Chapter 56: Pain Management

INTRODUCTION

- *Pain* is a subjective, unpleasant, sensory, and emotional experience associated with actual or potential tissue damage or abnormal functioning of nerves. It may be classified as acute, chronic, or cancer pain.

PATHOPHYSIOLOGY

Adaptive (Physiologic) Pain

- Nociceptive (eg, from touching something too hot, too cold, or sharp) and inflammatory pain (eg, trauma or surgery) are both adaptive and protective.
- The steps in processing pain are:

  ✔ Transduction—Stimulation of nociceptors.

  - Nociceptors, found in both somatic and visceral structures, are activated by mechanical, thermal, and chemical stimuli. Noxious stimuli may cause release of cytokines and chemokines that sensitize and/or activate nociceptors.

  ✔ Conduction—Receptor activation leads to action potentials that continue along afferent fibers to the spinal cord. Stimulation of large-diameter, sparsely myelinated fibers evokes sharp, well-localized pain. Stimulation of small-diameter, unmyelinated fibers produces aching, poorly localized pain.

  ✔ Transmission—Afferent nociceptive fibers synapse in the spinal cord's dorsal horn, releasing excitatory neurotransmitters (eg, glutamate and substance P). The spinothalamic tract and other pathways bring the signal to the brain's higher cortical structures.

  ✔ Perception—The experience of pain occurs when signals reach higher cortical structures. Relaxation, meditation, and distraction can lessen pain, and anxiety and depression can worsen pain.

  ✔ Modulation—Possible modulating factors include glutamate, substance P, endogenous opioids, γ-aminobutyric acid (GABA), norepinephrine, and serotonin.

- The interface between neurons and immune cells in the central nervous system (CNS) may facilitate maintenance of chronic pain.

Maladaptive (Pathologic) Pain

- Pathophysiologic pain (eg, postherpetic neuralgia, diabetic neuropathy, fibromyalgia, irritable bowel syndrome, chronic headaches) is often described as chronic pain. It results from damage or abnormal functioning of nerves in the CNS or peripheral nervous system (PNS). Pain circuits sometimes rewire themselves anatomically and biochemically, resulting in chronic pain, hyperalgesia, or allodynia.

CLINICAL PRESENTATION

Acute Pain

Symptoms

- Acute pain can be sharp or dull, burning, shock-like, tingling, shooting, radiating, fluctuating in intensity, varying in location, and occurring in a temporal relationship with an obvious noxious stimulus. Infants and older individuals may present differently.

Signs

- Hypertension, tachycardia, diaphoresis, mydriasis, and pallor. In some cases there are not obvious physical signs. There are no laboratory tests for pain.

Chronic Pain

Symptoms

- Symptoms can be very similar to acute pain, and may change over time (ie, sharp to dull). Attention must also be given to emotional factors that alter the pain threshold.

Signs

- In most cases there are no obvious signs. Depression, sleep disturbances, and anxiety are often present. No laboratory tests are diagnostic, but may identify etiology.

DIAGNOSIS

- Pain is always subjective and best diagnosed based on patient description, history, and physical examination. A baseline description of pain can be obtained using a symptom assessment mnemonic (ie, OLDCARTS or SOCRATES). Ongoing assessment should include a consistent and validated scale.

TREATMENT

- Goals of Treatment:

  ✔ Acute pain: pain relief that allows for attainment of defined functional goals.

  ✔ Chronic or noncancer pain: improve level of functioning, decrease pain, reduce medication use if possible, and improve quality of life.

  ✔ Cancer pain: pain relief that enables patients to tolerate diagnostic and therapeutic manipulations and preserves function as much as possible while minimizing adverse effects.

- **Figures 56-1** and **56-2** are algorithms for management of acute pain and pain in oncology patients, respectively.

FIGURE 56-1

Algorithm for acute pain.

image

FIGURE 56-2

Algorithm for cancer pain crisis.

Table adapted from reference 31

image

General Approach

- Multimodal therapy, with concomitant use of different nonpharmacologic and pharmacologic interventions to obtain additive therapeutic effects, should be employed to optimize management.
- Use of pharmacogenomic testing results may be beneficial in making therapeutic decisions among agents, because genetic variability in the CYP450 isoenzymes and opioid receptors may affect response and side effects.

Nonpharmacologic Therapy

- The use of nonpharmacologic therapies should always be considered first-line therapy, either alone or in combination with appropriate analgesics.
- Physical therapy, exercise programs, weight loss, and electroanalgesia as well as complementary and integrative approaches (ie, acupuncture, Tai chi, yoga, mindfulness, meditation, relaxation, and biofeedback).

Pharmacologic Therapy

Nonopioid Agents

Acetaminophen and Nonsteroidal Anti-Inflammatory Drugs

- Initiate treatment with the most effective analgesic with the fewest side effects. See **Table 56-1** for adult dosages of Food and Drug Administration (FDA)–approved nonopioid analgesics.
- **Acetaminophen** and **nonsteroidal anti-inflammatory drugs** (NSAIDS) are often preferred over opioids for mild to moderate pain. The NSAIDs reduce prostaglandins, decreasing the number of pain impulses received by the CNS.
- NSAIDs may be particularly useful for cancer-related bone pain and chronic low back pain. An adequate trial of an NSAID is about 1 month in duration. Chronic use may cause gastrointestinal (GI), cardiac, and renal toxicities.
- Topical NSAIDs may have similar efficacy as oral NSAIDs with improved safety when treating small or superficial joint arthritis.

