Section III:

Types of Treatments

A. Pharmacologic Treatment

Treatments for pain can be broadly categorized as pharmacologic and nonpharmacologic. This section of the monograph provides an overview of: 1) a commonly used analgesic classification system, 2) some commonly used analgesic classes and individual drugs, and 3) general principles of pharmacologic treatment.

1. Drug Classifications and Terminology

Pharmacologic treatment is the mainstay of pain therapy. Almost half of individuals who suffer from pain choose a nonprescription analgesic as their initial choice for pain relief.[1] Up to one in five Americans take an over-the-counter or prescription analgesic on a daily basis.[2] As with types of pain, multiple systems for classifying analgesics exist. In the below system, analgesics are broadly categorized as:

- *Nonopioid analgesics (nonopioids)*: acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin and other salicylic acid derivatives
- *Opioid analgesics (opioids)*: mu opioid agonists (i.e., morphine-like agonists) and agonist-antagonist opioids
- *Adjuvant analgesics or co-analgesics:* a diverse group of drugs, with primary indications for conditions other than pain, with analgesic properties relevant to some conditions. Commonly used adjuvant analgesics include antiepileptic drugs (AEDs), tricyclic antidepressants (TCAs), and local anesthetics (LAs).

Variations of this classification system exist,[a] and terminology in the field is also evolving. The term "opioids" has replaced "narcotics," and "co-analgesics" is an alternate term for "adjuvant analgesics."

[a] Because acetaminophen has some, albeit extremely limited, anti-inflammatory properties,[3] some experts consider acetaminophen an NSAID and use the term "NSAIDs" rather than "nonopioids." Other experts disagree with this classification due to the different mechanisms of action and side effects of these drugs.

2. Common Analgesic Agents

a. Nonopioids

i. Mechanism of action and effects

The primary mechanism of action of NSAIDs is inhibition of the enzyme cyclooxygenase (COX), resulting in blockade of prostaglandin synthesis.[4,5] Acetaminophen, another nonopioid, appears to act mostly via a central mechanism.[3,6-7] All nonopioids have anti-inflammatory, antipyretic, and analgesic effects, but the anti-inflammatory effect of acetaminophen is essentially negligible.[8] The analgesic effect of NSAIDs is prompt (minutes to hours), whereas the anti-inflammatory effect may take longer (1-2 weeks or longer).[9] This latter effect can indirectly relieve some pain by reducing tissue swelling.

The relatively recent discovery that COX has at least two isoforms, COX-1 and COX-2, has advanced NSAID pharmacology. COX-1 is constitutively expressed in most normal tissues,[10] but plays an especially important role in the gastrointestinal (GI) tract, kidneys, and platelets; COX-1 primarily produces prostaglandins with beneficial effects (e.g., regulation of blood flow to the gastric mucosa and kidneys).[8,11] In contrast, COX-2 is normally not present but may be induced in response to inflammatory stimuli; COX-2 primarily produces prostaglandins that activate and sensitize nociceptors (see I.B).[b] Nonselective NSAIDs inhibit COX-1 and COX-2, which contributes to both their therapeutic actions and side effects. Agents that selectively inhibit COX-2 were introduced to minimize the risk of GI side effects without compromising analgesic efficacy.[17-18] The "coxibs" affect COX-2 both centrally and peripherally. However, an increased risk of myocardial infarction, stroke, and death has been linked to selective COX-2 inhibitors, and this increased risk of cardiovascular side effects appears to be a class effect of NSAIDs, including nonselective agents.[18a] Rofecoxib and valdecoxib were voluntarily withdrawn from the market in 2004 and 2005, respectively, because of these cardiovascular safety concerns. Celecoxib is still available because its benefits appear to outweigh its potential risks in certain patients.

A third COX isoform, COX-3, recently was identified. There is evidence that inhibition of COX-3 represents the primary central mechanism by which acetaminophen relieves pain.[18b]

[b] The division of function between COX-1 and COX-2 is not perfect. COX-1 produces some prostaglandins that contribute to inflammation.[12] COX-2 is constitutively expressed in some organs (e.g., the kidney) where it produces prostaglandins with protective effects.[13-14]

Table 19. Examples of Nonopioid Analgesics

Chemical Class	Generic Name	Indications	Usual Oral Dosing Interval or Frequency	Dosage Forms and Routes of Administration	Major Side Effects	Comments
Paraaminophenols	Acetamin-ophen	Mild to moderate pain due to multiple causes including head-ache, toothache, muscular aches, backache, menstrual cramps, arthritis, common cold, and flu; fever reduction	q 4-6 h[a]	Multiple oral (e.g., tablets, caplets, powder, elixir, suspensions, liquid); rectal suppositories	Acute overdose: hepatic necrosis (liver damage)[b] Chronic overdose: liver toxicity, nephrotoxicity, thrombocytopenia	Lacks anti-inflammatory effects of NSAIDs, but no adverse effects on gastric mucosa or platelets Analgesic and antipyretic effects comparable to aspirin Useful in patients intolerant of NSAIDs and for fever control in children with flu
Salicylates	Aspirin Diflunisal CMT	Mild to moderate pain due to multiple causes including headache, toothache, sinus pain, muscular aches, bursitis, backache, sprains, arthritis, pain due to fever, cold, flu	ASA: q 4-6 h[a] Diflunisal: q 8-12 h CMT: QD, BID, or TID	Multiple oral (caplet, tablet, gelcap, effervescent tablet, gum, liquid); rectal suppositories	NSAID class effects[c] Diflunisal hypersensitivity: life-threatening reaction that may involve multiple organs	Combination formulations available (aspirin and acetaminophen, and/or caffeine) Diflunisal causes less GI irritation and antiplatelet effects than aspirin
	Trolamine salicylate	Mild muscle or joint pain, such as in inflammatory disease (e.g., RA)	BID, TID, or QID	Topical cream, lotion	Skin peeling	Not for use on acutely inflamed skin or raw, weeping surfaces
Propionic acid derivatives	Ibuprofen	Mild to moderate pain, including pain associated with the common cold, headache, toothache, muscular aches, backache, menstrual cramps, and arthritis; fever reduction	q 4-6 h	Oral (tablets, caplets, geltabs, suspension); rectal suppositories	NSAID class effects Toxic amblyopia	Commonly used NSAID OTC formulations available Combinations with codeine and hydrocodone available Fewer GI effects than other non-selective NSAIDs
	Naproxen	RA, OA, AS, JA, tendonitis, bursitis, gout, primary dysmenorrhea	q 6-12 h	Tablets, oral suspension, delayed-release tablets	NSAID class effects Other: pseudoporphyria	OTC formulations available Delayed-release tablets are NR for initial treatment of acute pain
	Ketoprofen	Signs and symptoms of OA and RA, pain, and primary dysmenorrhea	q 6-8 h; q 24 h for ER form	Capsules, ER capsules	NSAID class effects	OTC formulations available ER capsules NR for treatment of acute pain
	Flurbiprofen	OA, RA	BID, TID, or QID	Tablets	NSAID class effects	
	Oxaprozin	Acute and long-term management of OA and RA	q 24 h	Caplets	NSAID class effects Other: photosensitivity, rash	Long half-life (55 hours), thus can be given once daily
Indoleacetic acids	Indomethacin	Moderate to severe OA, RA, AS; acute gouty arthritis; acute painful shoulder (bursitis and/or tendonitis)	BID, TID, or QID	Oral (capsules, suspension, slow-release capsules) rectal suppositories	NSAID class effects Ocular effects (corneal deposits, retinal disturbances) Exacerbation of Parkinson's disease, epilepsy, or psychiatric disorders	Limited use due to side effects

Table 19. Examples of Nonopioid Analgesics (continued)

Chemical Class	Generic Name	Indications	Usual Oral Dosing Interval or Frequency	Dosage Forms and Routes of Administration	Major Side Effects	Comments
Benzothiazine derivatives (oxicams)	Piroxicam	Acute and long-term management of OA and RA	q 24 h	Capsules	NSAID class effects Insomnia	Single daily dose
	Meloxicam	OA	q 24 h	Tablets	NSAID class effects	Single daily dose
Pyrroleacetic acid derivatives	Diclofenac	OA, RA, AS, primary dysmenorrhea	BID, TID, or QID ER form q 24 h	Tablets, ER tablets	NSAID class effects Other: acute hemolytic anemia, aseptic meningitis, rash Avoid use in patients with porphyria Combination with misoprostol contraindicated in pregnant women	Lower risk of GI effects
	Ketorolac	Short term (<5 days) treatment of moderately severe acute pain that requires analgesia at the opioid level (e.g., postoperative pain)	Varies for parenteral therapy q 4-6 h oral form	Oral (tablets), IV (injector, sterile cartridges)	NSAID class effects Warning indicating potential for serious NSAID side effects if used inappropriately NR for minor or chronic pain	Parenteral form useful when PO NSAIDs are undesirable and for opioid-sparing effect Combined oral and parenteral therapy should not exceed 5 days IV administration provides pain relief comparable to 10 mg of IM morphine
Selective COX-2 inhibitors	Celecoxib	OA, RA, FAP	q 12 or 24 h	Capsules	Most common: HA, URI, dyspepsia NSAID class effects Rare anaphylactoid reactions	Does not inhibit platelet aggregation

Sources: References 8, 19-22, and 27-50.

[a]Some sources (e.g., 2001 Physicians' Desk Reference for Nonprescription Drugs and Dietary Supplements,[22] the American Pain Society's Principles of Analgesic Use in the Treatment of Acute Pain and Cancer Pain,[19] McCaffery and Pasero[23]) list the dosing interval for aspirin and acetaminophen as 4 to 6 hours. Other sources (e.g., Agency for Health Care Policy and Research Acute Pain Management: Operative or Medical Procedures and Trauma Clinical Practice Guideline No. 1)[24] list the dosing interval for these drugs as 4 hours.

[b]Use with caution in certain populations (i.e., patients with chronic alcoholism, liver disease, malnourishment).[19,25-26]

[c]Adverse effects of nonselective NSAIDs as a class include gastrointestinal problems (e.g., dyspepsia, ulcers, perforation, bleeding), liver dysfunction, bleeding due to inhibited platelet aggregation (i.e., "antiplatelet effect"), kidney problems (e.g., renal insufficiency, acute renal failure), hypersensitivity reactions (i.e., aspirin sensitivity), and CNS effects (e.g., attention and memory deficits, headache, dizziness, drowsiness).[19] Recommended monitoring includes standard laboratory tests (e.g., complete blood count, liver and kidney function) and stool guaiac test (for occult blood). NSAIDs are generally contraindicated in patients with a history of asthma, urticaria, or allergic-type reactions after taking NSAIDs, including aspirin.

