventions)

Plan*

- Patient and symptom-specific lifestyle modification (eg, weight loss, smoking cessation, self-pacing, and pain-trigger avoidance; see Table 79-2)

- Nonpharmacologic treatment modalities (see Table 79-3)
- Pharmacotherapy regimen including dose, route, frequency, and duration (see Table 79-4)
- Pharmacotherapy efficacy (analgesic and functional improvement), toxicity, and ongoing appropriateness using tools such as urine toxicology results, PDMP data, and risk assessment tools (see Table 79-6)
- Patient education on safe use, storage, disposal, and risk mitigation following formal Risk Evaluation and Mitigation Strategies when available (see Table 79-7)

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 timely follow-up as guided by best practices in medication monitoring, following all appropriate regulations

Follow-up: Monitor and Evaluate

- Attainment of treatment goals (eg, improved activity, improved sleep, improved work attendance)
- Presence of adverse effects
- Completion of validated ongoing risk assessment tools
- Frequent review of PDMP as clinically indicated and/or legally required
- Patient adherence to all facets of treatment plan, including nonpharmacologic modalities

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

TABLE 79-6

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
Physical dependence	Withdrawal symptoms upon abrupt discontinuation
Hypogonadism	Fatigue, depression, loss of analgesia, sexual dysfunction, amenorrhea
Sleep	Disrupts sleep–wake cycle, causes dose-dependent rapid eye movement (REM) suppression

Data from References 53 and 61.

TABLE 79-7

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 controlled release or long-acting (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 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 toxicology results 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 pharmacotherapy (ie, methadone or buprenorphine/naloxone) in combination with behavioral therapies.

MME, morphine milligram equivalent; CR, controlled release; LA, long acting.

Data from Reference 37.

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 nonsteroidal anti-inflammatory drugs (NSAIDs) are often preferred first-line therapies in the treatment of mild-to-moderate pain, although the efficacy of acetaminophen has been called into question (Table 79-8).[55,56] The exact mechanism of acetaminophen is not completely understood but likely involves central prostaglandin modulation.[57] The NSAIDs inhibit formation of varying prostaglandins produced in response to noxious stimuli, thereby decreasing neuronal pain transmission received by the CNS.[40] 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.[58,59] In addition, NSAIDs are recommended after nonpharmacologic therapy failure for acute, subacute, and chronic low back pain.[60]

TABLE 79-8

Nonopioid Analgesics

Class and Generic Name (Brand Name)	Approximate Half-Life (h)	Usual Dosage Range (mg)	Maximal Dose (mg/day)
Salicylates			

Acetylsalicylic acid[a]—aspirin (various)	0.25	325-1,000 every 4-6 hours	4,000
Diflunisal (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[a] (Oral: Tylenol, various; Parenteral: Ofirmev)	2-3	325-1,000 every 4-6 hours	4,000[b] 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[c]
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, 3 times per day Patch available: to be applied twice daily to painful area (intact skin only), gel and solution dosing joint specific	150[d]
Propionic acids			
Ibuprofen[a] (Motrin, Caldolor, various)	2-2.5	200-400 every 4-6 hours injectable, 400-800 every 6 hours (infused over 30 minutes)	3,200,[e] 2,400,[e] 1,200[f]
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 500 every 12 hours or 250 every 6-8 hours	1,000[c]

Naproxen sodium[a] (Aleve, various, combined with esomeprazole [Vimovo])	12-17	In some patients, 440 initial[f] 220 every 8-12 hours[f]	660[f]
Pyrrolizine carboxylic acid			
Ketorolac–parenteral (Toradol, various)	5-6	30[g]-60 (single IM dose only)	30[g]–60
		15[g]-30 (single IV dose only)	15[g]–30
		10[g]-30 every 6 hours (IV dose) (max. 5 days)	60[g]-120
Ketorolac—oral, indicated for continuation with parenteral only (various)	5-6	10 every 4-6 hours (max. 5 days, which includes parenteral doses)	40
Ketorolac—nasal spray, indicated for acute, moderate to moderately severe pain		1 spray (15.75 mg) in each nostril every 6-8 hours in adults <65 years of age and weight ≥50 kg	126
		1 spray (15.75 mg) in one nostril every 6-8 hours in adults >65 years of age or 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

[a]Available both as an over-the-counter preparation and as a prescription medication.

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

[c]Up to 1,250 mg on the first day.

[d]Up to 200 mg on the first day.

[e]Some 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.

[f]Over-the-counter dose.

[g]Dose for older patients and those under 50 kg (110 lb).

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

Data from References 53 and 61.

6 7 8 Studies comparing the efficacy of individual NSAIDs have failed to identify differences in efficacy. Therefore, the choice of a particular agent often depends on availability, cost, pharmacokinetics, pharmacologic characteristics, and the adverse effects. 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.[53] 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 and to a lesser extent liver toxicity. Topical NSAIDs may offer similar efficacy as oral NSAIDs with improved safety and tolerability in the treatment of small or superficial joint arthritis.[62] Appropriate patient selection for NSAID therapy is critical to ensure optimal benefit while minimizing potential adverse effects. Several NSAIDs are subject to pharmacogenomic variants.[63]

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. Chronic pain that has a neuropathic component (eg, diabetic neuropathy) often requires co-analgesic therapy. Antiseizure medications (eg, gabapentin, pregabalin, which may decrease neuronal excitability), tricyclic antidepressants and serotonin and norepinephrine reuptake inhibitor antidepressants (eg, 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.[64]