TABLE 56-1

Nonopioid Analgesics

Class and Generic Name (Brand Name)	Approximate Half-Life (hr)	Usual Dosage Range (mg)	Maximal Dose (mg/day)
Salicylates			
Acetylsalicylic acid[a]—aspirin (various)	0.25	325–1000 every 4-6 hr	4000
Choline and magnesium trisalicylate (various)	9–17	1000–1500 every 12 hr	3000
		750 every 8 hr (elderly)	
Diflunisal (Dolobid, various)	8–12	500–1000 initial, 250–500 every 8–12 hr	1500
Salsalate (various)	1	1000 every 12 hr or 500 every 6 hr	3000
***Para*-aminophenol**			
Acetaminophen[a] (oral: Tylenol, various;	2–3	325–1000 every 4–6 hr	4000[b]

parenteral: Ofirmev)			Dosing for peds lower based on weight
Fenamates			
Meclofenamate (various)	0.8–3.3	50–100 every 4–6 hr	400
Mefenamic acid (Ponstel)	2	Initial 500, 250 every 6 hr (max. 7 days)	1000[c]
Pyranocarboxylic acid			
Etodolac (various) (immediate release)	7.3	200–400 every 6–8 hr	1000 (1200 with extended-release product)
Acetic acid			
Diclofenac potassium (Cataflam, various, Flector [patch] Voltaren Gel, Pennsaid [solution])	1.9	In some patients, initial 100, 50 three times per day	150[d]
		Patch available: to be applied twice daily to painful area (intact skin only), gel and solution dosing joint specific	
Propionic acids			
Ibuprofen[a] (Motrin, Caldolor, various)	2–2.5	200–400 every 4–6 hr injectable, 400–800 every 6 hr (infused over 30 min)	3200[e], 2400[e], 1200[f]
Fenoprofen (Nalfon, various)	3	200 every 4–6 hr	3200
Ketoprofen (various)	2	25–50 every 6–8 hr	300
			(200 with extended-release product)
Naproxen (Naprosyn, Anaprox, various)	12–17	500 initial	1000[c]
		500 every 12 hr or	
		250 every 6–8 hr	
Naproxen sodium[a] (Aleve, various, combined with esomeprazole [Vimovo])	12–17	In some patients, 440 initial[f], 220 every 8–12 hr[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 hr (IV dose) (max. 5 days)	60[g]–120
Ketorolac—oral, indicated for continuation with parenteral only (various)	5–6	10 every 4–6 hr (max. 5 days, which includes parenteral doses)	40
		In non-elderly patients, initial oral dose of 20	126
Ketorolac—nasal spray, indicated for acute, moderate to moderately severe pain		1 spray (15.75 mg) in each nostril every 6–8 hr in adults <65 years and weight ≥50 kg	
Pyrazols			
Celecoxib (Celebrex)	11	Initial 400 followed by another 200 on first day, then 200 twice daily (note some recommend maintenance doses of 200 mg/day due to cardiovascular concerns)	400

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

[b]Food and Drug Administration maximum dose. OTC maximum dose 3000 mg daily. Lower with weight-based dosing in pediatric patients.

[c]Up to 1250 mg on the first day.

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

[e]Some individuals may respond better to 3200 mg as opposed to 2400 mg, although well-controlled trials show no better response; consider risk versus benefits when using 3200 mg/day.

[f]Over-the-counter dose.

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

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

Anticonvulsants

- Anticonvulsants **carbamazepine** and **oxcarbazepine** block voltage-gated sodium channels and potentiate the effects of GABA and are considered the drugs of choice for trigeminal neuralgia (**Table 56-2**).

  ✔ Common side effects during initiation include dizziness, drowsiness, unsteadiness, nausea, and vomiting and can be avoided with low starting doses.

  ✔ Serious dermatologic reactions can occur, including toxic epidermal necrolysis and Stevens–Johnson syndrome (SJS). The risk of dermatological adverse effects is higher in patients who come from Asian descent with an inherited variant, HLA-B*1502, so in at-risk ethnicities, patients should be tested for this allele before initiation of carbamazepine.

  ✔ Cardiovascular effects include hyper/hypotension, congestive heart failure, edema, arrhythmias, atrioventricular block. Elevation in hepatic enzymes should be monitored periodically during treatment.

  ✔ The primary metabolic pathway for carbamazepine is CYP3A4. Additionally, carbamazepine autoinduces its own metabolism, making titration difficult also resulting in many drug–drug interactions through induction of CYP3A4, CYP1A2, CYP2B6, CYP2C9, and CYP2C19.

✔ Oxcarbazepine is the keto-derivative of carbamazepine which has similar adverse reactions.

- Gabapentinoids, including **gabapentin** and **pregabalin**, are commonly used for treating neuropathic pain. Pharmacologically they decrease release of excitatory neurotransmitters glutamate, norepinephrine, and substance P.

  ✔ Common adverse effects, namely dizziness and sedation, can be mitigated with slow dose titration.

  ✔ All anticonvulsants are associated with increased risk for suicidal thoughts and behavior. Recent reports of misuse and abuse, resulted in them being controlled substances.

- **Lamotrigine** is a fourth-line agent for use in a specialist setting due to risk of life-threatening rash requiring increased monitoring and careful dose titration (**Table 56-2**).