AS: ankylosing spondylitis; ASA: aspirin; BID; twice daily; CMT: choline magnesium trisalicylate; CNS: central nervous system; COX-cyclooxygenase; ER: extended release; ESRD: end-stage renal disease; FAP: familial adenomatous polyposis; GI: gastrointestinal; HA: headache; HTN: hypertension; IM: intramuscular; IV: intravenous; JA: juvenile arthritis, NR: not recommended; NSAID: nonsteroidal anti-inflammatory drug; OA: osteoarthritis; OTC: over-the-counter; PI: package insert; PO: per os (by mouth); QD: once per day; QID: four times daily; RA: rheumatoid arthritis; TID: three times daily; URI: upper respiratory infection.

ii. Indications and uses

Nonopioids relieve a variety of types of acute and chronic pain (e.g., trauma, postoperative, cancer, arthritis pain) and are especially effective for certain types of somatic pain (e.g., muscle and joint pain, bone/dental pain, inflammatory pain, postoperative pain) (Table 19).[19-21] Acetaminophen and NSAIDs, alone, often relieve mild pain, and some NSAIDs relieve certain types of moderate pain (Table 19).[51] Even for moderate or severe pain that does require an opioid, nonopioids are often added to the regimen for their opioid-sparing effect (i.e., they lower the dose of opioid required).[19] Since nonopioids and opioids relieve pain via different mechanisms, combination therapy offers the potential for improved relief with fewer side effects. Nonopioids do not produce tolerance,

physical dependence, or addiction.[19] Choice of NSAID is influenced by factors including medication tolerance, dosing frequency, and cost.[52]

iii. Routes of administration, formulations, and dosing

Patients usually take nonopioids orally, but other forms (e.g., rectal, topical, parenteral) of some drugs exist.[19] Numerous formulations of acetaminophen and aspirin, as well as some nonselective NSAIDs, are available without a prescription. In addition, some nonopioids are marketed in combination with other drugs (e.g., other nonopioids, opioids, caffeine, sedatives).

Onset and duration of analgesia and, therefore, dosing frequency reflect drug half-life and special formulations (e.g., sustained-release preparations). Some NSAIDs only need to be taken once a day. In contrast to most opioids, all nonopioids have a dosage ceiling.[19] This means that a dose is reached beyond which additional side effects, but not pain relief, can occur. Patient responsiveness to NSAIDs varies greatly, so a patient who has not responded to the maximum therapeutic dose of one NSAID should try another.[19]

iv. Side effects

Inhibition of COX-1 causes some of the side effects of nonselective NSAIDs. Adverse effects of nonselective NSAIDs as a class include GI problems (e.g., dyspepsia, ulcers, perforation, bleeding, liver dysfunction), bleeding (i.e., "antiplatelet effect"), kidney dysfunction, hypersensitivity reactions, and CNS effects.[19] Table 20 summarizes precautions and methods of managing these adverse events.

Despite these shared effects, the side effect profiles of individual drugs do differ (see Table 19). For example, some nonselective NSAIDs (e.g., ibuprofen, naproxen) are less likely than others (e.g., ketoprofen) to cause GI problems. Side effects are generally less likely to occur when drugs are used at low doses or for short periods in appropriately selected patients.[19] In addition, the risk of some side effects can be reduced by protective mechanisms (e.g., coadministration of misoprostol to reduce the risk of gastric ulcer).[19] Therefore, in some clinical circumstances, treatment with a nonselective NSAID is relatively safe and use of a selective COX-2 inhibitor is not necessarily warranted. Conversely, use of a selective COX-2 inhibitor may be preferable in some situations (e.g., preoperative period, bleeding disorder). A warning recently was added to the labeling for all NSAIDs (nonselective NSAIDs as well as selective COX-2 inhibitors) stating that these medications are contraindicated immediately after coronary artery bypass grafting.[18a]

Acetaminophen or a selective COX-2 inhibitor may be an appropriate treatment alternative to nonselective NSAIDs in some patients. Acetaminophen does not damage the gastric mucosa or inhibit platelet aggregation and provides pain relief comparable to that of aspirin.[19] However, acetaminophen has negligible anti-inflammatory activity. In addition, acute or chronic overdose with acetaminophen may cause liver or kidney toxicity, so acetaminophen should be used with caution in patients with certain conditions (e.g., malnutrition, chronic alcoholism, liver disease).[25] Accidental overdosage also may occur in patients taking over-the-counter combination pain relievers containing acetaminophen.

Although product labeling for selective COX-2 inhibitors and nonselective NSAIDs is similar, evidence suggest that coxibs are less likely to cause GI side effects. For example, clinical trial data suggest that celecoxib produces comparable relief of rheumatoid arthritis (RA) pain and inflammation to diclofenac[57] and naproxen,[58] but a lower incidence of endoscopically diagnosed gastroduodenal ulcers. Celecoxib also appears to provide equal symptomatic relief of osteoarthritis (OA) pain to diclofenac but with fewer GI side effects.[59] Other data suggest that, due to its COX-1-sparing effect, celecoxib does not inhibit platelet aggregation.[60] Renal adverse effects are no less likely with COX-2 inhibitors than with nonselective NSAIDs. The decision to use celecoxib in a particular patient is made after weighing the potential advantages and disadvantages, especially the risk of cardiovascular and GI side effects.

b. Opioids

i. Mechanism of action and effects

Opioids bind to opioid receptors in the central nervous system (CNS) to: 1) inhibit the transmission of nociceptive input from the periphery to the spinal cord, 2) activate descending inhibitory pathways that modulate transmission in the spinal cord, and 3) alter limbic system activity (see I.B).[65-68] Thus, opioids modify sensory and affective aspects of pain. The different actions of opioids (i.e., agonist and antagonist) at various opioid receptors (e.g., mu, kappa, and delta) provide one means of classification. In this system, opioids are broadly classified as mu agonists or agonist-antagonists. Because experts do not recommend use of agonist-antagonists as

Table 20. Class Effects of Nonselective NSAIDs

System	Side Effect	Precautions and Contraindications	Prevention and Management
CV	Myocardial infarction, stroke, death	Contraindicated immediately after coronary artery bypass grafting	Use lowest effective dosage
GI	Dyspepsia, ulcer formation, perforation, bleeding (due to inhibited synthesis of PGs that regulate blood flow to gastric mucosa)	Patients at increased risk: • Elderly • History of GI disease (e.g., ulcer) • Concomitant steroid or anticoagulant therapy • High-dose NSAID therapy	Initiate treatment at low doses Take NSAID with food Avoid alcohol Co-administer gastroprotective agents (e.g., misoprostol, sucralfate, histamine$_2$-blockers)[a] Use NSAIDs with less risk of GI problems (e.g., ibuprofen, selective COX-2 inhibitors) Monitor patient with stool guaiac test (for occult blood) and complete blood count
GI	Liver dysfunction Rare hepatic necrosis	Patients at increased risk: • Alcoholics • History of liver disease Relative contraindications: • Elevated liver enzymes • Preexisting liver disease	Baseline and periodic monitoring of liver function enzymes
Heme	Bleeding due to: • Inhibited platelet aggregation[b] or "anti-platelet effect" (due to inhibition of PG synthetase) • Prolonged prothrombin time (due to drug interaction with oral anticoagulant)	Relative contraindications: • Anticoagulation • Coagulopathy • Thrombocytopenia Other patients at increased risk: • Surgical patients • Some patients with cancer	Use NSAIDs with minimal or no bleeding risk in high-risk patients (e.g., choline magnesium trisalicylate, selective COX-2 inhibitors) Consider replacing NSAID with acetaminophen Stop ASA therapy 1 week prior to surgery and most other NSAIDs 2-3 days prior to surgery
Renal	Renal insufficiency (uncommon) or acute renal failure (rare) Multiple causes, including inhibited synthesis of vasodilator PGs that preserve blood flow to kidneys	Patients at highest risk for renal insufficiency or failure: • Elderly • Volume-depleted • Preexisting renal disease • Coexisting illness (e.g., HTN, CHF, diabetes, cirrhosis, multiple myeloma) • Taking diuretics or medications that limit renal blood flow, especially angiotensin converting-enzyme inhibitors	Usually resolves with drug discontinuation For high-risk patients: • Use low doses • Monitor kidney function • Avoid indomethacin
Immune	Hypersensitivity reactions: • Respiratory reaction • Urticaria-angioedema reaction	Patients who are sensitive to aspirin may be cross-sensitive to other NSAIDs	Monitor patients for asthma, rhinitis, and nasal polyps (respiratory reaction) or wheals, urticaria, hypotension, shock (urticaria-angioedema reaction) Seek appropriate emergency treatment, as needed
CNS	CNS dysfunction including attention or memory deficits, headache, tinnitus	Patients at increased risk: • Elderly • Concomitant use of medications affecting CNS function	To manage cognitive dysfunction: • Lower dose • If dysfunction persists, discontinue NSAID • Switch to another NSAID and drug class

Sources: References 9, 18a, 19, 21, and 53-56.

[a]Consider gastroprotective agents, particularly in elderly patients and patients with a history of peptic ulcer disease, GI bleeding, or cardiovascular disease.[9]

[b]Aspirin causes irreversible inhibition of platelet aggregation, and other nonselective NSAIDs cause reversible inhibition of platelet aggregation.[19]

ASA: aspirin; CHF: congestive heart failure; CNS: central nervous system; COX: cyclooxygenase; CV: cardiovascular; GI: gastrointestinal; HTN: hypertension; NSAID: nonsteroidal anti-inflammatory drug; Heme: hematologic; PGs: prostaglandins.

first-line analgesics,[19,24] this discussion focuses on mu agonists.

ii. Indications and uses

Opioids are used to treat moderate to severe pain that does not respond to nonopioids alone.[19] They are often combined with nonopioids because this permits use of lower doses of the opioid (i.e., dose-sparing effect). Nearly all types of pain respond to opioids; however, nociceptive pain is generally more responsive to opioids than neuropathic pain,[69] which may require higher doses of opioids.[66,70] Opioids play a major role in the treatment of acute pain (e.g., trauma, postoperative pain), breakthrough pain, cancer pain, and some types of chronic noncancer pain (CNCP).[19,71] Because responsiveness to opioids varies greatly among individuals, a patient who has failed to respond to an adequate trial of one opioid should try another (Table 21).[19] Although opioids vary in potency, more potent agents are not necessarily superior. Opioids are also categorized as weak opioids and strong opioids (Table 21).

iii. Routes of administration, formulations, and dosing

Opioids are administered via multiple routes (e.g., oral, sublingual, rectal, parenteral, transdermal, intrathecal, epidural). Oral or transdermal administration is generally preferred for chronic treatment.[19] Intramuscular (IM) administration, especially repeated, should not be used due to its multiple disadvantages (e.g., pain, unreliable absorption, tissue fibrosis).[19,24]

Short-acting drugs often are used to manage intermittent pain and breakthrough pain (i.e., pain that "breaks through" pain relief provided by ongoing analgesia).[20] Long-acting and sustained-release opioids are useful for patients with continuous pain, as they lessen the severity of end-of-dose pain and often allow the patient to sleep through the night.[19] Most opioids may be given around the clock (ATC) for continuous pain or on an as-needed basis (PRN). ATC dosing is recommended after an optimal dose is established by dose titration.[19] Dose titration involves administering a small starting dose and gradually increasing or decreasing the dose based on levels of pain relief and side effects.

In contrast to nonopioids, strong mu agonist opioids do not have a ceiling effect (i.e., a dose beyond which no additional analgesia is achieved).[69] However, many opioids are marketed in combination with a nonopioid, which may limit the maximum dose.[19] The accumulation of toxic metabolites of some opioids (e.g., meperidine) also limits dose increases as well as treatment duration.[69,96] If these events preclude adequate pain relief, another opioid should be substituted. Equianalgesic dosing charts help clinicians determine the appropriate starting dose of an opioid when changing routes of administration or when changing from one opioid drug to another (see Table 22). These charts list analgesic doses (oral and parenteral) that are approximately equivalent in ability to provide pain relief.

iv. Side effects

Binding of mu agonist opioids to receptors in various body regions (e.g., CNS, GI tract) results in therapeutic effects and side effects. Side effects of mu agonist opioids as a class include sedation, mental clouding or confusion, respiratory depression, nausea, vomiting, constipation, pruritus (itching), and urinary retention. With the exception of constipation, these side effects tend to subside with time. Tables 23 and 24, respectively, summarize general and specific approaches to side effect prevention and management.