Antiseizure Medications

6 7 8 The antiseizure medications frequently employed for pain are presented in Table 79-9.[65-72] Carbamazepine and oxcarbazepine block voltage-gated sodium channels and potentiate the effects of GABA and are considered the agents of choice for trigeminal neuralgia according to multiple guidelines.[64,66,73,74] 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 medication interactions through induction of CYP3A4, CYP1A2, CYP2B6, CYP2C9, and CYP2C19. Common adverse effects during initiation include dizziness, drowsiness, unsteadiness, nausea, and vomiting and can be avoided with low starting doses. There are rare cases of aplastic anemia and agranulocytosis associated with carbamazepine use, so a complete blood count (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, and atrioventricular block. Hepatic enzymes should be monitored periodically during the treatment for potential elevation.[76]

TABLE 79-9

Co-Analgesics: Antiseizure Medications

Medication	Mechanism of Action	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 medication interactions • Monitor CBC, LFTs, sodium level • Recommended testing *HLA-B*15:02*[a] *HLA-A*31:02* in patients with Asian ancestry • Therapeutic medication levels only indicated for high-dose therapy to avoid toxicity. No correlation between analgesia and serum medication concentration
Gabapentin	Inhibition α2δ subunit of the voltage-gated calcium channel leading to decreased release of excitatory neurotransmitters including glutamate, norepinephrine, and	• PHN[a] • Neuropathic pain • Perioperative	• 100-300 mg steps • Increase every 3-5	• Median dose for response 1,600-2,400 mg/day • Risk for substance use disorder • Requires renal dose adjustment

	substance P	pain	days as tolerated by 100-300 mg increments	
Gabapentin (Gralise)	Refer to gabapentin	PHN[a]	• 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[a] • Restless leg syndrome (RLS)[a]	• 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 (fourth-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	• Initial: 150 mg PO BID • Titrate by 300	• Improved tolerability and less medication interactions compared to CBZ

		pain (specialist setting NICE guidelines)	mg q3 days • Target dose: 300-600 mg BID • Max dose: 1,800 mg/day	• Pharmacogenomic testing recommended in Asian patients due to *HLA-B*15:02* variant
Oxcarbazepine XR	Refer to oxcarbazepine	(See above under oxcarbazepine)	• Initial dose: 600 mg PO daily • Titrate by 600 mg/day weekly • Maximum: 2,400 mg/day	Refer to oxcarbazepine
Pregabalin	Refer to gabapentin	• DPN[a] • Fibromyalgia[a] • Neuropathic pain associated with spinal cord injury[a] • Neuropathic pain • PHN[a] • Perioperative pain	• Initial dose: 150 mg/day in two or three 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[a] • PHN[a]	• 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	• Initial dose: 25 mg PO daily × 1 week • Titrate by 25-50 mg week • Target dose: 50 mg PO BID (migraine ppx) or 200-	• Monitor serum bicarbonate and renal function • Increase risk for kidney stones • Weight loss • Decreased sweating/hyperthermia • Hyperammonemia • Paresthesias • Cognitive dulling

		NICE guidelines)	400 mg/day neuropathic pain	

[a]FDA-approved indication.

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

Data from References 61 and 65.

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 medications interactions and adverse effects compared to carbamazepine.[76] The most common adverse 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] 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.[64,74,77]

Gabapentinoids, including gabapentin and pregabalin, are common antiseizure medications 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.[64-67,74] 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] In general, evidence has not supported the use of gabapentinoids for the prevention of chronic post-surgical pain.[78,79] There are negative findings for pregabalin in acute and chronic sciatica as well as gabapentin and pregabalin for nonspecific low back pain.[80,81]

Gabapentinoids do not, as their name may suggest, alter GABA binding, uptake, metabolism, or degradation though their pharmacology does lead to GABA-mimetic effects. Primary pharmacodynamic effects are due to the inhibition of voltage-gated calcium channels specifically by binding to the presynaptic α2δ subunit. This results in decreased release of excitatory neurotransmitters glutamate, norepinephrine, and substance P.[70]

Common adverse medication effects, namely dizziness and sedation, can be mitigated with slow dose titration. Gabapentinoids may lead to peripheral edema and weight gain which may be dose-limiting adverse effects. All antiseizure medications have been associated with increased risk for suicidal thoughts and behavior. There have been increasing reports of unhealthy gabapentinoid use, which has resulted in some states classifying them as controlled substances and including them in their PDMPs.[82,83] Gabapentionoids are cleared renally and have recommended renal dose adjustments as well as supplemental doses after hemodialysis.[84]

Several neuropathic pain guidelines place lamotrigine as a fourth-line agent or medication for use in a specialist setting.[64,66,74] The mechanism of action of lamotrigine is not entirely known but thought to be related to the 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, and blurred vision. Utilizing lamotrigine is further complicated by the potential for multiple medication 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.[66,74] Additionally, topiramate has been evaluated for radicular low back pain in two small studies with conflicting data on benefits versus risk.[85,86] 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 the carbonic anhydrase enzyme. Topiramate has numerous

warnings and precautions including secondary angle closure glaucoma, metabolic acidosis, hyperammonemia/encephalopathy, kidney stones, oligohidrosis, 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. Dose-related adverse 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 79-10).[61,65,87] In general, the tricyclic antidepressants (TCAs) are often used for the treatment of neuropathic pain. According to the Canadian Pain Society, the Neuropathic Pain Special Interest (NeuPSIG) from the International Association of the Study of Pain, and the European Federation for Neurological Societies (EFNS), TCAs are first-line options for neuropathic pain.[63-65] The NICE guidelines list amitriptyline as a first-line option for neuropathic pain.[64-66] Interestingly, the American Diabetes Association does not list TCAs as first-line because they are not FDA-approved for this indication.[67] Other evidence-based uses of TCAs include low back pain, fibromyalgia, and migraine prophylaxis.[69]