  ✔ Additional side effects include dizziness, nausea, headache, insomnia, somnolence, fatigue, rhinitis, abdominal pain diplopia, ataxia, and blurred vision.

- **Topirmate** is also listed as a fourth-line agent for migraines and low back pain.

TABLE 56-2

Co-analgesics: Oral Anticonvulsants

Medication	Dosing	Notes
Carbamazepine and carbamazepine XR	Initial dose: 100 mg twice daily Titrate dose by 100 mg twice daily Target dose: 300–900 mg/day Maximum dose: 1200 mg/day	Significant drug–drug interactions Monitor CBC, LFTs, sodium level Recommended testing HLA-B[a]1502 in patients with Asian ancestry Therapeutic drug levels only indicated for high-dose therapy to avoid toxicity. No correlation between analgesia and serum drug concentration
Gabapentin	100–300 mg steps Increase every 3–5 days as tolerated by 100–300 mg increments	Median dose for response 1600–2400 mg/day Risk of misuse/abuse Requires renal dose adjustment
Gabapentin (Gralise)	Take once daily with evening meal Day 1: 300 mg Day 2: 600 mg Day 3–6: 900 mg Days 7–10: 1200 mg Days 11–14: 1500 mg Day 15: 1800 mg Maximum dose: 1800 mg/day	Refer to gabapentin
Gabapentin enacarbil	Initial dose: 600 mg every morning × 3 days Titrate dose: 600 mg twice daily Maximum dose: 1200 mg/day	Refer to gabapentin
Lamotrigine	Initial 25 mg daily Titrate every 2 weeks to 50 mg/day, 100 mg/day, and 200 mg/day Maximum dose: 400 mg/day	Stevens–Johnson syndrome

Oxcarbazepine	Initial: 150 mg BID Titrate by 300 mg every 3 days Target dose: 300–600 mg twice daily Max dose: 1800 mg/day	Improved tolerability and less drug–drug interactions compared to CBZ
Oxcarbamazepine XR	Initial dose: 600 mg daily Titrate by 600 mg/day weekly Maximum: 2400 mg/day	Refer to oxcarbazepine
Pregabalin	Initial dose: 150 mg/day in 2 or 3 divided doses Titrate dose by 300 mg/day at 1 week Maximum dose: varies by indication. Overall 600 mg/day	Refer to gabapentin
Pregabalin CR	Initial dose: 165 mg daily Maximum dose: 330 mg/day (DPN) or 330–660 mg/day (PHN)	Refer to gabapentin
Topiramate and Topiramate XR	Initial dose: 25 mg daily × 1 week Titrate by 25–50 mg week Target dose: 50 mg twice daily (migraine) or 200–400 mg/day neuropathic pain	Monitor serum bicarbonate and renal function Increase risk for kidney stones Weight loss Decreased sweating/hyperthermia Hyperammonemia

[a]FDA-approved indication.

DPN, diabetic peripheral neuropathy; PHN, postherpetic neuralgia.

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

Antidepressants

- **Tricyclic antidepressants** (TCAs) are often used for the treatment of neuropathic pain (**Table 56-3**) and some guidelines list them as first line.
- **Duloxetine, venlafaxine**, and **milnacipran** are serotonin norepinephrine reuptake inhibitors (SNRIs) that have evidence to support their use in various chronic pain syndromes.

TABLE 56-3

Co-analgesics: Antidepressants

Medication	Role	Dosing	Notes
Tricyclic antidepressants (TCAs)			
Amitriptyline Desipramine Imipramine Nortriptyline	Fibromyalgia Low back pain Migraine prophylaxis Neuropathic pain	Initial: 10–25 mg at bedimte Titrate by 10–25 mg every 3–7 days Maximum: 150 mg	Secondary amines (desipramine, nortriptyline) less anticholinergic activity = less ADE Multiple cardiac ADE (including QTc prolongation, orthostatic hypotension, arrhythmias, tachycardia) Doses >100 mg/day associated with sudden cardiac death Lowers seizure threshold
Serotonin norepinephrine reuptake inhibitors (SNRIs)			
Duloxetine	Chronic musculoskeletal pain (low back pain [LBP], osteoarthritis)[a] Diabetic peripheral neuropathy (DPN)[a] Fibromyalgia[a] Chemotherapy-induced neuropathic pain (CINP)	Initial: 30 mg daily × 1 week (2 weeks if elderly) Target dose: 60 mg daily Maximum dose: 120 mg/day though limited evidence for doses >60 mg providing additional benefit in pain	Avoid CrCl <30 mL/min (0.50 mL/sec) Avoid chronic liver disease or cirrhosis Hypertension Hyponatremia Increased risk of bleeding (GI and CNS)
Milnacipran	Fibromyalgia[a]	Day 1: 12.5 mg daily Days 2–3: 12.5 mg BID Days 4–7: 25 mg BID Then increase to 50 mg BID Target dose: 100 mg/day Maximum dose: 200 mg/day	Avoid CrCl <30 mL/min (0.50 mL/sec) Caution with severe hepatic impairment Increase risk for bleeding
Venlafaxine	CINP DPN Fibromyalgia LBP Migraine prophylaxis Painful polyneuropathy Tension-type headache	Initial: venlafaxine SA 37.5 mg daily Titrate: by no more than 75 mg/day every 4 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

[a]FDA-approved indication(s).