Most opioids should be used with caution in patients with impaired ventilation, bronchial asthma, liver failure, or increased intracranial pressure.[19] Opioid-induced respiratory depression is usually short-lived, antagonized by pain, and most common in the opioid-naive patient.[97]

c. Antiepileptic drugs

i. Mechanism of action and effects

AEDs are a type of adjuvant analgesic. The increasing use of AEDs for neuropathic pain is based on their ability to reduce membrane excitability and suppress abnormal discharges in pathologically altered neurons.[98-100] However, the exact basis of their analgesic effects is unclear. It does not appear to be specifically related to their antiepileptic activity. Other drugs that suppress seizures (e.g., barbiturates) do not relieve pain, and AEDs with effective antiepileptic activity do not necessarily have good analgesic activity.[101]

ii. Indications and uses

AEDs (Table 25) are used to treat neuropathic pain, especially lancinating (i.e., episodic shooting, stabbing, or knife-like) pain from peripheral nerve syndromes.[19,102-103] Most of this use is "off-label." Exceptions include two first-generation AEDs, carbamazepine and valproate, which have FDA approval for the management of trigeminal

Table 21. Examples of Opioid Analgesics

Generic Name	Indications	Usual Dosing Interval	Routes of Administration[a] and Dosage Forms	Potential Side Effects[b]	Comments
Morphine	Severe acute pain (e.g., trauma, postoperative pain, MI), cancer pain, chronic pain	Varies with IR and CR	PO (IR and CR), PR, IV, SC, EA, IA, SL	Mu agonist class side effects[c] Class precautions, warnings, and contraindications[d] Metabolite can accumulate in setting of RF or hepatic dysfunction	Used as a standard of comparison for all opioid drugs; can stimulate histamine release IR and CR oral preparations available CR tablets are to be taken whole and must not be broken, chewed, or crushed, to prevent potential toxic dosage
Hydromorphone	Oral: management of pain where opioid therapy is appropriate Parenteral: moderate to severe pain (e.g., trauma, MI, surgery, burns, renal colic, biliary colic, cancer)	4-6 h for oral and parenteral 6-8 h for rectal	PO, PR, IV, SC, EA, IA	Mu agonist class side effects, precautions, warnings, and contraindications	Useful alternative to morphine Available as high-potency injectable that facilitates SC administration
Fentanyl	Severe acute pain, cancer pain, CNCP TD fentanyl is only indicated for treatment of chronic pain that requires continuous administration and cannot be managed by lesser means	Varies with ROA and form 72 h for TD fentanyl	IV, EA, IA, TD, OTFC	Mu agonist class side effects, precautions, warnings, and contraindications TD fentanyl is contraindicated for acute pain, postoperative pain, mild or intermittent pain responsive to PRN or nonopioid therapy, and at doses above 25 mcg/h at the initiation of opioid therapy TD fentanyl should not be used in children <12 years or patients <18 years who weigh <110 lb, except in research setting	TD and oral transmucosal formulations available, including OTFC (fentanyl in sweetened matrix) IV fentanyl is fast-acting and it is often combined with benzodiazepines for procedural analgesia and sedation TD fentanyl is long-acting and can control pain for up to 72 hours but a small number of patients may require q 48-hour dosing Ensure patients follow the correct patch application procedure for TD fentanyl and avoid direct exposure of application site to heat
Oxycodone	Moderate to moderately severe pain (e.g., trauma, postoperative pain, musculoskeletal disorders, abdominal pain, dental pain, cancer pain) CR formulation for moderate to severe pain where opioid is required for an extended period of time	Varies with IR and CR	PO (IR and CR)	Mu agonist class side effects, precautions, warnings, and contraindications CR tablets are to be taken whole and must not be broken, chewed, or crushed, to prevent potential toxic dosage CR (80 and 160 mg) tablets for use in opioid-tolerant patients only	IR and CR preparations Available as single entity and in combination with a nonopioid Can be used like oral morphine for severe pain Often combined with a nonopioid for moderate pain
Meperidine	Moderate to severe pain (e.g., migraine, trauma, postoperative pain, acute abdominal pain)	3-4 h[e]	PO, IV SC, EA, IA	Mu agonist class side effects, precautions, warnings, and contraindications High doses may cause agitation, muscle jerking, and seizures or hypotension Use with care in patients with renal insufficiency, convulsive disorders, cardiac arrhythmias	Not recommended for management of chronic pain due to accumulation of toxic metabolite (normeperidine) that may cause CNS excitement, convulsions Metabolite limits use to less than 48 hours or 600 mg in 24 hours Oral administration NR for severe pain

Table 21. Examples of Opioid Analgesics (continued)

Generic Name	Indications	Usual Dosing Frequency	Routes of Administration[a]	Potential side effects[b]	Comments
Hydrocodone	Moderate to severe pain (e.g., trauma, back pain, postoperative pain, abdominal pain, dental pain)	4-6 h	PO	Mu agonist class side effects, precautions, warnings, and contraindications Combination hydrocodone + ibuprofen NR for OA or RA or for patients with NSAID hypersensitivity or other contraindication to NSAIDs	Available in combination with nonopioid Hydrocodone plus acetaminophen for moderate or moderately severe pain Hydrocodone plus ibuprofen combination product indicated for short-term (generally <10 days) management of acute pain (e.g., trauma, musculoskeletal and back pain, postoperative pain, abdominal pain, dental pain)
Codeine	Mild to moderately severe pain	4 h	PO, SC	Mu agonist class side effects, precautions, warnings, and contraindications Most common side effects are lightheadness, dizziness, shortness of breath, sedation, nausea, and vomiting	Used orally for mild-to-moderate pain, with limited use for severe pain Usually used in combination with nonopioid, which has an analgesic ceiling Codeine is a pro-drug and not all patients convert it to an active form to achieve analgesia

Sources: References 19-20, 22, 24, 50, 69, and 72-95. Product information (references 76-95) is from the Physicians' Desk Reference, 55th edition.[50]

[a]Although many of these opioids can be administered by intramuscular (IM) injection, IM administration is not recommended due to its multiple disadvantages (e.g., painful administration, unpredictable absorption, complications including tissue fibrosis and abscesses).[19]
[b]Many of these opioids only come in combination with a nonopioid (e.g., acetaminophen, NSAID). Therefore, additional contraindications, warnings, and side effects of that nonopioid drug apply. These combination products also are subject to a ceiling effect.
[c]Common side effects of mu agonists as a class include sedation, nausea, vomiting, constipation, pruritus (itching), and respiratory depression.[19] Less common side effects include euphoria or dysphoria. mu_1 receptors mediate supraspinal analgesia, and mu_2 receptors mediate spinal analgesia, physical dependence, and class side effects.[68]
[d]Mu agonists are generally contraindicated or need to be used with extreme caution in patients with known hypersensitivity to the drug, head injury or lesion associated with increased intracranial pressure, asthma and other respiratory conditions, or paralytic ileus.
[e]The 2001 Physicians' Desk Reference entry for Demerol® lists the dosing interval for meperidine as 3-4 hours, as necessary.[50] The 1992 Agency for Health Care Policy and Research Acute Pain Management: Operative or Medical Procedures and Trauma Clinical Practice Guideline No. 1 lists the dosing interval for meperidine as 2-3 hours.[24]
CNCP: chronic noncancer pain; CNS: central nervous system; CR: controlled-release; EA: epidural anesthesia; IA: intrathecal anesthesia; IM: intramuscular; IR; immediate-release; IV: intravenous; MI: myocardial infarction; NR: not recommended; NSAID: nonsteroidal anti-inflammatory drug; OA: osteoarthritis; OTFC: oral transmucosal fentanyl citrate: PO: per os (oral); PR rectal; PRN: as needed; RA: rheumatoid arthritis; RF: renal failure; ROA: route of administration; SC: subcutaneous; SL: sublingual; TD: transdermal.

Table 22. Equianalgesic Dose Chart

	Equianalgesic Dose (mg)	
Opioid	Oral	Parenteral
Morphine	30	10
Hydromorphone	7.5	1.5
Fentanyl	—	0.1
Oxycodone	20	—
Meperidine	300 (NR)	75

Source: Reference 19.
NR: not recommended.

Table 23. General Management of Mu Agonist Opioid Side Effects

- Use preventive measures, especially in populations at high risk.
- Titrate drug doses slowly.
- If a symptom occurs, verify its cause (i.e., opioid side effect or another problem).
- If opioid-related side effects occur, consider changing the dosing regimen or route of administration to obtain relatively constant blood levels.
- Whenever possible, add (or increase dose of) nonopioid or adjuvant analgesic for opioid-sparing effect.
- Consider switching to another opioid.
- Add another drug that counteracts the effect (Table 24).
- Assume constipation will develop and treat it preemptively.

Sources: References 19, 24, 69, and 74.

Table 24. Specific Approaches to Management of Mu Agonist Opioid Side Effects

Side Effect	Precautions and Contraindications	Prevention and Management
Sedation	Elderly Concurrent sedating medications	General approach[a] plus: • Eliminate other nonessential medications with sedating effects • Consider use of mild stimulants during the day (e.g., caffeine) • Consider use of psychostimulant (e.g., methylphenidate) for persistent sedation, although exercise caution in combining psychoactive drugs in the elderly
Confusion Mental clouding	Elderly Preexisting CNS condition	General approach plus: • Eliminate other nonessential medications with CNS effects • Consider use of neuroleptics for persistent delirium
Respiratory depression	Opioid-naïve patients taking large opioid doses Head injury, lung disorder	General approach plus: • Monitor sedation level and respiratory status regularly, especially during first 24 hours of treatment in opioid-naïve patients • Stop opioid until respiratory depression resolves and reinstitute opioid at 75% of the previous dosage • Stop opioid and administer naloxone[b] for minimally responsive or unresponsive patients • Use spirometry and oxygen, as needed
Pruritus (itching)		General approach plus: • Consider administering diphenhydramine or hydroxyzine • Consider naloxone infusion titrated to the desired effect if other treatments fail
Nausea and vomiting	Concomitant conditions or treatments producing nausea and vomiting	General approach plus: • If nausea is due to stimulation of chemoreceptor trigger zone (central mechanisms), consider adding ondansetron, prochlorperazine, or hydroxyzine • If nausea is due to slowed gastric motility, consider adding metoclopramide • For chronic nausea, consider metoclopramide and/or other antiemetics
Constipation	Advanced age Immobility Abdominal problems or concurrent constipating medications	General approach plus: • Implement appropriate dietary changes • Assess regularly and use stool softeners and mild peristaltic stimulants for all patients on ATC opioids (prevention) • If no BM in a 48-hour period, add one or two additional agents (e.g., lactulose, milk of magnesia, senna) • If no BM in a 72-hour period, assess for (and treat) fecal impaction • If not impacted, try additional method (e.g., enema, mineral oil, magnesium citrate) • If impacted, use glycerine suppository or oil retention enema (as needed) to facilitate manual disimpaction, with appropriate analgesia

Sources: References 19, 24, 69, and 74.