TABLE 79-10

Co-Analgesics: Antidepressants

Medication	Mechanism of Action (MOA)	Role	Dosing	Notes
Tricyclic antidepressants (TCA)				
• Amitriptyline • Desipramine • Imipramine • Nortriptyline	• Inhibit reuptake serotonin and norepinephrine which in turn inhibit 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 AME (including QTc prolongation, orthostatic hypotension, arrhythmias, tachycardia) • Doses >100 mg/day associated with sudden cardiac death • Lowers seizure threshold • Impacted by Pharmacogenomics
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)[a] • Diabetic	• Initial: 30 mg PO daily × 1 week (2 weeks if an older patient) • Target dose: 60 mg PO daily • Maximum dose: 120	• Avoid eGFR <30 mL/min (0.50 mL/s) • Avoid chronic liver disease or cirrhosis • Hypertension • Hyponatremia

		peripheral neuropathy (DPN)[a] • Fibromyalgia[a] • Chemotherapy-induced neuropathic pain (CINP)	mg/day though limited evidence for doses >60 mg providing additional benefit in pain	• 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[a]	• 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 eGFR <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	• CINP • 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

[b]FDA-approved indication(s).

AME, adverse medication effect.

Data from References 61, 65 and 87.

TCAs exert their effects through inhibition of serotonin and norepinephrine reuptake that enhances the descending inhibitory pain pathway, often at doses significantly less than used for the treatment of depression.[69] Additionally, TCAs interact with and inhibit acetylcholine muscarinic receptors, alpha-adrenergic receptors, histamine-1 receptors, and voltage-gated sodium channels, all of which contribute to their many adverse effects.[88,89] Notably, TCAs can be divided into two 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.[70] TCAs are also impacted by pharmacogenomic variants though existing guidelines focus on the role of TCAs for depression with a small section discussing neuropathic pain (see Personalized Pharmacotherapy section).[90]

The major downfall with TCAs is their adverse-effect profile, as they are associated with 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.[91] There are varying recommendations regarding electrocardiogram monitoring with TCAs but may be appropriate in patients greater than or equal to 40 to 50 years of age prior to starting and periodically during continued use.[70,91] 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 major depressive disorder (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.[60] 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.[68,92-96] Duloxetine and venlafaxine are considered first-line options for neuropathic pain according to several neuropathic pain guidelines.[64-67,73] Milnacipran is FDA-approved for fibromyalgia syndrome only.[97]

More likely adverse 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, transient elevations in blood pressure should be anticipated. Therefore, it is important to ensure optimal blood pressure control prior to initiation and ongoing monitoring 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.[98] There are no agreed upon recommendations for QTc monitoring with venlafaxine. All SNRIs have liver and renal considerations; however, the specific criteria vary among 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.[99]

Skeletal Muscle Relaxants

6 7 8 Skeletal muscle relaxants (SMRs) are composed of antispasmodic and antispasticity medications (Table 79-11).[61,100-104] Diazepam and Tizanidine have properties of both categories. Spasticity and spasms have several differences including etiology, symptoms, and causes.[105]

TABLE 79-11

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 TID • 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 four times daily	• Meprobamate (a barbiturate) is primary metabolite and has physical dependence potential • Schedule IV controlled substance

				• Withdrawal syndrome • Respiratory depression with opioids, benzodiazepines, or barbituates • Metabolized by CYP2C19 which has genetic variabilities
Chlorzoxazone	Antispasmodic	Works in spinal cord and subcortical areas of brain by inhibiting multisynaptic reflex arcs	• Initial: 250-500 mg three to four times daily • Maximum dose: 750 mg three to four 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 • Older patients: 5 mg dose with less frequent doses • Doses used in fibromyalgia 10 mg QAM, 20 mg QHS	• Anticholinergic effects • Avoid in older patients • Caution in patients with cardiac conduction/arrhythmias • Avoid closed angle glaucoma • Hepatic dose adjustments
Diazepam	Antispasmodic/antispasticity	Postsynaptic inhibition of GABA neurons in spinal cord	Adults: 2-10 mg three to four times daily	• Long half-life • Avoid in older patients and those renal/hepatic impairment • Withdrawal with abrupt discontinuation
Methocarbamol	Antispasmodic	Unknown, sedative properties	• Initial: 1,500	• Urine discoloration

			mg PO four times daily × 2-3 day • Then: 750-1,000 mg PO four times daily	• Respiratory depression with opioids, benzodiazepines, or barbiturates
Metaxalone	Antispasmodic	Unknown, sedative properties	800 mg PO three to four 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 q6-8 h • Maximum: 36 mg/day	• Hypotension • Hepatotoxicity • Tablets and capsules not bioequivalent • Withdrawal syndrome with abrupt discontinuation

Data from References 61 and 105.

Spasticity involves an upper motor neuron disorder.[105] Symptoms include stiffness, hypertonicity, and hyperreflexia.[105] Causes of spasticity include multiple sclerosis, cerebral palsy, spinal cord injury, traumatic brain injury, and post-stroke syndrome.[105] 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 Ca^{2+} and K^+ channels located pre- and postsynaptically. 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, and nausea are possible adverse effects, with the most concerning being associated with baclofen as hallucinations or seizures may occur during withdrawal with abrupt discontinuation. Therefore, baclofen must be tapered slowly.[105] Baclofen also requires dose adjustment for decreased renal function.[106]

Diazepam is not often used for non-cancer pain because of its sedative effects and potential for physical dependence. Its mechanism of action involves 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, namely seizures. Diazepam has a long half-life (20-50 hours for parent and up to 100 for active metabolites) which is problematic especially for older patients. Avoid the use of diazepam in patients with renal or hepatic impairment.[105]