ADE, adverse drug event; GI, gastrointestinal; and CNS central nervous system.

Skeletal Muscle Relaxants

- Skeletal muscle relaxants (SMRs) include antispasmodic and antispasticity medications (**Table 56-4**).
- Medications used for spasticity include **baclofen**, **dantrolene**, **diazepam**, and **tizanidine**.
- Antispasmodics include **carisoprodol**, **chlorzoxazone**, **cyclobenzaprine**, **diazepam**, **metaxalone**, **methocarbamol**, **orphenadrine**, and **tizanidine**.

TABLE 56-4

Skeletal Muscle Relaxants

Medication	Dosing	Notes
Baclofen	Initial: 5 mg 3 times daily Titrate: every 3 days to effect Maximum: 80 mg/day	Withdrawal syndrome (hallucinations, seizures) Respiratory depression Requires renal dose adjustment
Carisoprodol	250–300 mg 4 times daily	Meprobamate (a barbiturate) is primary metabolite and has abuse potential Schedule IV controlled substance Withdrawal syndrome Respiratory depression with opioids, benzodiazepines, or barbiturates Metabolized by CYP2C19 which has genetic variabilities
Chlorzoxazone	Initial: 250–500 mg 3–4 times daily Maximum dose: 750 mg 3–4 times daily	Rare hepatotoxicity Urine discoloration Respiratory depression when combined with opioids, benzodiazepines, or barbiturates
Cyclobenzaprine	Initial: 5 mg 3 times daily Titrate: increase to 7.5–10 mg 3 times daily × 2–3 weeks Elderly: 5 mg dose with less frequent doses	Anticholinergic effects Avoid in elderly Caution in patients with cardiac conduction/arrhythmias Avoid closed angle glaucoma Hepatic dose adjustments
Dantrolene	Initial: 25 mg PO daily × 1 week Titrate dose: 25 mg 3 times daily × 7 days 50 mg 3 times daily × 7 days 100 mg three times daily Maximum dose: 400 mg/day	Black box warning—hepatitis (dose-dependent) Discontinue at 45 days if no benefit
Diazepam	Adults: 2–10 mg 3–4 times daily	Long half-life Avoid in elderly and renal/hepatic impairment Withdrawal with abrupt discontinuation
Methocarbamol	Initial: 1500 mg 4 times daily × 2–3 days Then: 750–1000 mg 4 times daily	Urine discoloration Respiratory depression with opioids, benzodiazepines, or barbiturates
Metaxalone	800 mg 3–4 times daily	Respiratory depression when used with opioids, benzodiazepines, or barbiturates Contraindicated in severe liver/renal impairment
Orphenadrine	100 mg twice daily	Anticholinergic effects Rare aplastic anemia
Tizanidine	Initial: 4 mg Titrate by 2–4 mg every 6–8 hours Maximum: 36 mg/day	Hypotension Hepatotoxicity Tablets and capsules not bioequivalent Withdrawal syndrome with abrupt discontinuation

Topicals

- Topicals address local symptoms while minimizing systemic exposure and risk for adverse effects (**Table 56-5**) and guidelines suggest use of topical NSAIDS before oral treatment for knee or hand osteoarthritis.
- **Capsaicin** is recommended for peripheral neuropathic pain. Capsaicin is more effective if used on a schedule basis, and the burning that may occur with initial application also decreases over time with repeated, scheduled use.
- **Lidocaine** may also be applied topically and may be the treatment of choice when CNS adverse effects are a concern.
- For managing cancer pain, radiopharmaceuticals (eg, **strontium-89** or **samarium**), **corticosteroids, denosumab**, and certain bisphosphonates are useful co-analgesics in treating bone pain.

TABLE 56-5

Topical Analgesics

Medication	Uses	Mechanism of Action	Dosing	Notes
Capsaicin cream (various)	Temporary relief of minor aches and pains of muscles and joints Localized neuropathic pain	Transient receptor potential vanilloid 1 (TRPV1) receptor agonist	Apply 3–4 times daily	Continue scheduled use for 2–4 weeks for best results
Capsaicin 8% patch (Qutenza)	PHN	Transient receptor potential vanilloid 1 (TRPV1) receptor agonist	Apply 1–4 patches to affected area for 60 min Repeat no more frequently than every 3 months Max: 4 patches	Administer under supervision of physician Specific administration directions in packaging information Apply topical anesthetic before applying Monitor blood pressure due to transient increase in blood pressure during application
Diclofenac 1% gel (Voltaren)	Pain of osteoarthritis of joints amenable to topical treatment (knees, hands)	Nonsteroid anti-inflammatory drugs (NSAIDs)	Lower extremities: 4 g four times daily, max. 16 g/day Upper extremities: 2 g 4 times daily, 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 twice daily	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 twice daily	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 hr	Apply to intact skin only
Lidocaine 5% patch (Lidoderm)	PHN	Sodium channel blocker	Apply 1–3 patches to site of pain for 12 hr Maximum: 3 patches	May cut lidocaine patches Apply to intact skin only Severe hepatic impairment increases risk of side effects
Menthol/Methyl salicylate (various)	Minor aches and pains of muscles and joints (simple backache, arthritis, strains, bruises, sprains)	Rubefacient	Apply topically 3–4 times a day to affected area	Do not apply to damaged skin
Trolamine salicylate cream 10% (various)	Aches and pains of muscles and joints (arthritis, simple backache, bruises, sprains, strains)	Rubefacient	Apply topically 3–4 times a day to affected area	Do not apply to damaged skin

Emerging Agents

- **Cannabis** has been primarily studied in the treatment of neuropathic pain; however, the route of administration, dose, and monitoring recommendations are still unclear.
- Guidelines for the use of **ketamine** for treating maladaptive pain syndrome are available, but appropriate dose, duration, and patient selection for chronic pain are still unclear.