[a]The general approach to managing side effects consists of changing the dosage or route of administration, trying a different drug in the same class, or adding a drug that counteracts the effect.

[b]For comatose patients, place endotracheal tube prior to administering naloxone. Also, titrate naloxone carefully to avoid profound withdrawal, seizures, and severe pain.[19]

ATC: around-the-clock administration; BM: bowel movement; CNS: central nervous system.

Table 25. Examples of Antiepileptic Drugs, Antidepressants, and Local Anesthetics[a]

Class	Generic Name	Indications	Uses in Pain[b]	Dosage Forms and Routes of Administration	Potential Side Effects	Comments
Antiepileptic drugs	Gabapentin	Epilepsy	Neuropathic pains including PDN, PHN, RSD, deafferentation pain, thalamic pain, HIV-related neuropathy, phantom limb pain, migraine prophylaxis	Oral (capsules, tablets, solution)	Generally well tolerated Most common SE: somnolence, dizziness, fatigue, ataxia	First-line off-label treatment for neuropathic pain Well-established efficacy for PHN, PDN, and migraine headache prophylaxis Comparable efficacy to TCAs for PHN and PDN with superior side effect profile
	Pregabalin	Epilepsy, PDN, PHN	Neuropathic pains including PDN and PHN	Oral (capsules)	Most common SE: dizziness, somnolence Other SE: dry mouth, edema, blurred vision, weight gain	Approved by FDA in 2005
	Carbamazepine	Epilepsy Trigeminal neuralgia	Neuropathic pains including TN, PHN, PDN, glossopharyngeal neuralgia, tabetic lightening pain, paroxysmal MS pain, PSP, dysethesia (spinal cord injury), post-laminectomy pain, cancer pain, phantom limb pain	Oral (tablets, ER tablets, suspension)	Most common SE: sedation, mental clouding, dizziness, nausea, unsteadiness Other SE: thrombocytopenia, liver damage, hyponatremia, rash	First FDA-approved anticonvulsant for the treatment of neuropathic pain Well-established efficacy in managing TN, PDN, PHN, but side effects limit use Baseline and regular monitoring of hematologic and liver function Monitor serum drug levels
	Divalproex sodium	Mania Epilepsy Migraine HA prophylaxis	Migraine (prophylaxis), TN, PHN	Oral (tablets)	Most common SE: sedation, nausea, vomiting, dizziness, HA Boxed warning for hepatic toxicity and pancreatitis Other SE: thrombocytopenia, inhibited platelet aggregation, hyperammonemia with or without lethargy, abnormal thyroid function tests, androgenization with hirsutism, amenorrhea, hair loss, polycystic ovaries	FDA approved for migraine HA prophylaxis Side effects limit wider use in chronic pain Monitor serum drug levels

Table 25. Examples of Antiepileptic Drugs, Antidepressants, and Local Anesthetics[a] (continued)

Class	Generic Name	Indications	Uses in Pain[b]	Dosage Forms and Routes of Administration	Potential Side Effects	Comments
	Phenytoin	Epilepsy	PHN, PDN, TN, glossopharyngeal neuralgia, tabetic lightening pain, central pain, cancer pain, PSP, Fabry's disease	Oral (suspension, capsules, ER capsules, tablets) Parenteral (solution)	Most common SE: dose-related CNS effects (e.g., confusion, nystagmus, ataxia, decreased coordination) Other SE: lymphadenopathy, hepatotoxicity, hypersensitivity reaction, exfoliative dermatitis, gingival hyperplasia, toxicity and conduction disturbances at high blood levels	First anticonvulsant used for pain management Less commonly used now due to side effects and contradictory evidence of analgesic efficacy Monitor drug levels and watch for signs of toxicity (e.g., nystagmus, gait impairment, nausea, vomiting, sedation)
Antidepressants	Amitriptyline	Depression	Various types of CNCP (e.g., migraine and other HA, OA, chronic LBP, fibromyalgia), and neuropathic pain (e.g., PHN, PDN, central pain, chronic facial pain, cancer pain)	Oral (tablets, capsules, solution)	Common SE: sedation, anticholinergic effects (dry mouth, blurred vision, constipation, urinary retention), orthostatic hypotension Other SE: arrhythmias, MI, stroke, worsening schizophrenic psychosis, hyperpyrexia, paralytic ileus Contraindications: status-post acute MI, hypersensitivity, concomitant MOAI use Use with caution in patients with seizures, urinary retention, angle-closure glaucoma, hyperthyroidism, CV disease, advanced age	Well-established analgesic efficacy Most used TCA for pain but least tolerated Produces the most anticholinergic side effects of all antidepressants Commonly associated with sedation, so administer at night Baseline ECG recommended and avoid use if QTc >440, AV block
	Nortriptyline	Depression	PDN, mixed neuropathic pains	Capsules, suspension	Common SE: insomnia, some sedation, anticholinergic effects Other SE and contraindications: see Amitriptyline	Better tolerated than amitriptyline due to less sedation and anticholinergic SE May cause insomnia, so administer during daytime
Local anesthetics (topical)	Lidocaine Lidoderm	Postherpetic neuralgia	PHN, PDN, stump pain, reflex sympathetic dystrophy, painful HIV-related neuropathy	Patch	Most common SE: localized reaction that usually resolves Less common SE: allergic and systemic reactions Use precautions in patients with severe hepatic damage and avoid eye exposure Contraindicated in patients with known sensitivity to LAs or for use on non-intact skin	Only FDA-approved treatment for PHN Anecdotal data suggest may be effective for other pain Low blood levels due to topical application Convenient and generally well tolerated

Table 25. Examples of Antiepileptic Drugs, Antidepressants, and Local Anesthetics[a] (continued)

Class	Generic Name	Indications	Uses in Pain[b]	Dosage Forms and Routes of Administration	Potential Side Effects	Comments
	EMLA®	Local anesthesia on intact skin for procedures or superficial surgery on skin	Needle insertion, intravenous cannulation, spinal needle insertion, electrosurgery of cutaneous lesions, biopsies, PHN, other neuropathic pain	Cream, disc	Toxicity with repeated dosing, eye irritation, allergic reactions, methemoglobinemia	Placebo-controlled trials support efficacy in relieving acute pain associated with multiple procedures
Local anesthetics (other routes)	Bupivacaine	Local or regional anesthesia or analgesia for surgery; oral surgical and obstetrical procedures; and diagnostic and therapeutic procedures	Acute pain management: local infiltration, nerve blocks, epidural blocks, arthroscopy	Parenteral, epidural	Most common SE: dose-related CNS (e.g., anxiety, dizziness) and CV (e.g., arrhythmias, myocardial depression) effects Use with caution in patients with liver or heart disease due to risk of hepatic toxicity and arrhythmias Other SE: familial malignant hyperthermia	Moderate to fast acting, with long duration of action Better able to selectively block nociceptive nerve fibers Can be combined with opioids for epidural analgesia Only use 0.25% and 0.5% concentrations for obstetrical surgery
	Lidocaine	Local or regional anesthesia by infiltration techniques and IV regional anesthesia	Local infusion: local infiltration, nerve blocks, epidural blocks (e.g., postoperative pain, obstetrical pain), arthroscopy IV infusion: (rarely used) for some nociceptive and neuropathic pain, burn pain	IV, SC	Dose-related CV and CNS toxicity may progress to cardiac arrest, acidosis, and death with IV administration CNS SE: lightheadedness, dizziness, drowsiness, tinnitus, tremors, convulsions, unconsciousness CV SE: bradycardia, hypotension, CV collapse IV lidocaine contraindicated in patients with hypersensitivity to amide-type LAs, Adams-Stoke syndrome, severe heart block	Considered most widely used LA Can be combined with opioids for epidural analgesia IV use for pain normally reserved for pain refractory to other treatments due to risk of toxicity and unclear efficacy Topical lidocaine (see EMLA®, Lidocaine patch) is not associated with same side effects

Sources: References 19, 20, 50, and 104-142a.

[a]This is a representative, not comprehensive, list.

[b]Most uses are off label.

AV: atrioventricular; CNCP: chronic noncancer pain; CNS: central nervous system; CV: cardiovascular; ECG: electrocardiogram; EMLA®: Eutectic Mixture of Local Anesthetics (lidocaine and prilocaine); ER: extended release; FDA: Food and Drug Administration; HA: headache; HIV: human immunodeficiency virus; IN: intranasal; IV: intravenous; LA: local anesthetics; LBP: lower back pain; MI: myocardial infarction; MOAI: monoamine oxidase inhibitor; MS: musculoskeletal; OA: osteoarthritis; PDN: peripheral diabetic neuropathy; PHN: postherpetic neuralgia; PSP: postsympathectomy pain; QTc: QT interval corrected for heart rate on ECG; RSD: reflex sympathetic dystrophy; SC: subcutaneous; SE: side effects; TCAs: tricyclic antidepressants; TN: trigeminal neuralgia.

neuralgia and migraine prophylaxis, respectively. Phenytoin was the first AED used to treat pain, but clinical trial evidence of its analgesic efficacy is limited and conflicting.[c,108-109] Clinical trial data support the use of carbamazepine in the treatment of trigeminal neuralgia, diabetic peripheral neuropathy, and postherpetic neuralgia,[112] but serious, albeit rare, side effects limit its use.[101] Recent data suggest that newer AEDs such as gabapentin are better alternatives to older AEDs.[101,110,112]

Placebo-controlled clinical trials have demonstrated that gabapentin provides effective analgesia comparable to TCAs for diabetic peripheral neuropathy[146-147] and postherpetic neuralgia;[114] it also has a more favorable side effect profile.[110,112] Data from a large study and a recent placebo-controlled trial also suggest that gabapentin effectively reduces the likelihood of migraine headaches.[115-116] Uncontrolled studies suggest that gabapentin also may be useful in the management of trigeminal neuralgia, central pain, phantom limb pain, and neuropathy associated with human immunodeficiency virus (HIV) infection.[120,148-150] Placebo-controlled trials of pregabalin, a new AED that binds to the alpha$_2$-delta subunit protein of voltage-gated calcium channels, have demonstrated that the drug provides effective analgesia for patients with painful diabetic peripheral neuropathy or postherpetic neuralgia. [150a]

iii. Side effects

Side effects of AEDs vary (Table 25). Common side effects of AEDs as a class include sedation, mental clouding, dizziness, nausea, or unsteadiness.[107] Initiating treatment at low doses and slowly titrating upward to optimal efficacy or toxicity diminishes the risk of these effects. Table 26 summarizes other ways to prevent and manage side effects. Less common but more serious adverse effects of some of the older AEDs include hematologic abnormalities, liver dysfunction, hypersensitivity reactions, and rash (Table 25). Thus, use of some of these agents requires close monitoring of drug levels, hematologic parameters, and liver function.[105] Unlike these older AEDs, gabapentin offers easy monitoring and relatively low toxicity (i.e., minimal drug-drug interactions and side effects).[101,110,112,119-120]