Similar to diazepam, tizanidine has both antispasticity and antispasmodic uses and is a centrally acting α_2-agonist. Presynaptically, 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 and rebound hypertension seen with abrupt discontinuation. 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.[105,107]

Spasms are involuntary contractions of the muscle and antispasmodics treat musculoskeletal conditions and symptoms like jerks, twitches, and cramps.[105,107] Associated causes include musculoskeletal pain, fibromyalgia, mechanical low back pain, sciatica, disc herniation, and myofascial pain.[105] Skeletal muscle relaxants or NSAIDs are recommended as pharmacologic treatment for patients with acute or subacute low back pain.[60] While studies suggest SMRs are associated with a small increase in pain relief, there is no evidence to support improvement in function with SMRs.[60] Importantly, SMRs should be used short-term. If used long-term, SMRs may increase the risk for adverse effects and polypharmacy, particularly in older patients, as many appear (like other medications used to manage pain) on the Beer's List of Potentially Inappropriate Medications for Use in the Elderly from the American Geriatrics Society.[108,109] 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 physical dependence. 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.[105,107]

Chlorzoxazone blocks multisynaptic reflex arcs in the spinal cord and subcortical areas of the brain. Sedation is a common effect and rare adverse effects include hepatotoxicity or GI bleeding. If used chronically, hepatic transaminase monitoring is recommended. Urine discoloration may be experienced and respiratory depression may occur when combined with opioids, benzodiazepines, or barbiturates.[105,107]

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 adverse 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 and those of older age. With mild hepatic impairment, dose adjustments are recommended and cyclobenzaprine should be avoided in those with moderate-to-severe hepatic impairment.[105,107]

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 be avoided. Rare adverse effects of metaxalone include leukopenia, hemolytic anemia, or hepatic transaminase elevation. Again, respiratory depression can occur when combined with opioids, benzodiazepines, or barbiturates.[105,107]

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.[105,107]

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 and NMDA receptors. With orphenadrine, GI irritation may occur and there is a 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 older patients. 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.[105,107]

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).[110,111] According to the NICE osteoarthritis guidelines, topical NSAIDs should be considered for knee or hand OA before a trial of oral NSAIDs.[112] The American College of Rheumatology (ACR) guidelines for hand, hip, and knee OA also strongly recommend topical NSAIDs for knee OA and conditionally for hand OA. Additionally, topical capsaicin may be considered as an adjunct to core treatments for hand and knee osteoarthritis according to the NICE guidelines although ACR conditionally recommends against capsaicin in hand OA, while recommending conditionally for

capsaicin use in knee OA.[58,112] Capsaicin appears in several neuropathic pain guidelines as either second-line, third-line, or fourth-line for various peripheral neuropathic pain syndromes.[64-66,74] Capsaicin activates transient receptor potential vanilloid 1 (TRPV1) channels. There are various over-the-counter and prescription strength products available. 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 several neuropathic pain syndromes 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.[112] Lidocaine is also used topically and works by inhibiting voltage-gated sodium channels. For PHN, one guideline places lidocaine as a first-line option and may even be preferred over other first-line options in older patients when CNS adverse effects are of concern.[63] Other guidelines list topical lidocaine as second-line or fourth-line options for neuropathic pain.[65,66] Table 79-16 includes commonly used topical analgesics.

Emerging Agents

Two agents have received widespread attention 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.[113,114] 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.[115,116]

Ketamine, a non-competitive NMDA 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.[117] Use of this agent should be supervised by clinicians experienced in its use.

Opioid Agents

1 7 8 9 10 11 Opioids are often the next step in the management of acute pain and cancer-related chronic pain (see Chapter 150 for use in cancer pain). This medication class may also be an effective treatment option in the management of chronic noncancer pain; however, this continues to be 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 use disorder or overdose.[118]

Opioid choice should be based on patient acceptance, analgesic effectiveness, as well as pharmacokinetic, pharmacodynamic, and adverse-effect profiles with the attributes provided in Tables 79-5 and 79-12.[53,61]

TABLE 79-12

Dosing Guidelines

Agent(s)	Doses (Use Lowest Effective Dose, Titrate Up or Down Based on Patient Response, Opioid-Tolerant Patients May Need Dose Modification)	Notes
Morphine	PO 5-30 mg every 4 hours[1]	Medication of choice in severe pain
	IM 5-20 mg every 4 hours[1]	Use immediate-release product with SR product to control breakthrough pain in cancer patients
	IV 5-15 mg every 4 hours[1]	Typical patient-controlled analgesia IV dose is 1 mg with a 10-minute lock-out interval

	SR 15-30 mg every 12 hours (may need to be every 8 hours in some patients)	Every 24-hour products available
	Rectal 10-20 mg every 4 hours[1]	
Hydromorphone	PO 2-4 mg every 4-6 hours[1]	Use in severe pain
	XR 8 mg to 64 mg every 24 hours	More potent than morphine; otherwise, no advantages
	IM 1-2 mg every 4-6 hours[1]	
	IV 0.5-2 mg every 4 hours[1]	Typical patient-controlled analgesia IV dose is 0.2 mg with a 10-minute lock-out interval
	Rectal 3 mg every 6-8 hours[1]	Every 24-hour product (Exalgo) available
Oxymorphone	IM 1-1.5 mg every 4-6 hours[1]	Use in severe pain
	IV 0.5 mg every 4-6 hours[1]	No advantages over morphine
	PO immediate-release 5-10 mg every 4-6 hours[1]	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 hours[1]	Manufacturer recommends 5 mg every 12 hours in opioid-naïve patients
		Take ER on empty stomach
Levorphanol	PO 2-3 mg every 6-8 hours[1] (Levo-Dromoran)	Use in severe pain
	PO 2 mg every 3-6 hours[1] (Levorphanol Tartrate)	Extended half-life useful in cancer patients
	IM 1-2 mg every 6-8 hours[1]	In chronic pain, wait 3 days between dosage adjustments
	IV 1 mg every 3-6 hours[1]	
Codeine	PO 15-60 mg every 4-6 hours[1]	Use in mild-to-moderate pain
	IM 15-60 mg every 4-6 hours[1]	Weak analgesic; analgesic prodrug
Hydrocodone	PO 5-10 mg every 4-6 hours[1]	Use in moderate/severe pain
Oxycodone	PO 5-15 mg every 4-6 hours[1]	Use in moderate/severe pain
	Controlled release 10-20 mg every 12 hours	
		Use immediate-release product with controlled-release product to control breakthrough pain in cancer or chronic pain patients