Opioid Agents

- Limited data support the safety and efficacy of opioids for chronic noncancer pain. If used it should follow a complete assessment of the pain complaint, the patient's functionality goals, and risk factors for opioid misuse, abuse, diversion, or overdose.
- For definitions of physical dependence, substance abuse, substance dependence, tolerance, and withdrawal, see Chapters 69 and 72.
- The onset of action of oral opioids is about 45 minutes, and peak effect usually is seen in about 1–2 hours.
- Equianalgesic doses, dosing guidelines, and major adverse effects are shown in **Tables 56-6, 56-7, and 56-8**. Equianalgesic doses are only a guide, and doses must be individualized.
- Combining opioid analgesics with alcohol or other CNS depressants amplifies CNS depression and is potentially lethal.
- Partial agonists and antagonists (eg, **nalbuphine**) compete with agonists for opioid receptor sites and exhibit mixed agonist–antagonist activity. They may produce analgesia with fewer side effects.
- Initially give analgesics around-the-clock for acute pain. As pain subsides, as-needed schedules can be used. Around-the-clock administration is also useful for management of chronic pain.
- Patients with severe pain may receive high doses of opioids with no unwanted side effects, but as pain subsides, patients may not tolerate even low doses.

- Most opioid-related itching or rash is due to histamine release from cutaneous mast cells, and is not a true allergic response. When opioid allergies occur, an opioid from a different structural class may be cautiously tried. For these purposes, the mixed agonist–antagonist class behaves most like the morphine-like agonists.
- With patient-controlled analgesia (PCA), patients self-administer preset amounts of IV opioids via a syringe pump electronically interfaced with a timing device. PCA provides better pain control, improved patient satisfaction, and relatively few differences in side effects compared to traditional as needed administration.
- Administration of opioids directly into the CNS (see **Table 56-9**) (eg, epidural and intrathecal/subarachnoid routes) is commonly used by anesthesiology pain consult services for acute pain, chronic noncancer pain, and cancer pain. These methods require very careful monitoring as marked sedation, respiratory depression, pruritus, vomiting, urinary retention, and hypotension can occur. All agents administered directly into the CNS should be preservative-free.
- **Naloxone** is used to reverse respiratory depression, but continuous infusion may be required. Monitor respiratory function for at least 24 hours after a single dose of intrathecal or epidural morphine with standing orders for naloxone if needed.

TABLE 56-6

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 (hr)[b]
Phenanthrenes (morphine-like agonists)					
Morphine (Embeda[j], Arymo ER[j], MorphaBond[j])	Naturally occurring	Phase II via glucuronidation/M3G[j] (inactive) and M6G[l] (active)	IM/IV	10	10–20/2
			PO	25–30	
Hydromorphone (Dilaudid, Exalgo, various)	Semisynthetic	Phase II via glucuronidation/H3G (active)[m], H6G[n]	IM/IV	7.5	10–20/2–3
Oxymorphone (Numorphan, Opana)	Semisynthetic	Phase II via glucuronidation/O3G (inactive)[o]	IM/IV[a]	1	10–20/2–3
			PO	10	
Levorphanol (various)	Semisynthetic	Phase II via glucuronidation/Levorphanol-3-glucuronide (inactive)	PO	Variable	10–20/12–16
Codeine (various)	Naturally occurring	CYP2D6/Morphine (active), Phase II glucuronidation/codeine-6-glucuronide (unknown), CYP3A4/norcodeine (inactive)	PO	15–30[c]	10–30/3
Hydrocodone (available as combination, single entity extended release—Hysingla ER[j], Zohydro ER)	Semisynthetic	CYP3A4/Norhydrocodone (inactive); CYP2D6/hydromorphone (active)	PO	5–10[c]	30–60/4

Oxycodone (OxyContin[j], Xtampza[j], RoxyBond[j] Troxyco ER[j] [oxycodone and acetaminophen])	Semisynthetic	CYP3A4/Noroxycodone (active), CYP2D6/oxymorphone (active)	PO	15–30[d]	30–60/2–3
Phenylpiperidines (meperidine-like agonists)					
Meperidine (Demerol, various)	Synthetic	Phase II hydrolysis/Meperidinic acid, CYP2B6, CYP3A4, and CYP2C19/normeperidine	IM / IV	75	10–20/3–5
			PO	300[d]; not recommended	
Fentanyl (Sublimaze, Duragesic, Lazanda, Abstral, Fentora, Subsys, OTFC, various)	Synthetic	CYP3A4/Norfentanyl (inactive)	IM/IV	0.125[e]	7–15/3–4
			Transdermal, buccal, transmucosal, sublingual, nasal, nebulized	Variable[f]	
				Variable[f]	
Diphenylheptanes (methadone-like agonists)					
Methadone (Dolophine, various)	Synthetic	CYP3A4, CYP2B6, CYP2C19, CYP2C9, CYP2D6/EDDP (inactive)[p]	IM/IV	Variableg (acute)	
			PO	Variableg (acute)	30–60/12–190
Phenylpropanolamines					
Tramadol (Ultram, Rybix, Ryzolt, ConZip, various)	Synthetic	CYP3A4/Nortramadol (inactive), CYP2D6/*O*-desmethyltramadol (active)	PO	50–100[c,h,i]	<60/5–7
Tapentadol (Nucynta)	Synthetic	Phase II glucuronidation/tapentadol-o-glucuronide (inactive), CYP2C9 and CYP2C19/*N*-desmethyltapentadol (inactive), CYP2D6/hydroxytapentadol	PO	50–10[c,h,i]	Within 60/4
Agonist–antagonist derivatives					
Pentazocine (Talwin, various)	Synthetic	Liver/Alcoholic and carboxylic acid derivatives (inactive), pentazocine glucuronide (inactive)	IM	Not recommended	