[c] Double-blind, placebo-controlled trials have demonstrated analgesic efficacy for diabetic neuropathy[143] and Fabry's disease,[144] although another small trial failed to demonstrate efficacy for diabetic neuropathy.[145]

d. Antidepressants

i. Mechanism of action and effects

Antidepressants exhibit analgesic properties in animal models of nociceptive, inflammatory, and neuropathic pain, and some relieve chronic and neuropathic pain in humans.[151] These analgesic effects may reflect the ability of some antidepressants to block the reuptake of serotonin and norepinephrine in the CNS, thus increasing the activity of endogenous pain-modulating pathways.[152-154] Their analgesic actions do not depend on antidepressant activity,[155] and antidepressants are equally effective in patients with and without depression.[19] While analgesia may occur at lower doses and sooner than antidepressant activity, maximum efficacy may require high antidepressant doses and trial duration.

ii. Indications and uses

TCAs (e.g., amitriptyline, nortriptyline, imipramine) are adjuvant analgesics used to treat a variety of types of chronic (e.g., migraine, other headaches, low back pain, cancer pain, fibromyalgia) and neuropathic (e.g., painful diabetic neuropathy, postherpetic neuralgia, central pain, cancer-related) pain (Table 25).[107,122] All of these uses are "off-label." Although often considered most effective for continuous dysesthesias (i.e., burning pain or hypersensitivity), TCAs also may relieve lancinating neuropathic pain.[122,156-157]

The analgesic efficacy of TCAs is well documented. Placebo-controlled clinical trial data suggest that TCAs provide effective[158-159] and comparable pain relief to AEDs for postherpetic neuralgia and diabetic neuropathy.[117,122,160-161] Amitriptyline has the best-documented analgesic effects but also the most side effects.[19] Intolerance of side effects, particularly among elderly patients, often limits TCA use.[118-119] Whereas newer antidepressants (e.g., serotonin-norepinephrine reuptake inhibitors, selective serotonin reuptake inhibitors [SSRIs]) are generally better tolerated,[123-124] randomized controlled trials have yet to demonstrate analgesic efficacy.[d,123,149,162] There is preliminary evidence that venlafaxine, a serotonin-norepinephrine reuptake inhibitor that lacks TCA side effects, may be efficacious in the treatment of neuropathic pain.[123,124] However, these results await formal evaluation in a randomized placebo-controlled trial. Duloxetine, a new serotonin-nor-

[d] Data regarding the analgesic efficacy of SSRIs are conflicting[159,162-165] but generally suggest that SSRIs have less consistent analgesic effects than TCAs.[122,155,160,166]

Table 26. Approaches to Management of Antiepileptic Drugs, Tricyclic Antidepressants, and Local Anesthetic Side Effects

Side Effect	Populations at Increased Risk and Precautions	Prevention and Management
Sedation	Elderly	Titrate drug slowly and monitor drug levels, if recommended Consider changing dosing regimen or drug Administer drug at bedtime Eliminate other nonessential medications with sedating effects Consider use of mild stimulants during the day (e.g., caffeine) Consider use of psychostimulant (e.g., methylphenidate, dextroamphetamine) for persistent sedation, but exercise caution in elderly patients
Confusion Mental clouding	Elderly	Titrate drug slowly and monitor drug levels, if recommended Eliminate other nonessential medications with CNS effects Consider changing dosing regimen or drug
Dizziness/ orthostatic hypotension	Elderly	Titrate drug slowly and monitor drug levels, if recommended Encourage patient to change positions slowly and remain well hydrated Consider changing dosing regimen or drug if unmanageable
Anticholinergic effects	Elderly Patients with urinary retention or angle-closure glaucoma	Lower dose or change to drug with fewer anticholinergic effects Use sugarless hard candies or chewing gum for dry mouth and ensure regular dental examinations Use laxatives and stool softeners for constipation Consider bethanechol
Nausea and vomiting		Consider prochlorperazine or hydroxyzine
Cardiovascular effects	History of CAD, arrhythmias, or heart block	Obtain baseline ECG in all patients Monitor closely Be prepared to manage emergencies, including cardiac arrest

Source: Reference 19.

CAD: coronary artery disease; CNS: central nervous system; ECG: electrocardiogram.

epinephrine reuptake inhibitor, appears to alleviate painful physical symptoms associated with depression, fibromyalgia (with or without depression), and diabetic peripheral neuropathy.[124a,124b124c] Further research is needed.

iii. Side effects

TCA selection is largely based on patient characteristics and the drug side effect profile, because analgesic efficacy among individual TCAs is comparable.[122] Lethal side effects of TCAs are uncommon at dosages typically prescribed for pain, but cardiotoxicity with dangerous conduction abnormalities (arrhythmias) may occur.[125] Therefore, TCAs are relatively contraindicated in patients with conduction abnormalities (e.g., prolonged QT interval corrected for heart rate on the electrocardiogram), and a baseline electrocardiogram is recommended.[19]

Common and sometimes significant class effects of TCAs include sedation, orthostatic hypotension, and anticholinergic effects (i.e., dry mouth, blurred vision, constipation, urinary retention) (Table 25). Amitriptyline has the strongest sedative and anticholinergic side effects, so bedtime administration is recommended.[19] Elderly patients are at greatest risk for some side effects, including sedation and orthostatic hypotension. Nortriptyline is less likely than amitriptyline to produce these effects,[19] so it may be a more appropriate initial choice for an elderly patient. Nortriptyline should be administered during the day if it produces insomnia.[19] Table 26 summarizes some ways to prevent and manage common TCA side effects.

e. Local anesthetics

i. Mechanism of action

LAs are another type of adjuvant analgesic. These drugs block sodium channels and inhibit the generation of abnormal impulses by damaged nerves to exert their peripheral analgesic effects.[167] When used systemically, they do not produce conduction block (anesthesia) as they do with local injection and topical application but may suppress aberrant electrical activity in structures associated with pain.[107,168-169]

ii. Indications and uses

LAs are used to manage acute and chronic pain (Table 25) and are administered in several ways for different purposes. Topical application provides localized analgesia for a painful procedure or con-

dition with minimal systemic absorption or side effects.[106] EMLA® (Eutectic Mixture of Local Anesthetics [lidocaine and prilocaine]) is a topically applied LA used to prevent pain associated with various procedures (e.g., needle insertion, intravenous cannulation, superficial skin surgery).[170] Placebo-controlled trial data suggest that EMLA® effectively relieves acute pain associated with procedures, including venipuncture,[171-173] spinal needle insertion,[174] and excisional biopsy or curretage of cutaneous lesions.[175-176]

Topical LAs are also used to treat neuropathic pain.[106] The lidocaine patch (Lidoderm®) is the first FDA-approved treatment for postherpetic neuralgia.[177] A large, multicenter, placebo-controlled trial showed that it relieved pain in patients with long-standing postherpetic neuralgia and mechanical allodynia.[178] Other controlled studies suggest that both the patch and gel forms of lidocaine significantly reduce postherpetic neuralgia, produce no significant side effects, and are easy to use.[106,179-180] Anecdotal evidence suggests that the lidocaine patch also may be useful for other neuropathic pain, including diabetic neuropathy, HIV-related neuropathy, complex regional pain syndrome, postmastectomy pain, postthoracotomy pain, and stump pain.[106,181]

LAs also can be used in more invasive approaches collectively referred to as regional anesthesia. For example, LAs (e.g., lidocaine, bupivacaine, ropivacaine) can be injected into tissue (local infiltration), around nerves (i.e., nerve blocks), or into various spaces surrounding the spine (i.e., epidural and intrathecal analgesia). Epidural blocks with LAs with or without opioids play an important role in managing postoperative and obstetrical pain.[107] Nerve blocks with LAs sometimes are used to manage chronic pain (e.g., occipital headaches, lower back pain), and LAs can be combined with other agents (e.g., corticosteroids, saline) for trigger point injections.[182]

Rarely, intravenous LAs (e.g., lidocaine) are used to manage neuropathic pain, arthritis, poststroke pain, or headache[107,126-128] or, somewhat more often, to anesthetize an upper extremity. Oral LA-type antiarrhythmic drugs (e.g., flecainide, mexiletine) have, in some cases, been used to manage neuropathic or cancer pain.[129-130] However, use of these drugs is generally not recommended, because they may cause serious side effects and evidence of their analgesic efficacy is limited and conflicting.[107]

iii. Side effects

Major dose-dependent toxicities associated with systemic administration of LAs include CNS (e.g., dizziness, tremor, paresthesias, encephalopathy, seizures) and cardiovascular (e.g., conduction disturbances, depression of myocardial function) side effects (Table 25). Thus, treatment in some patient populations is contraindicated, and all patients need to be closely monitored (e.g., with plasma drug levels, electrocardiography). In contrast, topical LAs are well tolerated with a low incidence of side effects.[106] As serum concentrations of the LA remain low, even with chronic use,[177] topical LAs can even be used in patients with cardiovascular disease.

f. Other

Nonopioids and opioids are used to manage most nociceptive pain, although LAs are also useful for postoperative pain management. Systemic analgesics (e.g., opioids), topical lidocaine, certain antidepressants, gabapentin, and pregabalin are used for the treatment of neuropathic pain.[182a] However, this does not account for all drugs used in pain management. Table 27 summarizes information about other drugs and drug classes used for specific conditions or clinical circumstances. These include drugs used for arthritis pain (e.g., capsaicin), cancer and inflammatory pain (e.g., corticosteroids), migraine headaches (e.g., "triptans," beta-blockers), chronic pain (e.g., tramadol, baclofen) and pain refractory to other treatments (N-methyl-D-aspartate antagonists).

Ziconotide is the first agent in a new class of analgesics that block N-type calcium channels, which are responsible for transmitting pain signals to the CNS.[200a] It is given by the intrathecal route and is indicated for the management of severe chronic pain in patients who are intolerant of or refractory to other systemic therapies, including intrathecal morphine.

3. General Principles of Analgesic Therapy

Some principles of analgesic therapy are drug specific. However, some general principles guide all pharmacologic treatment of pain:

a. Identify and treat the source of the pain.