		CR reformulated to deter unhealthy use
Meperidine	IM 50-150 mg every 3-4 hours[1]	Use in severe pain
	IV 5-10 mg every 5 minutes prn[1]	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/hours	Used in severe pain
	IM 50-100 mcg every 1-2 hours[1]	Do not use transdermal in acute pain
	Transdermal 25 mcg/hr every 72 hours	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 minutes 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 minutes after first dose is started, then titrate	
	Intranasal (Lazanda Spray) 100 mcg (one spray) in one nostril. Wait 2 hours prior to redosing	
	Sublingual (Subsys Spray) 100 mcg (1 spray). Wait 4 hours prior to redosing	
	Sublingual (Abstral Tablet) 100 mcg tablets placed sublingually. Must wait 2 hours prior to redosing	
Methadone	PO 2.5-10 mg every 8-12 hours[1]	Effective in severe chronic pain
	IM 2.5-10 mg every 8-12 hours[1]	
		Some chronic pain patients can be dosed every 12 hours
		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 hours[2] (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 patients with physical opioid dependence; parenteral doses not recommended

	PO 25 mg every 4 hours[2] (max. 150 mg daily, for those 25 mg tablet containing 325 mg of acetaminophen)	
Butorphanol	IM 1-4 mg every 3-4 hours[2]	Second-line agent for moderate-to-severe pain
	IV 0.5-2 mg every 3-4 hours[2]	May precipitate withdrawal in patients with physical opioid dependence
	Intranasal 1 mg (1 spray) every 3-4 hours[2]	
	If inadequate relief after initial spray, may repeat in other nostril × 1 in 60-90 minutes	
	Max. 2 sprays (one per nostril) every 3-4 hours[2]	
Nalbuphine	IM/IV 10 mg every 3-6 hours[2] (max. 20 mg dose, 160 mg daily)	Second-line agent for moderate-to-severe pain; may precipitate withdrawal in patients with physical opioid dependence
		Used frequently in low doses to treat/prevent opioid-induced pruritus
Buprenorphine	IM 0.3 mg every 6 hours[2]	Second-line agent for moderate-to-severe pain
	Slow IV 0.3 mg every 6 hours[2]	May precipitate withdrawal in patients with physical opioid dependence
		Transdermal delivery systems (5, 7.5, 10, 15, 20 mcg/hr) available for every 7 day administration. Detailed manufacturer dosing conversion recommendations exist
		Buccal delivery system (75, 150, 300, 450, 600, 750, and 900 mcg) available. Detailed manufacturer dosing conversion recommendations exist
		Naloxone may not be effective in reversing respiratory depression
Tramadol	PO 50-100 mg every 4-6 hours[1]	Maximum dose for nonextended-release, 400 mg/24 hr; maximum for extended release, 300 mg/24 hr
	If rapid onset not required, start 25 mg/day and titrate over several days	Decrease dose in patient with renal impairment and in older patients
	Extended release PO 100 mg every 24 hours	
Tapentadol	PO 50-100 mg every 4-6 hours[1]	First day of therapy may administer second dose after the first within 1 hour maximum dose first day 700 mg, max. dose thereafter 600 mg (maximum dose for CR 500 mg)

[1]May start with an around-the-clock regimen and switch to prn if/when the painful signal subsides or is episodic.

[2]May reach a ceiling analgesic effect.

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

transmucosal fentanyl citrate; CR, controlled release; XR, extended release; mcg, microgram; mg, milligram.

Data from References 53, 61, and 119.

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 noceptin (OLR-1), which have variable physiologic effects. Therapeutic activities and adverse 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. Depending on the inherent agonist and antagonist properties, these medications may precipitate opioid withdrawal and pain crisis if initiated in patients with physical MOR dependence or tolerance.[120] Additionally, patients stable on a partial or mixed MOR agonists may exhibit an attenuated response to pure MOR agonists when administered for pain. Efficacy and adverse effects also may further differ among opioid agents because of receptor subtype variability and partially explain why some patients respond differently to certain opioids, specifically MOR agonists.[121] Opioid antagonists may act centrally (eg, naloxone or naltrexone) or be limited to peripheral action only (eg, alyimopan, naloxegol, methylnaltrexone, or naldemedine) (Table 79-13).[61,122]

TABLE 79-13

Central and Peripheral Opioid Antagonists

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

[a]Chronic nonmalignant pain.

[b]Opioid-induced constipation.

[c]Alcohol use disorder.

[d]Opioid use disorder.

[e]Starting doses to be used in cases of opioid overdose.

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.[9,120] While sensations of touch and proprioception are preserved, undesirable adverse effects may increase as the dose is escalated (Table 79-6).[9,120] 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.