			PO	50[c]	15–30/2–3
Butorphanol (Stadol, various)	Synthetic	CYP3A4/Hydroxybutorphanol (active), norbutorphanol (inactive)	IM/IV	2	10–20/3–4
			Intranasal	1[c] (one spray)	
Nalbuphine (Nubain, various)	Synthetic	CYP3A4 CYP2C19/Nornalbuphine, 6-ketonalbuphine	IM/IV	10	<15/5
Buprenorphine (Buprenex, Butrans, Suboxone, Belbuca, Subutex, various)	Synthetic	CYP3A4/Norbuprenorphine (active)	IM/IV	0.3	10–20/2–3
			Transdermal	Variable	
			Sublingual		

[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]Starting dose only (equianalgesia not shown).

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

[e]Equivalent PO morphine dose = variable.

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

[g]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.

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

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

[j]FDA approved as abuse-deterrent formulation.

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

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

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

[n]Hydromorphone-6-glucuronide.

[o]Oxymorphone-3-glucuronide.

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

[q]Oral transmucosal fentanyl citrate (OTFC).

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

TABLE 56-7

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
NSAIDs/Acetaminophen/Aspirin	Use lowest effective dose for the shortest duration possible	Used in mild-to-moderate pain
		May use in conjunction with opioid agents to decrease doses of each
		Regular alcohol use and of acetaminophen may result in liver toxicity
		Care must be exercised to avoid overdose when combination products containing these agents are used
		Underlying renal impairment, hypovolemia, and CHF may predispose to nephrotoxicity
Morphine	PO 5–30 mg every 4 hr[a]	Drug of choice in severe pain
	IM 5–20 mg every 4 hr[a]	Use immediate-release product with SR product to control breakthrough pain in cancer patients
	IV 5–15 mg every 4 hr[a]	Typical patient controlled analgesia IV dose is 1 mg with a 10-min lock-out interval
	SR 15–30 mg every 12 hr (may need to be every 8 hr in some patients)	Every 24-hr products available
	Rectal 10–20 mg every 4 hr[a]	
Hydromorphone	PO 2–4 mg every 4–6 hr[a]	Use in severe pain
	XR 8 mg to 64 mg every 24 hr	More potent than morphine; otherwise, no advantages
	IM 1–2 mg every 4–6 hr[a]	
	IV 0.5–2 mg every 4 hr[a]	Typical patient-controlled analgesia IV dose is 0.2 mg with a 10-min lock-out interval
	Rectal 3 mg every 6–8 hr[a]	Every 24-hr product (Exalgo) available

Oxymorphone	IM 1–1.5 mg every 4–6 hr[a]	Use in severe pain
	IV 0.5 mg every 4–6 hr[a]	No advantages over morphine
	PO immediate-release 5–10 mg every 4–6 hr[a]	Use immediate-release product with controlled-release product to control breakthrough pain in cancer or chronic pain patients
	PO extended-release 5–10 mg every 12 hr[a]	Manufacturer recommends 5 mg every 12 hr in opioid-naïve patients
		Take ER on empty stomach
Levorphanol	PO 2–3 mg every 6–8 hr[a] (Levo-Dromoran)	Use in severe pain
	PO 2 mg every 3–6 hr[a] (Levorphanol Tartrate)	Extended half-life useful in cancer patients
	IM 1–2 mg every 6–8 hr[a]	In chronic pain, wait 3 days between dosage adjustments
	IV 1 mg every 3–6 hr[a]	
Codeine	PO 15–60 mg every 4–6 hr[a]	Use in mild-to-moderate pain
	IM 15–60 mg every 4–6 hr[a]	Weak analgesic; analgesic prodrug
Hydrocodone	PO 5–10 mg every 4–6 hr[a]	Use in moderate/severe pain
Oxycodone	PO 5–15 mg every 4–6 hr[a]	Use in moderate/severe pain
	Controlled release 10–20 mg every 12 hr	Use immediate-release product with controlled-release product to control breakthrough pain in cancer or chronic pain patients
		CR reformulated to deter abuse
Meperidine	IM 50–150 mg every 3–4 hr[a]	Use in severe pain
	IV 5–10 mg every 5 min prn[a]	Oral not recommended
		Do not use in renal failure
		May precipitate tremors, myoclonus, and seizures
		Monoamine oxidase inhibitors can induce hyperpyrexia and/or seizures or opioid overdose symptoms
Fentanyl	IV 25–50 mcg/hr	Used in severe pain