Whenever possible, identify and treat the

Table 27. Other Drugs Used in Pain Management

Class	Generic Name	Indications	Uses in Pain	Routes of Administration and Dosage Forms	Potential Side Effects	Comments
Topical analgesics	Capsaicin	Arthritis, neuropathic pain	PHN, PDN, OA, RA	Topical	Mild to severe burning on application	RCT have shown efficacy for OA and RA but mixed results for PDN and PHN Available OTC
Corticosteroids	Dex-amethasone	Multiple, including endocrine, rheumatic, collagen-vascular, dermatologic, allergic, ophthalmologic, respiratory, oncologic, hematologic disorders	Cancer-related pain (e.g., malignant epidural spinal cord compression, raised intracranial pressure, superior vena cava syndrome); symptoms of bowel obstruction; pain related to musculoskeletal conditions (e.g., OA, RA, bursitis, tendonitis)	PO (tablets, elixir), injectable form	Contraindicated in patients with systemic fungal infections or hypersensitivity to drug Drug-induced adrenocortical insufficiency, mask signs of infection, eye problems (e.g., glaucoma, cataracts), increased blood pressure, electrolyte/body fluid imbalances, increased risk of infection, psychiatric disturbances, GI problems (e.g., ulceration, bleeding), osteoporosis, pathological fractures, withdrawal syndrome with sudden discontinuation	Generally tolerated for short-term treatment, but toxicities often arise with prolonged high-dose therapy Dosage must be tapered before discontinuation to prevent withdrawal symptoms
	Methylpred-nisolone			PO		
Mixed mu agonist opioid and NE/5-HT reuptake inhibitor	Tramadol	Moderate to moderately severe pain	Types of CNCP (e.g., OA, fibromyalgia, PDN, LBP)	PO	Common SE: dizziness, nausea, constipation, headache, sedation Uncommon SE: increased risk of seizures with high doses (>400 mg/day) or history of seizure disorder; rare anaphylactoid reaction	Contraindicated in patients with hypersensitivity or acute drug intoxication Comparable pain relief to acetaminophen + codeine May have lower potential for abuse than opioids
Selective $5\text{-HT}_{1B/1D}$ receptor agonist	Zolmitriptan	Acute treatment of migraine with or without aura in adults	Acute treatment of migraine with or without aura in adults	PO (tablets)	Dizziness, drowsiness, nausea, atypical or pressure sensations Certain contra-indications (see comments)	Effective abortive treatment for migraine Contraindicated/NR in patients with: • Ischemic heart (e.g., MI) or cerebrovascular (e.g., stroke) disease • Uncontrolled HTN • Hemiplegic or basilar migraine • Hypersensitivity • Recent ergots or MAOI use

Table 27. Other Drugs Used in Pain Management (continued)

Class	Generic Name	Indications	Uses in Pain	Routes of Administration and Dosage Forms	Potential Side Effects	Comments
	Rizatriptan	Acute treatment of migraine with or without aura in adults	Acute treatment of migraine with or without aura in adults	PO (tablets, orally disintegrating tablets)	Warm/cold sensations, diarrhea, nausea, flushing Certain contraindications: see Zolmitriptan	
	Sumatriptan	Acute treatment of migraine with or without aura in adults	Acute treatment of cluster headache episodes (SC form only)	PO (tablets), IN, SC	Atypical (e.g., flushing, tingling, warmth) and pressure sensations; nausea Certain contraindications: see Zolmitriptan	Intranasal sumatriptan also contraindicated in patients with severe hepatic impairment
	Almotriptan	Acute treatment of migraine with or without aura in adults	Acute treatment of migraine with or without aura in adults	PO (tablets)	Nausea, somnolence, headache, paresthesias, dry mouth	Certain contraindications: see Zolmitriptan
	Eletriptan	Acute treatment of migraine with or without aura in adults	Acute treatment of migraine with or without aura in adults	PO (tablets)	Asthenia, nausea, dizziness, somnolence	Contraindicated in patients with peripheral vascular disease (e.g., ischemic bowel disease) or certain other conditions (see Zolmitriptan)
	Frovatriptan	Acute treatment of migraine with or without aura in adults	Acute treatment of migraine with or without aura in adults	PO (tablets)	Dizziness, paresthesias, headache, dry mouth, fatigue, flushing, hot/cold sensations	Certain contraindications: see Zolmitriptan
	Naratriptan	Acute treatment of migraine with or without aura in adults	Acute treatment of migraine with or without aura in adults	PO (tablets)	Paresthesias, dizziness, drowsiness, fatigue	Contraindicated in severe renal or hepatic impairment, certain other conditions (see Zolmitriptan)
Beta-blockers	Propranolol	HTN, MI, migraine prophylaxis, essential tremor, HSS, pheochromocytoma	Migraine prophylaxis	PO (tablets, LA capsules), injectable	Common SE: bradycardia, hypotension Other SE: lethargy, depression Contraindicated in patients with cardiogenic shock, heart block, bronchial asthma, CHF Use caution in patients with history of CHF or angina, diabetes, hyperthyroidism	Effective migraine prophylaxis
$GABA_B$ receptor agonists	Baclofen	Spasticity	Intraspinal baclofen is used for some chronic neuropathic pain refractory to other treatments	Intraspinal	Abrupt discontinuation can trigger withdrawal symptoms, including delirium and seizures	Useful for pain caused by spasticity

Table 27. Other Drugs Used in Pain Management (continued)

Class	Generic Name	Indications	Uses in Pain	Routes of Administration and Dosage Forms	Potential Side Effects	Comments
NMDA receptor antagonists	Ketamine	General anesthetic	Neuropathic pain (e.g., phantom limb pain), cancer pain, procedural pain (rarely used)	Parenteral	CNS side effects: sedation, ataxia, delirium, hallucinations, psychosis, nightmares, dysphoria Sedation is most common side effect at low doses	Rarely used due to debilitating CNS side effects New NMDA receptor antagonists are in development
N-type calcium channel blocker	Ziconotide	Management of severe chronic pain in patients who are intolerant of or refractory to other systemic therapies, including intrathecal morphine	Management of severe chronic pain in patients who are intolerant of or refractory to other systemic therapies, including intrathecal morphine	Intrathecal	Severe psychiatric symptoms and neurological impairment	Should not be used in patients with history of psychosis

Sources: References 19, 50, 104-106, 183-200a.
5-HT: 5-hydroxytryptamine (serotonin); 5-$HT_{1B/1D}$: 5-hydroxytryptamine receptor subtypes $_{1B/1D}$; CHF: congestive heart failure; CNCP: chronic noncancer pain; CNS: central nervous system; $GABA_B$: γ-aminobutyric acid (GABA) type B receptor; GI: gastrointestinal; HSS: hypertrophic subaortic stenosis; HTN: hypertension; LA: long-acting; LBP: lower back pain; MAOI: monoamine oxidaase inhibitor; MI: myocardial infarction; NE: norepinephrine; NMDA: N-methyl-D-aspartate; NR: not recommended; OA: osteoarthritis; OTC: over-the-counter (nonprescription); PDN: peripheral diabetic neuropathy; PHN: postherpetic neuralgia; PO: per os (oral); RA: rheumatoid arthritis; RCT: randomized controlled trials; SC: subcutaneous; SE: side effects.

underlying cause of the pain. However, pain management can begin before the source of the pain is determined.

b. Select the simplest approach to pain management.

Although invasive methods are sometimes required, most pain can be relieved via simple methods. Cost of treatment is also a consideration in some cases.

c. Select an appropriate drug.

Individualization of a pain management regimen begins with selection of an appropriate drug. Factors that guide this process include:[19-20]

- Characteristics of the pain (e.g., duration, intensity, quality)
- Characteristics of the agent (e.g., analgesic ceiling, expected time of onset and duration of analgesia, available routes of administration, dosing interval, side effects, potential for accumulation of toxic metabolites, potential for addiction)
- Patient factors (e.g., age, coexisting diseases, other medications, preferences, response to previous treatments).

d. Establish a management plan.

The next step is to establish a management plan, which may include the later addition of other drugs. Use of several analgesics in combination offers several advantages. It may:

- Allow use of lower doses of some agents, thus reducing the risk of side effects
- Inhibit nociceptive processing at multiple (i.e., peripheral and central) levels, thus enhancing analgesia
- Facilitate treatment of pain in patients who do not respond to a single agent.

Common acceptable combination regimens include: 1) a nonopioid plus an opioid or 2) a nonopioid plus an opioid plus an adjuvant analgesic.[20]

Table 28. Routes of Administration

Route	Definition and Notes	Drug Types	Comments
Oral	By mouth (per os) Requires functioning GI tract, intact swallowing mechanism, sufficient GI tract for absorption to occur	Nonopioids, opioids, adjuvant analgesics	Advantages: convenient, noninvasive, cost-effective, flexible, less discomfort than injections with comparable efficacy Disadvantages: requires functional GI system; slow onset of action and relatively delayed peak effects; requires patient compliance
Rectal	Insertion of suppository into rectum	Nonopioids, opioids	Useful in patients who cannot take medications by mouth Any opioid may be compounded for rectal administration
Intramuscular	Injection into large muscle (e.g., gluteus or vastus lateralis)	Some nonopioids, opioids	IM administration should not be used, especially for chronic treatment, due to multiple disadvantages: • Painful injections • Wide fluctuations in drug absorption make it difficult to maintain consistent blood levels • Rapid fall-off of action compared with PO administration • Chronic injections may damage tissue (fibrosis, abscesses) IV and SC injections are appropriate alternatives
Intravenous	Injection into vein; may be single or repetitive bolus or continuous infusion with or without PCA	Some nonopioids, opioids, adjuvant analgesics	IV is most efficient ROA for immediate analgesia and permits rapid titration IV bolus produces rapid onset of effect, but shorter duration of action than IM; not recommended for drugs with long half-lives Continuous IV infusion provides steadier drug blood levels, which maximize pain relief while minimizing side effects
Subcutaneous	Placement of drug just under skin with small needle Continuous SC infusion can be obtained with a small needle	Some opioids	Advantages: produces steady blood levels; time until onset of effect is comparable to IM administration and effects are longer lasting, with less painful administration; cheaper than IV administration; obviates need for GI function Disadvantages: slower onset and offset and lower peak effects than IV administration, time consuming, often disliked by patients
Topical	Applied directly to the skin, where the drug penetrates	NSAIDs, local anesthetics (e.g., lidocaine patch and gel, EMLA®), capsaicin	Advantages: local effect (i.e., no significant serum levels) limits side effects to local reactions; no drug-drug interactions; easy to use, no titration needed Disadvantages: may cause local skin reactions
Transdermal	Absorbed through skin with gradual release into the systemic circulation	Some opioids, adjuvant analgesics	Advantages: convenient, noninvasive, provides prolonged, relatively stable analgesia Disadvantages: delayed onset of action with first dose, drug absorption influenced by internal or external heat
Oral transmucosal	Delivery of drug to mouth, including sublingual (under tongue) and buccal/gingival administration	Some opioids	Advantages: easy, requires little staff supervision; avoids significant liver metabolism associated with oral opioids Disadvantages: variable absorption, bitter taste, dose is limited
OTFC	Fentanyl incorporated into a sweetened matrix on a stick for consumption	Fentanyl	Some absorption via oral mucosa, but most via GI tract; yields higher drug levels and better bioavailability than oral fentanyl
Intranasal	Small aerosol device placed inside nostril that delivers a calibrated dose of a drug	Butorphanol, sumatriptan	Takes advantage of rich blood supply to nose and also avoids significant liver metabolism associated with some drugs
Intraspinal	Epidural and intrathecal administration (see Table 29)		
Other (sublingual, vaginal)	Placement of drug under the tongue (sublingual) or in the vagina	Opioids	Most opioids can be absorbed sublingually or vaginally in patients who have problems such as impaired swallowing, short gut syndrome, or poor IV access

Sources: References 19, 20, 69, and 201.

EMLA®: Eutectic Mixture of Local Anesthetics (lidocaine and prilocaine); GI: gastrointestinal; IM: intramuscular; IV: intravenous; NSAIDs: nonsteroidal anti-inflammatory drugs; OTFC: oral transmucosal fentanyl citrate; PCA: patient-controlled analgesia; PO: per os (oral); ROA: route of administration; SC: subcutaneous.

e. Select a route of administration.

No single route of drug administration is appropriate for all clinical situations. Patient factors (e.g., preferences, comfort, convenience, GI function) and drug characteristics (e.g., absorption, half-life) influence the selection of an appropriate route. Table 28 reviews advantages and disadvantages of various routes of administration.