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, physical dependence, pruritus, and tolerance are evident in varying degrees with all agents.[120] Tolerance to adverse effects (except to constipation) often develops over time. Some differences exist between the opioids in regards to incidence of adverse 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.[9,53] 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.[33] The relative potency, defined by the equianalgesic dose, of opioids differs greatly (Table 79-5). 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.[53,119]

Although true opioid allergies are rare, Table 79-5 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.[123-125] Although caution is always advised, a decrease in potential cross-sensitivity is thought to exist when moving from one opioid structural class to another.[124] The classes are phenanthrenes (morphine-like agonists), benzomorphans (pentazocine), phenylpiperidines (fentanyl-like agonists), and diphenylheptanes (methadone-like agonists). When considering hypersensitivity cross-reactivity, the mixed agonist–antagonist and partial agonist class acts much like the morphine-like agonists.[125]

8 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 adverse 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 improves 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 chronic noncancer pain, around-the-clock administration schedules can be considered. While rare, as-needed immediate-release opioids may be used in conjunction with ER/LA opioids for times when patients experience significant breakthrough pain (Fig. 79-2). This practice is more common in treatment pain associated with cancer or its treatment.

7 Continuous IV infusion of opioids should be reserved for opioid-tolerant patients.[126,127] 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 adverse effects.[126,128]

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 79-14).[129,130]

TABLE 79-14

Intraspinal Opioids

Agent	Single Dose (mg)	Onset of Pain Relief (min)	Duration of Pain Relief (hr)	Continual Infusion Dose (mg/hr)
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 53, 61, and 130.

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 after 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.[126,127] Analgesia and adverse 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.

Full Mu Opioid Receptor Agonists

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 adverse-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.[37,119] 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.

Adverse 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.[120] Opioid-induced nausea typically subsides over time with continued dosing, although this adverse effect may be incredibly troublesome to patients, especially following surgery.[131] 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.[132] Respiratory depression often manifests as a decrease in respiratory rate (although minute volume and tidal exchange also are affected).[120] End-tidal capnography has become commonplace as a means to monitor opioid-induced respiratory depression, especially in those at increased risk.[133]

10 11 Opioid-induced respiratory depression can be rapidly reversed by the opioid antagonist, naloxone.[120] 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.[134] 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.[37]

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.[135]

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 adverse 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.[53] Therapeutic doses of morphine are not contraindicated in head injury, but medication-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.[120]

Morphine is metabolized to morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G). Whereas M6G contributes to analgesia, M3G may contribute to unwanted neurologic adverse effects. The metabolites are renally cleared and can accumulate in patients with renal impairment, contributing to greater adverse effects.[120] 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). Male patients may present with symptoms of erectile dysfunction, decreased libido, and decreased analgesic efficacy. Females 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.[136] 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.[53,120]

Hydromorphone is more potent than morphine, but its overall pharmacologic profile is similar. Some clinicians believe hydromorphone is associated with fewer adverse effects, especially pruritus, compared with other opioids. However, the research is limited and does not conclusively demonstrate this difference. Oxymorphone is available both orally and parenterally, although it offers no pharmacologic advantage over morphine. 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.[137,138]

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 adverse 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, in particular, infants being fed human milk.[139] Hydrocodone is perhaps the most commonly prescribed opioid 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. Oliceridine, a novel opioid analgesic medication approved for IV use for moderate-severe pain, is classified as a biased opioid agonist. It displays selective mu opioid receptor agonism and is structurally dissimilar from other opioid analgesics. Oliceridine is associated with fewer tolerability concerns than traditional opioids; however, more literature is needed to support this claim. 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 older patients, those with renal dysfunction, or for prolonged treatment durations.[53,140]

Fentanyl is a synthetic opioid structurally related to meperidine but is significantly more potent and faster acting. It can be administered parenterally, transmucosally, sublingually, intranasally, and transdermally.[9,120] Numerous fentanyl-like agents exist including remifentanil, alfentanil, and sufentanil. Remifentanil and alfentanil are limited to use as part of general anesthesia, whereas sufentanil can be used for acute pain as a sublingual tablet in medically supervised settings.[141]

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.[120,142] These properties may prove useful in the treatment of neuropathic and chronic pain. However, few trials have thoroughly evaluated methadone's risks versus benefits.[142,143] Epidemiologic studies suggest an increased 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.[132] Recommendations exist for specific echocardiogram monitoring for methadone.[143] 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-live.[143] Thus, given the risks, methadone should be reserved to specialists with experience in its use.

Mixed Opioid Agonist–Antagonists

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.[120] Agents in this class are considered to less physical dependence 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.[144]

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.[145] 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. While buprenorphine's use for opioid use disorder previously required a special DEA license to prescribe, practitioners may now bypass this training requirement and obtain a waiver under the Controlled Substances Act by submitting a letter of intent to the Substance Abuse and Mental Health Services Administration (SAMHSA). The decrease in requirements for prescribing buprenorphine for OUD expands access to treatment.[146]

Central-Acting Opioids

Tramadol and tapentadol are the only centrally acting opioids available in the United States. Tramadol binds to MOR receptors and inhibits the reuptake of serotonin, and to a lesser extent, norepinephrine.[147] 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 adverse-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. Seizure risk, as well as risk of hypoglycemia and hyponatremia, may be elevated in patients taking tramadol.[147,148] 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).[149,150] Tapentadol is also associated with less physical dependence over time when compared with morphine and pentazocin.[151]

Opioid Antagonists

11 The opioid antagonist naloxone binds competitively to opioid receptors but does not produce an analgesic or opioid adverse 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 substance use disorder treatment, while naloxegol, naldemedine, and methylnaltrexone are peripherally acting only and used for opioid-induced constipation.[122]

11 With the growing prevalence of heroin and fentanyl analogs overdoses, healthcare providers are increasingly being called upon to assist in the prevention of these deaths. Many states have legislation in place that allow pharmacists to provide expanded access to naloxone which may be administered intranasally in addition to the traditional intravenous or intramuscular formations.[152] Further discussion of naloxone education, administration, and monitoring is provided in Chapter 85, "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, and physical dependence. Tolerance is the reduction of medication effect over time as a result of exposure to the agent.[120] 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.[153] The mechanism or true clinical impact of this phenomenon is not understood.