	IM 50–100 mcg every 1–2 hr[a]	**Do not use transdermal in acute pain**
	Transdermal 25 mcg/h every 72 hr	Transmucosal for breakthrough cancer pain in patients already receiving or tolerant to opioids
	Transmucosal (Actiq/OTFC Lozenge and Onsolis buccal film) 200 mcg may repeat × 1, 30 min after first dose is started, then titrate	**Always start with lowest dose despite daily opioid intake; product-specific titration recommendations exist**
	Transmucosal (Fentora Buccal Tablet) 100 mcg, may repeat × 1, 30 min after first dose is started, then titrate	
	Intranasal (Lazanda Spray) 100 mcg (one spray) in one nostril. Wait 2 hr prior to redosing	
	Sublingual (Subsys Spray) 100 mcg (1 spray). Wait 4 hr rprior to redosing	
	Sublingual (Abstral Tablet) 100 mcg tablets placed sublingually. Must wait 2 hr prior to redosing	
Methadone[g]	PO 2.5–10 mg every 8–12 hr[a]	Effective in severe chronic pain
	IM 2.5–10 mg every 8–12 hr[a]	Some chronic pain patients can be dosed every 12 hr
		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 hr[b] (max. 600 mg daily, for those 50 mg tablet containing 0.5 mg of naloxone)	Second-line agent for moderate-to-severe pain; may precipitate withdrawal in opiate-dependent patients; parenteral doses not recommended
	PO 25 mg every 4 hr[b] (max. 150 mg daily, for those 25 mg tablet containing 325 mg of acetaminophen)	
Butorphanol	IM 1–4 mg every 3–4 hr[b]	Second-line agent for moderate-to-severe pain
	IV 0.5–2 mg every 3–4 hr[b]	May precipitate withdrawal in opiate-dependent patients
	Intranasal 1 mg (1 spray) every 3–4 hr[b]	
	If inadequate relief after initial spray, may repeat in other nostril × 1 in 60–90 min	

	Max. 2 sprays (one per nostril) every 3–4 hr[b]	
Nalbuphine	IM/IV 10 mg every 3–6 hr[b] (max. 20 mg dose, 160 mg daily)	Second-line agent for moderate-to-severe pain; may precipitate withdrawal in opiate-dependent patients
		Used frequently in low doses to treat/prevent opioid-induced pruritus
Buprenorphine	IM 0.3 mg every 6 hr[b]	Second-line agent for moderate-to-severe pain
	Slow IV 0.3 mg every 6 hr[b]	May precipitate withdrawal in opiate-dependent patients
		Transdermal delivery systems (5, 7.5, 10, 15, 20 micrograms/h) available for every 7 day administration. Detailed manufacturer dosing conversion recommendations exist
	May repeat × 1, 30–60 min after initial dose	Naloxone may not be effective in reversing respiratory depression
Naloxone	IV/IM 0.4–2 mg	When reversing opiate side effects in patients needing analgesia, dilute and titrate (0.1–0.2 mg every 2–3 min) so as not to reverse analgesia
Tramadol	PO 50–100 mg every 4–6 hr[a]	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 the elderly
	Extended release PO 100 mg every 24 hr	
Tapentadol	PO 50–100 mg every 4–6 hr[a]	First day of therapy may administer second dose after the first within 1 hr, maximum dose first day 700 mg, max. dose thereafter 600 mg (maximum dose for CR 500 mg)

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

[b]May reach a ceiling analgesic effect.

CR, controlled release; HCL, hydrochloride; IM, intramuscular; IV, intravenous; ; mcg, microgram; mg, milligram; NSAID, nonsteroidal anti-inflammatory drug; OTFC, Oral transmucosal fentanyl citrate; PO, oral; prn, as needed; SR, sustained release; XR, extended release.

TABLE 56-8

Major Adverse Effects of the Opioid Analgesics

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

TABLE 56-9

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.

Morphine and Congeners (Phenanthrenes)

- Many clinicians consider **morphine** the first-line agent for moderate-to-severe pain. It may be used for pain associated with myocardial infarction, as it decreases myocardial oxygen demand, but this is controversial.

  ✔ Tidal exchange and minute volume can be affected by opioids. Patients with underlying pulmonary dysfunction are at increased risk for respiratory depression, which can be reversed by **naloxone**.

  ✔ Morphine-induced respiratory depression can increase intracranial pressure and cloud the neurologic examination results.

  ✔ Hypovolemic patients are at risk for morphine-induced orthostatic hypotension.

  ✔ Most clinicians avoid morphine in patients with creatinine clearance less than or equal to 30ml/min [0.5 ml/sec] due to accumulation of active metabolites.

- Counsel patients to take the extended-release **oxymorphone** without food, as high-fat meals can greatly increase absorption, increasing risk of toxicity.

- **Hydromorphone** may have fewer side effects, especially pruritus, compared with other opioids and **levorphanol** has an extended half-life and purported NMDA glutamate receptor activity.

- **Codeine**, alone or combined with other analgesics (eg, acetaminophen), is commonly used for mild-to-moderate pain. **Oxycodone** is useful for moderate-to-severe pain, especially when combined with nonopioids.

Meperidine and Congeners (Phenylpiperidines)

- **Meperidine** is less potent and has a shorter duration of action than morphine.