Oral administration of drugs, especially for chronic treatment, is generally preferred because it is convenient, flexible, and associated with stable drug levels.[19] Although often used, IM administration has multiple disadvantages (e.g., pain, erratic absorption, fluctuating drug levels, tissue fibrosis), thus should not be used.[19,24] Intravenous (IV) administration provides a rapid onset of pain relief and, along with rectal, sublingual, and subcutaneous administration, is useful in patients who cannot take medications by mouth. Continuous infusions produce consistent drug blood levels but are expensive, require frequent professional monitoring, and may limit patient mobility.[19] Transdermal administration is a convenient alternate means of continuous drug delivery that does not involve needles or pumps.[202] Some data suggest that some patients prefer transdermal opioid (fentanyl) to sustained-release oral morphine.[203-205]

Table 29 describes some "high-tech" methods of providing analgesia, including patient-controlled analgesia (PCA), intraspinal (epidural and intrathecal) drug administration (neuroaxial blockade), and other interventional techniques. PCA permits administration of a small dose of drug upon patient command and is especially useful in patients expected to require opioids over a period that exceeds 12 hours. It has mostly been used for IV administration of opioids for acute pain (e.g., postoperative pain), but newer PCA techniques include subcutaneous and epidural drug administration.[208] Interventional methods of analgesia include tissue infiltration (e.g., trigger point injections with local anesthetics), sensory nerve blocks, sympathetic blocks, spinal injections (e.g., epidural injections of corticosteroids, caudal blocks, nerve root injections), and continuous spinal analgesia (e.g., infusion of opioids, clonidine, baclofen) (Table 29). Nerve blocks can be used for diagnostic, prognostic, and therapeutic purposes.

f. Titrate the dose.

It may be necessary to titrate the dose of an analgesic to achieve an optimal balance between pain relief and side effects. The goal is to use the smallest dosage necessary to provide the desired effect with minimal side effects.[19] Nonopioids have a ceiling effect and may cause significant toxicity at high doses. However, most opioids do not have an analgesic ceiling, so the dosage can be titrated upwards until pain relief occurs or limiting side effects develop.

g. Optimize administration.

Medications can be administered around-the-clock (ATC) after an optimal dose over a 24-hour interval is determined.[19] Experts recommend ATC dosing for patients with continuous pain, because it provides superior pain relief with fewer side effects.[19] It also helps to break the undesirable undermedication-overmedication cycle that often develops with use of PRN medications alone. However, a short-acting, rapid-onset PRN medication should be used to manage breakthrough pain (i.e., pain that "breaks through" pain relief provided by ongoing analgesics). PRN dosing is also useful for intermittent pain, but patients need to be taught to request pain medication early, before the pain becomes severe.

h. Watch for and manage side effects.

Patients with new or altered analgesic regimens should be observed and assessed for side effects as well as pain relief. Tables 20, 23, 24, and 26 review some specific approaches to managing common side effects of nonopioid, opioid, and adjuvant analgesics. The general strategy to managing side effects consists of:[19]

- Changing the dosage or route of administration (to achieve stable drugs levels),
- Trying a different drug within the same class, and/or
- Adding a drug that counteracts the effect (e.g., antihistamine for pruritus, laxative for constipation).

Combination therapy can alleviate some side effects. For example, adding a nonopioid or adjuvant analgesic to an opioid regimen may allow use of a lower dose of the opioid. Severe side effects, on occasion, may require administration of an opioid antagonist (e.g., naloxone for opioid-induced respiratory depression).[19] Use of agents with potentially hazardous metabolites (e.g., meperidine) should be restricted to short-term treatment.[19]

Table 29. PCA and Regional Anesthesia

Route	Definition	Example Drug Types	Comments
PCA	Use of infusion pump that allows patient to self-administer small doses of analgesics via one of several routes (e.g., IV, SC, epidural)	Opioids (e.g., morphine, hydromorphone, fentanyl, meperidine), some NSAIDs	Used for numerous surgeries (e.g., C-section, abdominal, orthopedic) and medical conditions (cancer pain, sickle cell crisis, burn pain, HIV pain, pancreatitis, kidney stones, fractures) Advantages: less delay in onset of analgesia than PRN dosing Compared with IM, improved analgesia with smaller doses of opioids and fewer side effects Disadvantages: Patient must understand technique, so less useful in some clinical populations
Single or repetitive epidural bolus	Injection or infusion of agent into the epidural space via insertion of a needle (single bolus) or catheter (repetitive bolus)	Opioids (e.g., morphine, fentanyl hydromorphone), local anesthetics (e.g., bupivacaine, ropivacaine), corticosteroids, clonidine, baclofen	Used for diagnostic and therapeutic nerve blocks; the latter include surgeries (e.g., C-section, gynecologic, urological surgeries) Advantages: simple, no need for infusion device, delivery to site close to site of action (spinal cord) permits more intense analgesia (greater analgesia for given drug) Disadvantages: limited number of suitable agents, higher incidence of side effects, requires personnel to reinject catheter, higher risk of catheter contamination, does not permit PCA
Continuous epidural	Continuous infusion of agent(s) into the epidural space via a catheter. A long-term catheter can be tunneled under the skin or surgically implanted for long-term pain management (e.g., cancer pain, CNCP)	Opioids, local anesthetics	Used for acute pain (e.g., postoperative, obstetrical, posttraumatic pain) and chronic pain (e.g., cancer pain, neuropathic pain) Advantages: permits concomitant use of local anesthetic and shorter-acting opioids, eliminates need for catheter reinjection, reduces rostral spread of analgesia, less risk of catheter contamination, greater potency than systemic administration Disadvantages: Potential for catheter migration and side effects (e.g., of skin and subcutaneous tissue around catheter site; rarely, hematoma, abscess, or meningitis)
PCEA	Continuous infusion of drugs into epidural space, controlled by a patient-operated infusion pump	Opioids	Allows patient to manage dynamic changes in pain related to activity
Bolus or continuous intrathecal (spinal)	Injection or infusion of agent into the subarachnoid space via insertion of a needle (single bolus) or catheter (repetitive bolus); an indwelling intrathecal catheter can be placed for long-term analgesia to reduce the risk of infection	Opioids (e.g., morphine, hydromorphone, fentanyl), local anesthetics (e.g., lidocaine, bupivacaine, mepivacaine)	Uses include cancer pain (regionalized pain below T1), neuropathic pain Single bolus more commonly used for acute pain due to difficulty in maintaining indwelling intrathecal catheters. May be cost-effective for patients with cancer or CNCP Advantages: provides intense analgesia at lower doses than systemic administration Disadvantages: can be difficult to titrate drug effect, risk of infection and other side effects Onset and duration of effect reflect lipid solubility of agent; greater effects of drug at given dose than with systemic administration
Local infiltration	Infiltration of various body structures with local anesthetics and/or corticosteroids	Local anesthetics (e.g., bupivacaine), corticosteroids	Used for acute pain (e.g., postoperative pain, postoperative joint pain, acute bursitis, tendonitis, muscle spasm) and chronic pain (e.g., painful scars, neuromata, trigger points for myofascial syndromes, arthritis, facet syndrome)
Spinal nerve block	Blockade of spinal neurons outside the spinal canal in the paravertebral region or anywhere along its course	Local anesthetics	Includes cervical spinal blocks, occipital blocks, thoracic spinal blocks, lumbar and sacral spinal nerve blocks, sympathetic blockade Used for severe acute or chronic pain (e.g., postoperative, posttraumatic, postamputation, PVD, cancer pain, visceral pain, CRPS, neuralgias)
Topical application	Application of local anesthetics to skin (e.g., patch, gel, cream, paste)	Topical local anesthetics (e.g. lidocaine, EMLA®); other local anesthetics (e.g., cocaine, benzocaine)	Oral agents used for pain in mucous membranes of mouth Topical anesthetics used for procedural pain (EMLA®) and some chronic pain (e.g., lidocaine patch or gel for postherpetic neuralgia)

Sources: References 19, 69, 206-207.

C-section: Cesarean section; CNCP: chronic noncancer pain; CRPS: chronic regional pain syndrome; EMLA®: Eutectic Mixture of Local Anesthetics (lidocaine and prilocaine); HIV: human immunodeficiency virus; IM: intramuscular; IV: intravenous; NSAIDs: nonsteroidal anti-inflammatory drugs; PCA: patient-controlled analgesia; PCEA: Patient controlled epidural analgesia; PRN: as needed; PVD: peripheral vascular disease; SC: subcutaneous.

i. Differentiate among tolerance, physical dependence, and addiction and appropriately modify therapy.

Section I.E.5 reviews the definitions of tolerance, physical dependence, and addiction recently recommended by the American Society of Addiction Medicine (ASAM), the American Academy of Pain Medicine (AAPM), and the American Pain Society (APS).[209] Confusion regarding these terms is common and adversely influences pain management.

Tolerance normally occurs with use of certain agents (e.g., opioids). Its earliest sign is a decrease in the duration and/or degree of pain relief, which can be managed by increasing the drug dose and/or frequency of administration.[19] Combining opioids with nonopioids, or switching to a lower dose of another opioid, may delay the development of opioid tolerance.[19] However, the latter approach requires a great deal of care and significant expertise.

Signs of physical dependence include the appearance of an abstinence syndrome with abrupt cessation or diminution of chronic drug administration.[19] The nature and time of onset of this syndrome vary with drug actions and half-life. Slow tapering of the drug (e.g., 10-15% reduction in dosage per day or every other day) usually avoids the appearance of an abstinence syndrome.[210]

Although not usually encountered in patients without a history of preceding drug abuse, the administration of some drugs (e.g., opioids) may cause addiction. Signs of drug craving and/or drug-seeking behavior (e.g., missed appointments with after-hour calls for prescription renewals; solicitation of prescriptions from multiple physicians; reports of lost, destroyed, or stolen medications; selling and buying drugs off the street)[19] should alert the clinician to such a possibility. However, diagnosing addiction requires extreme caution. Similar behaviors, called "pseudoaddiction," sometimes occur in patients who are not receiving adequate pain management (e.g., doses of opioids too low or infrequent).[211] It is critical that addiction be diagnosed because it is a treatable but serious condition and failure to treat it will hinder efforts to manage pain.

j. Avoid use of placebos to treat pain.

Placebos are sometimes used to assess whether pain is responsive to sympatholysis or other interventions. However, the deceptive use of placebos to treat pain is considered unethical and inappropriate.[19]

B. Nonpharmacologic Treatments for Pain

Pharmacologic approaches to pain management are the mainstay of treatment for acute pain and cancer pain and are increasingly being used to manage chronic noncancer pain (CNCP). However, optimal pain management also includes psychological, physical rehabilitative, and in some cases, surgical treatment strategies. For example, the 1992 Agency for Health Care Policy and Research clinical practice guideline on acute pain management recommends cognitive-behavioral approaches (e.g., patient education, simple relaxation, imagery, hypnosis, and biofeedback) and physical therapeutic agents and modalities (e.g., superficial heat or cold, massage, exercise, immobility, and electroanalgesia) as part of the management of acute pain.[24]

Nonpharmacologic strategies should supplement, but not replace, the use of medications.[24] In addition to supplementing the pain-relieving effects of analgesics, nonpharmacologic approaches offer other advantages. For example, they can improve mood, reduce anxiety, increase a patient's sense of control, strengthen coping abilities, assist with sleep, relax muscles, and improve quality of life.[212-213] Factors that influence the choice of a nonpharmacologic approach to pain management include the pain type, duration, and severity; the patient's preferences, coping skills, and capabilities; the availability of support (e.g., family members); the availability of care within the community; and cost.