Opioid physical dependence is characterized by an abstinence syndrome following administration of an antagonist medication or abrupt dose reduction or discontinuation of an opioid.[120,121] Clinicians must understand that physical dependence and tolerance are not equivalent to substance use disorder, and with chronic opioid use, physical dependence is expected.[121]

A baseline assessment and ongoing evaluation of patient behaviors is critical to mitigate risks of chronic opioid therapy and to balance effective pain management and patient safety.[154,155] Risk for opioid use disorder is associated with a family history of a substance use disorder, and/or underlying psychiatric diagnoses. Modifications to the treatment plan, which should be stratified based on patient risk, include baseline and random urine toxicology results, patient–provider treatment agreements, pill counts, a smaller prescription supply, and regular assessment of use behaviors. Table 79-7 outlines the CDC's guidelines to assist clincians.[156] Combining these approaches with regular and ongoing assessments of pain and functionality may result in improved outcomes. Chapter e84, "Introduction to Substance Use Disorders" contains additional information.

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).[9,121] 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 adverse-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 79-15).[130,157,158] 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.[65] 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.[157] This syndrome is called LAST (local anesthetic systemic toxicity).[159] 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 79-15

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

[a]Unless otherwise indicated, values are for infiltrative anesthesia.

[b]Epidural administration.

Data from Reference 61.

TABLE 79-16

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	PHN, DPN	Transient	• Apply 1-4 patches to affected	• Administer under supervision of

(Qutenza)		receptor potential vanilloid 1 (TRPV1) receptor agonist	area for 60 minutes (PHN) or 30 minutes (DPN) • Cleansing gel must be used on application site following patch removal • Repeat no more frequently than q3 months • Max: 4 patches	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, also available in 4% over the counter)	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 adverse 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	
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 61.

SPECIAL POPULATIONS

6 9 Some patients are at a higher risk for under-treatment because of potential inability to communicate or rate their pain (eg, infants, noncommunicative adults, or those with dementia). 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) are 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.[160]

In addition, those living with chronic, debilitating, and life-threatening illnesses need specialized pain control and care that is palliative in nature.[158] 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.[161,162]

PERSONALIZED PHARMACOTHERAPY

6 8 9 Pharmacogenomics is one factor that can impact medication response, and pharmacogenomic differences can contribute both to a lack of response (analgesia) and toxicity (adverse effects).[163] Guidance is available for prescribing and dosing certain NSAIDs, opioids, and antidepressants that are used in pain management when pharmacogenomic information is available.[63,90,164] However, guidance is not available on when to use pharmacogenomic testing in pain management as it is not a routine practice. Pharmacogenomic testing may be considered in polypharmacy, high-risk patients, potential for significant adverse effects, and medications with specific dosing considerations.[165,166]

Several NSAIDs are metabolized by CYP2C9 and impacted by pharmacogenomic variability. NSAIDs involved include celecoxib, flurbiprofen, ibuprofen, meloxicam, and piroxicam. Those that are intermediate or poor metabolizers of CYP2C9 are at increased risk of adverse effects due to reduced metabolism. Dosing recommendations vary depending on the phenotype, from use of standard doses to initiation at lower doses or use of alternate NSAIDs not metabolized through CYP2C9 like aspirin, ketorolac, naproxen, or sulindac.[63]

Tricyclic antidepressants are metabolized by CYP2D6 and CYP2C19. While CPIC guidelines exist for TCAs, they are geared toward TCA use in the management of depression, not pain. Since TCAs, when used in pain management, are used at lower doses than used for depression, those that are poor or intermediate CYP2D6 or CYP2C19 metabolizers are less likely to encounter adverse effects, so dose adjustments are not recommended. However, if higher doses of amitriptyline are used for managing pain than the recommendations for depression should be considered.[90]

Other antidepressants used in the management of pain are either partially or significantly metabolized by CYP2D6 though have less clear pharmacogenomic guidance. Duloxetine is metabolized more so by CYP1A2, with some contribution by CYP2D6 to hydroxy metabolites. Venlafaxine is metabolized by CYP2D6 to O-desmethylvenlafaxine. Guidance from the Royal Dutch Association for the Advancement of Pharmacy does not recommend any dose adjustments for duloxetine based on pharmacogenomics as it is not a gene-drug interaction.[167] For venlafaxine in intermediate and poor CYP2D6 metabolizers, there is unclear information if there is an increased risk of adverse effects and thus no firm guidance on how to adjust the dose is provided; alternate recommendations include the use of an alternate antidepressants not impacted by CYP2D6.[168] In CYP2D6 ultrarapid metabolizers, the dose of venlafaxine can be increased by 150% the standard dose; however, if dose adjustment is not effective or leads to adverse effects, then venlafaxine should be avoided.