  ✔ With high doses or in patients with renal failure, the metabolite normeperidine accumulates, causing tremor, muscle twitching, and

possibly seizures. In most settings, meperidine offers no advantages over morphine.

✔ Do not combine meperidine with monoamine oxidase inhibitors because severe respiratory depression or serotonin syndrome may occur.

- **Fentanyl**, often used as an adjunct to general anesthesia, is more potent and faster acting than meperidine.

Methadone and Congeners (Diphenylheptanes)

- **Methadone** has extended duration of action. Studies show a growing number of methadone-related deaths. High doses cause cardiac arrhythmias. Do not titrate more frequently than every 5–7 days. Although effective for acute pain, it is used for chronic cancer pain.
- There is a growing number of methadone-related deaths. The equianalgesic dose of methadone may decrease with higher doses of the previous opioid.

Opioid Agonist–Antagonist Derivatives

- This analgesic class may cause less respiratory depression than opioids and may have lower abuse potential than morphine. However, psychotomimetic responses (eg, hallucinations and dysphoria), a limited analgesic effect, and the propensity to initiate withdrawal in opioid-dependent patients have limited their use.
- Buprenorphine is a pharmacologically complex opioid. When used with or without naloxone, for opioid use disorder, a special DEA license is required by the prescriber.

Centrally Acting Opioids

- **Tramadol** and **tapentadol** are indicated for relief of moderate to moderately severe pain.

  ✔ Their side effects are similar to other opioids, although the seizure risk with tramadol may be higher.

Opioid Antagonists

- **Naloxone**, a pure opioid antagonist that binds competitively to opioid receptors, does not produce analgesia or opioid side effects. It reverses the toxic effects of agonist and agonist–antagonist opioids. In some states in the United States, pharmacists are assuming greater roles in administering or dispensing naloxone for patients who have experienced opioid overdoses.
- Opioid antagonists may act centrally (eg, naloxone or **naltrexone**) or be limited to peripheral action only (eg, **naloxegol**, **methylnaltrexone**, **or naldemedine**).
- **Table 56-10** lists dosing for central and peripheral opioid antagonists.

TABLE 56-10

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)	Systemic	Opioid reversal	IV, IM, IN	0.4–2 mg[e]	Onset 1–2 (IV) minutes, 2–5 (IM) minutes Half-life 0.5–1.3 hr
Methylnaltrexone (Relistor)	Peripheral	Cancer and CNMP[a] OIC[b]	SC (both), PO (CNMP)	Variable	Renal dose adjustments
Naltrexone (ReVia, Vivitrol)	Systemic	AUD[c], OUD[d]	PO, IM	12 mg Qday-Q12 (PO) 380 mg q4weeks (IM)	Opioid free for 7–10 days before initiation
Alvimopan (Entereg)	Peripheral	Postoperative ileus	PO	12 mg PO 30 min–5 hr before surgery then 12 mg PO BID starting day after surgery for maximum of 7 days	Limited to 15 doses
Naloxegol (Movantik)	Peripheral	CNMP[a], OIC[b]	PO	12.5–25 mg qday 1 hour before, 2 hours after a meal	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.

Regional Analgesia

- Regional analgesia with local anesthetics (**Table 56-11**) is useful for both acute and chronic pain. Anesthetics can be positioned by injection (eg, in the joints, epidural or intrathecal space, nerve plexus, or along nerve roots), or applied topically.
- High plasma concentrations of local anesthetics can cause dizziness, tinnitus, drowsiness, seizures, and respiratory arrest. Cardiovascular effects include myocardial depression, heart block, hypotension, bradycardia, and cardiac arrest. Skillful application, frequent administration, and specialized follow-up are required.

TABLE 56-11

Local Anesthetics[a]

Agent (Brand Name)	Onset (min)	Duration (hr)
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.

SPECIAL POPULATIONS

- The elderly and young are at higher risk of undertreatment. In these populations, it is important to monitor signs (eg, heart rate) and to talk with parents or caregivers.
- Those with chronic, debilitating, and life-threatening illnesses need specialized pain control and palliative care.
- Pharmacologic therapy of cancer pain (see **Figure 56-2**) should be coupled with psychological, surgical, and supportive therapies using an interdisciplinary approach. Continuous assessment of pain response, side effects, and behavior are required.

EVALUATION OF THERAPEUTIC OUTCOMES

- Pain intensity, pain relief, and medication side effects must be assessed regularly. The frequency of assessment depends on the type of pain, analgesic used, route of administration, and concomitant medications. Postoperative pain and acute exacerbations of cancer pain may require hourly assessment. Chronic nonmalignant pain may need only daily (or less frequent) monitoring. Quality of life must be assessed regularly.

- The four A's (eg, ***a***nalgesia, ***a***ctivity, ***a***berrant drug behavior, and ***a***dverse effects) are key assessment measures for patients with chronic pain.
- Patients taking opioids should be counseled on proper intake of fluids and fiber, and a stimulant laxative should be added with chronic opioid use. Peripherally acting mu-opioid receptor antagonists (PAMORAs) are available for treating opioid-induced constipation.
- Concomitant use of CNS depressants should be avoided with opioid analgesics.

See Chapter 77, Pain Management, authored by Chris M. Herndon, James B. Ray, and Courtney M. Kominek, for a more detailed discussion of this topic.