1. Psychological Approaches

Psychological interventions used in pain management include contingency management, cognitive behavioral therapy, biofeedback, relaxation, imagery, and psychotherapy. Table 30 defines these terms and describes potential uses of these methods. Some methods (e.g., relaxation, imagery) are simple and can be taught

quickly, whereas others require more time. Patient education materials (e.g., printed instruction sheets, audiotapes) can supplement, but not replace, clinician efforts to instruct patients in these methods.[24]

Patients in whom psychological interventions may be most appropriate include those who express interest in such approaches, manifest anxiety or fear, have inadequate pain relief after appropriate pharmacologic interventions, or experience chronic or recurrent pain.[24] When pain is acute, psychological preparation (such as preparation for surgery or for an invasive procedure) or psychological intervention such as relaxation may help to control the affective dimension of pain.[218] This, in turn, helps minimize the biological stress response that the patient experiences, as well as emotional distress and suffering.[215] When pain is chronic, learning history and operant conditioning (Table 30) sometimes contribute to the persistence of pain and disability, and counterproductive beliefs may impede a positive response to medical intervention.[214] Therefore, psychological methods are typically an integral part of the interdisciplinary approach to the management of chronic pain. Because such management usually involves rehabilitation, psychological approaches are typically integrated with rehabilitation efforts built around physical therapy.

Psychologists rarely treat pain directly but rather work with other health care professionals to integrate psychological principles into the interdisciplinary management of pain. For example, a psychologist can improve communication between a health care provider and patient or work with a clinician to alter the characteristics of a treatment regimen (e.g., complexity, dosing frequency, cost). Such psychological interventions may help assess and enhance patient adherence with treatment (e.g., medications, physical therapy), thus increasing the probability of successful management.[e,215] Unfortunately, psychological approaches to pain management are not used as often as they should be,[215] due to a variety of reasons (e.g., lack of awareness of the role of psychological factors in the response and adaptation to pain, time constraints, reimbursement policies).

[e] One reason that medical interventions sometimes fail or minimally succeed is poor patient adherence to treatment regimens. Estimates of the prevalence of medication nonadherence for the population as a whole are relatively high (30% to 60%), and patients tend to underreport poor adherence and overreport good adherence.[219] Although few studies have addressed the prevalence of nonadherence with pain medication regimens, it appears to be a problem.[220-222]

2. Physical Rehabilitative Approaches

Physical rehabilitative methods of pain management are appropriate for many types of pain and are essential in patients with CNCP. In addition to relieving pain, such methods can reduce fear and anxiety, improve physical function, and alter physiological responses to pain. Treatments used in physical rehabilitation include stretching, exercises/reconditioning (to improve strength, endurance, and flexibility), gait and posture training, and attention to ergonomics and body mechanics.[182] Other noninvasive physical treatments for pain include thermotherapy (application of heat), cryotherapy (application of cold), counter-irritation, and electroanalgesia (e.g., transcutaneous electrical stimulation) (Table 31).[182] In some cases, patients choose to pursue non-allopathic (alternative treatments) such as acupuncture or therapeutic massage.

3. Surgical Approaches

Most pain can be managed by simple noninvasive methods. However, more invasive approaches, including surgery, are sometimes needed. Orthopedic approaches to pain management include both nonsurgical ("conservative") approaches and various surgeries (e.g., total joint replacement, laminectomy, spinal fusion). Neurosurgical procedures for managing pain include neurolysis (i.e., injection of a chemical or application of heat or cold to destroy neural tissue), neuroaugmentation procedures, and neuroablative surgeries (i.e., disruption of neural signals and/or removal of neural structures associated with pain).[229] For example, microvascular decompression of the trigeminal nerve is sometimes used to manage trigeminal neuralgia.

Although beyond the scope of this monograph, a variety of other surgical approaches to pain management exist. Other sources (e.g., Bonica's Management of Pain, 3rd ed.) provides complete coverage of these methods.

Table 30. Examples of Psychological Methods Used to Manage Pain

Intervention	Definition	Purpose/Goals	Uses
Patient education	Provision of detailed information about disease or interventions and methods of assessing and managing pain (e.g., preoperative instruction about importance of deep breathing, coughing, and ambulating postoperatively; teaching patients with chronic pain about what may aggravate and relieve pain)	Can reduce pain, analgesic use, and length of hospital stay	Postoperative pain, chronic pain
Contingency management[a]	CM involves the manipulation of environmental consequences of pain behavior in a way that helps patients to modify their behavior; it involves use of social reinforcers to increase "well behavior" (e.g., exercise, non-medical conversation) and decrease "sick role" behavior	Refers to methods not for treating the pain per se but rather helping patients to change behaviors Studies suggest that CM effectively reduces pain	Chronic pain
CBT	CBT combines cognitive therapy techniques (e.g., attention diversion) with behavioral techniques (e.g., relaxation, assertiveness training); there are two major CBT subtypes: cognitive restructuring and coping skills training	Helps patients alter their perceptions or labeling of pain (i.e., decrease negative thoughts, emotions, and beliefs), increase sense of control, and decrease maladaptive behaviors	Chronic pain especially, but also useful for acute pain
Cognitive restructuring	Type of CBT in which patients are taught to monitor and evaluate negative thoughts	The goal is to generate more accurate and adaptive thoughts	Chronic pain
Coping skills training	Type of CBT that helps patients develop coping skills, which includes relaxation and imagery techniques, adaptive coping self-statements, and group psychotherapy	Directed at helping patients to develop skills to manage pain and stress	Multiple types of pain (see below)
Relaxation with imagery	Includes progressive muscle relaxation, imagery, visualization, and meditation One of most widely used nonpharmacologic treatments for pain that can increase focus on feelings of well-being as well as diminish tension, anxiety, depression, and pain-related inactivity.[b]	Relaxation decreases patient's focus on pain, muscle tension, and autonomic and emotional arousal; imagery provides a competing cognitive focus, which can block the perception of pain	Postoperative pain, chronic headache, chronic LBP, cancer pain, arthritis pain, labor pain, TMD
Hypnosis	Technique in which a patient's susceptibility to suggestion is heightened, facilitating modification of memory and perception; hypnosis can be used alone or as a means of enhancing the effectiveness of another clinical intervention	Hypnosis may provide comfort and reduce anxiety and suffering associated with acute, recurrent, and chronic types of pain; it reduces cortical activation associated with painful stimuli	Postoperative, burn, dental, labor, cancer, procedural, neuropathic, and musculoskeletal pain; headache
Distraction	Includes repeating reaffirming phrases, singing, talking, etc., to distract attention from unpleasant awareness of pain; in patients with CNCP, it also may include social and recreational activities	The goal is for the patient to actively occupy his or her attention with an activity or topic other than pain	Multiple acute and chronic types of pain
Biofeedback	Patient learns to take voluntary control over physiological body activities by receiving input (e.g., visual or auditory cues) about these activities (e.g., heart beat, muscle tension, skin temperature)	Directed at teaching a patient how to take control of body responses via mental activity	Most support for use with vascular HA; also used for chronic LBP and other HA, myofascial pain, rectal pain
Psychotherapy	Treatment for a mental illness or maladaptive behaviors that involves a therapist establishing a relationship with a patient to achieve certain goals; includes individual (supportive and dynamic), group, and family psychotherapy	Goals of psychotherapy include modifying symptoms, changing maladaptive behaviors, and promoting growth and development	Chronic pain, cancer pain, pain associated with HIV infection

Sources: References 24, 72, and 214-218.

[a]The terms "contingency management" and "operant conditioning" are used interchangeably. Overlap exists between CM and CBT, but CM focuses more on modifying behavior and CBT helps more with altering patient perceptions or labeling of sensations.[214]
[b]These methods can be taught quickly but patients do best with encouragement from health care professionals and family members. Audiotapes and printed materials also can be helpful.[24]

CBT: cognitive-behavioral therapy; CM: contingency management; CNCP: chronic noncancer pain; HA: headache; HIV: human immunodeficiency virus; LBP: low back pain; TMD: temporomandibular disorder.

Table 31. Examples of Physical Methods Used to Manage Pain

Intervention	Definition	Purpose/Goals	Examples of Uses
Stretching	Gentle exercise to improve flexibility	Improve ROM, function, comfort	Arthritis, LBP, fibromyalgia, myofascial pain syndrome
Exercise/ reconditioning	Reconditioning exercises can improve strength and endurance as well as combat stiffness and weakness associated with pain-related inactivity	Useful in regaining muscle and tendon strength, as well as improving ROM, endurance, comfort, and function Transforms painful activities into more easily tolerated ones Minimizes atrophy, demineralization, and deconditioning	Arthritis, LBP, fibromyalgia, CRPS
Gait and posture training	Appropriate attention to gait and posture, including preventive and therapeutic ergonomics	Relieve pain and restore function; prophylaxis against further pain	LBP, neck pain, tension HA
Applied heat or cold	Application of cold (cryotherapy) to decrease pain and swelling and improve function; later application of heat (thermotherapy) to augment performance and diminish pain	Application of cold produces local analgesia, slows nerve conduction, and promotes tendon flexibility Application of heat produces local analgesia, dilates (widens) blood vessels, and promotes flexibility	Acute trauma (e.g., injury, surgery); repetitive trauma, arthritis, muscle pain or spasm, acute LBP
Immobilization	Reduction of activity and avoidance of strain for certain duration; may involve brace to assist, restrict, or limit function of joint	May be needed to maintain proper alignment during post-injury repair but is generally harmful for patients with CNCP	Some postoperative, injury (e.g., fracture)
TENS	Selective stimulation of cutaneous receptors sensitive to mechanical stimuli (mechanoreceptors) by applying low-intensity current via skin electrodes[a]	TENS can reduce pain and analgesic use and improve physical mobility, presumably by interfering with transmission of nociceptive impulses in nerve fibers	Trauma, postoperative, labor, abdominal pain; neuralgias, other neuropathic pain, PVD, angina, musculoskeletal pain
PNS SCS IC	Electrical stimulation of selected regions of the nervous system via implantable devices[b]	The goal of electrical stimulation is to disrupt nociceptive signaling	Chronic pain of the trunk and limbs (e.g., PVD), neuropathic pain (deafferentation, poststroke pain), cancer pain
Massage	Rubbing of painful or nonpainful adjacent area	Facilitates relaxation and decreases muscle tension and pain	Postoperative pain, arthritis, fibromyalgia
Acupuncture	Old Chinese healing technique involves insertion of fine needles into the skin at varying depths; application of pressure at acupuncture sites is called acupressure	Acupuncture may cause the secretion of endorphins and interfere with transmission of nociceptive information to relieve pain	Postoperative, radiculopathy, chronic LBP, fibromyalgia

Sources: References 24, 72, 182, and 223-228.

[a]TENS appears to work best when applied to skin close to the pain's site of origin and when sense of touch and pressure are preserved.
[b]The implanted portion of the device consists of a pulse generator and leads connected to electrodes located in fascia in close proximity to a peripheral nerve (PNS), the spinal canal (SCS), or brain (IC). The patient or clinician controls stimulation using non-implanted system components.

CNCP: chronic noncancer pain; CRPS: chronic regional pain syndrome types I and II; HA: headache; IC: intracerebral stimulation; LBP: lower back pain; PNS: peripheral nerve stimulation; PVD: peripheral vascular disease; ROM: range of motion; SCS: spinal cord stimulation; TENS: transcutaneous electrical nerve stimulation.