For patients of Asian ancestry, the FDA recommends testing for *HLA-B*15.02* and HLA-A*31.01 prior to initiation of carbamazepine and *HLA-B*15.02* before starting oxcarbazepine due to the increased risk for life-threatening dermatologic reactions including Steven–Johnson Syndrome (SJS)/toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and maculopapular exanthema (MPE). Those with *HLA-B*15.02* and/or *HLA-A*31.01* positive genotyping should not be started on carbamazepine or if *HLA-B*15.02* do not initiate oxcarbazepine if naïve. Severe dermatologic reactions usually occur within the first 3 months, so if a patient used carbamazepine for 3 months without issue, it can be considered in those that are *HLA-B*15.02* positive or *HLA-A*31.01* positive.[164]

CPIC guidelines cover CYP2D6, mu opioid-receptor-1 (OPRM1), and catechol-o-methyltransferase (COMT) consideration with specific opioids.[169] Codeine and tramadol are both metabolized by CYP2D6 to active metabolites which are responsible for their analgesic and adverse effects. In CYP2D6 rapid metabolizers, codeine and tramadol should be avoided due to increased formation of their active forms contributing to significant adverse

effects including respiratory depression. For CYP2D6 poor metabolizers, codeine and tramadol should be avoided to the potential for lack of analgesic benefit. Hydrocodone has less evidence supporting need for dose adjustment in CYP2D6 ultrarapid metabolizers compared to codeine and tramadol. There is some evidence showing decreased metabolism of hydrocodone to hydromorphone in CYP2D6 poor metabolizers but no specific dose adjustments are recommended. Oxycodone and methadone are not thought to be impacted significant by CYP2D6, so no recommendations are provided.

In some cases, genotype results may further help explain cases where patients require higher doses to achieve adequate analgesia. For example, data suggest 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.[170-172] CPIC does not provide recommendations based on COMT or OPRM1 genotypes.[169]

Use of pharmacogenomic testing results may be beneficial in the accurate interpretation of urine toxicology test results when assessing adherence to chronic opioid therapy. For instance, results from a urine toxicology report reveal only parent medication and no expected metabolites, which may be explained by medication interactions, CYP poor metabolizer phenotype, or diversion (pill shaving).

For more information regarding specific medication gene pairs related to pharmacogenomics, 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.[28,34] Pain management efficacy, any change in pain, and medication adverse 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 for using the five "A's" (analgesia, activity, aberrant drug behavior, adverse effects, affect) as key assessment measures for any patient with chronic pain.

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.

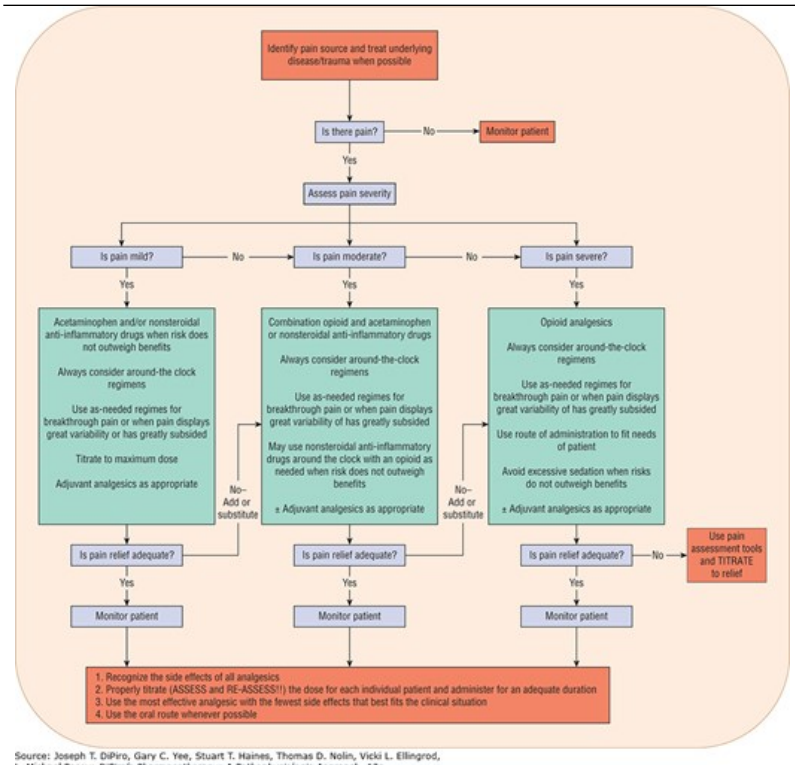
8 9 All opioids can cause constipation. The best management of constipation is prevention and patients should be counseled on the proper intake of fluids and fiber. A stimulant laxative with or without a stool softener should be added with chronic opioid use. For constipation that doesn't respond to 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 the occurrence of a substance use disorder while these agents are employed is essential. Adverse effects of all pharmacologic therapy for pain require judicious anticipation and treatment (Fig. 79-2).

FIGURE 79-2

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



ABBREVIATIONS

ASAM	American Society of Addiction Medicine
CNS	central nervous system
COX-2	cyclooxygenase-2
CPIC	Clinical Pharmacogenomics Implementation Consortium
CYP	cytochrome P450
DOR	delta opioid receptor
GABA	γ-aminobutyric acid
GI	gastrointestinal
IgE	immunoglobulin E
IM	intramuscular
IV	intravenous
KOR	kappa opioid receptor
M3G	morphine-3-glucuronide
M6G	morphine-6-glucuronide
MOR	mu-opioid receptor
NMDA	*N*-methyl-D-aspartate
NSAIDs	nonsteroidal anti-inflammatory drugs
OPRM1	opioid receptor, mu-1 gene subtype
ORL-1	opioid receptor-like receptor (nociceptin receptor)
PCA	patient-controlled analgesia
PNS	peripheral nervous system
SAMHSA	Substance Abuse and Mental Health Services Administration
TENS	transcutaneous electrical nerve stimulation
WHO	World Health Organization

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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. Ɣ-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% to 15% of the total daily dose of opioids

C. 25% to 50% of the total daily dose of opioids

D. 50% to 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 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 who is treated with erythromycin (potent CYP 3A4 inhibitor) for diabetic gastroparesis, having 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?

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 unhealthy use 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 79-3).

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 be proven effective as a ratio of the total daily opioid dose (see Table 79-4).

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 79-8).

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 79-12).

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 79-14).

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 79-11.)

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 79-4).