CHAPTER 62

Pain Management

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KEY CONCEPTS

1. It is important, whenever possible, to ask patients if they have pain, to identify the source of pain, and to assess the characteristics of the pain.
2. Patients taking analgesics should be monitored for response and side effects, particularly sedation and constipation associated with the opioids.
3. Oral analgesics are preferred over other dosage forms whenever feasible, but it is important to adjust the route of administration to the needs of the patient.
4. Equianalgesic doses are useful as a guide when converting from one agent to another, but further dose titration usually is required to achieve treatment goals.
5. Doses must be individualized for each patient and administered for an adequate duration of time. Around-the-clock regimens should be considered for acute and chronic pain. As-needed regimens should be used for breakthrough pain or when acute pain displays wide variability and/or has subsided greatly.
6. For chronic pain that has a maladaptive inflammatory and/or neuropathic component, anticonvulsants, tricyclic antidepressants, and opioids should be considered.
7. Whenever possible, a multidisciplinary approach and nonpharmacologic strategies should be used.
8. Placebo therapy should not be used as an attempt to diagnose psychogenic pain.

Although the world is full of suffering, it is also full of the overcoming of it.

Helen Keller[1]

Humans have always known and sought relief from pain.[2] The act of relieving pain probably is as old as the medical profession itself. Today, pain's impact on society still is great, and indeed pain complaints remain a primary reason patients seek medical advice.[3]

Regrettably, many healthcare providers do not receive adequate training in this area, and new information is not widely disseminated and/or understood. Clearly, pain management is enhanced when a multidisciplinary approach is applied. Thus, understanding the pathophysiology of pain therapy and maintaining a working knowledge of individual pain regimens are important key factors in addressing pain control.

Learning Objectives, Review Questions, and other resources can be found at **www.pharmacotherapyonline.com.**

DEFINITION

An acceptable definition of pain remains an enigma. Once thought to be a punishment from the gods, the word is derived from the Latin *peone* and the Greek *poine,* meaning "penalty" or "punishment."[2] Aristotle considered pain a feeling and classified it as a passion of the soul, where the heart was the source or processing center of pain.[2] This Aristotelian concept predominated for 2,000 years, although Descartes, Galen, and Vesalius postulated that pain was a sensation in which the brain played an important role. In the 19th century, Mueller, Van Frey, and Goldscheider hypothesized the concepts of neuroreceptors, nociceptors, and sensory input.[2] These theories developed into the current definition of pain: "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage."[4] Pain often is so subjective, however, that many clinicians define pain as whatever the patient says it is. The best care is achieved (a) when the patient comes first and (b) when in doubt remember number 1.[5]

EPIDEMIOLOGY

Fifty million Americans are partially or totally disabled because of pain.[3] The annual cost of pain to U.S. society can be estimated to be in the billions of dollars.[6] In 1 year, an estimated 25 million Americans will experience acute pain due to injury or surgery, and one third of Americans will experience severe chronic pain at some point in their lives.[7] These numbers are expected to rise, as increasingly more Americans work beyond age 60 years and survive into their 80s.[6]

Unfortunately, pain often remains undertreated in hospitals, long-term care facilities, and the community. Seriously ill hospitalized patients have reported a 50% incidence of pain; 15% had extremely or moderately severe pain occurring at least 50% of the time, and 15% were dissatisfied with overall pain control.[8] In a followup report, the authors state that pain control persists as a major problem in hospitalized patients, and some of these patients were still in pain many months after hospitalization and experienced pain even on their deathbeds.[9] In addition, problems with inadequate use of analgesics have been reported in cancer patients residing in nursing homes.[10] In the Michigan pain study, 70% of chronic pain patients claimed to have pain despite treatment, with 22% believing that treatment worsened pain.[6]

PATHOPHYSIOLOGY

The pathophysiology of pain involves a complex array of neural networks in the brain that are acted on by afferent stimuli to produce

the experience we know as pain. In acute pain, this modulation is short-lived, but in some situations, the changes may persist, and chronic pain develops.[11,12]

NOCICEPTIVE PAIN

Nociceptive pain typically is classified as either somatic (arising from skin, bone, joint, muscle, or connective tissue) or visceral (arising from internal organs such as the large intestine or pancreas).[13] Whereas somatic pain most often presents as throbbing and well localized, visceral pain can manifest as pain feeling as if it is coming from other structures (referred) or as a well-localized phenomenon.[13] We can think of nociception in terms of stimulation, transmission, perception, modulation,[13] and adaptive inflammation.[12]

Stimulation

The first step leading to the sensation of pain is stimulation of free nerve endings known as *nociceptors.* These receptors are found in both somatic and visceral structures. They distinguish between noxious and innocuous stimuli, and they are activated and sensitized by mechanical, thermal, and chemical impulses.[13] The underlying mechanism of these noxious stimuli (which in and of themselves may sensitize/stimulate the receptor) may be the release of bradykinins, potassium ion (K^+), prostaglandins, histamine, leukotrienes, serotonin, and substance P (among others) that sensitize and/or activate the nociceptors.[14,15] Receptor activation leads to action potentials that are transmitted along afferent nerve fibers to the spinal cord (Fig. 62–1). [13]

Transmission

Nociceptive transmission takes place in Aδ and C-afferent nerve fibers.[13] Stimulation of large-diameter, sparsely myelinated Aδ fibers evokes sharp, well-localized pain, whereas stimulation of unmyelinated, small-diameter C fibers produces dull, aching, poorly localized pain.[13]

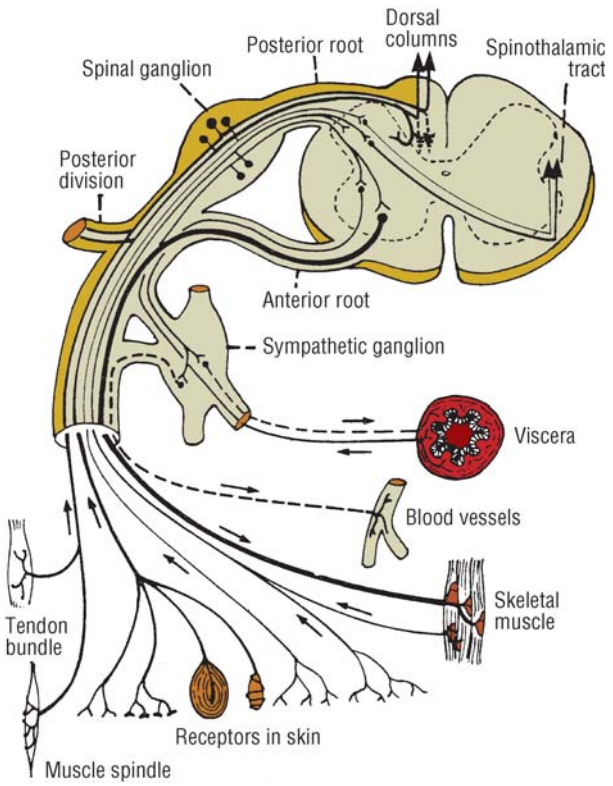

FIGURE 62-1. Schematic representation of nociceptive pain. *(Adapted from reference 15 with permission.)*

These afferent, nociceptive pain fibers synapse in various layers (laminae) of the spinal cord's dorsal horn,[15] releasing a variety of neurotransmitters, including glutamate, substance P, and calcitonin gene–related peptide.[16] The complex array of events that influence pain can be explained in part by the interactions between neuroreceptors and neurotransmitters that take place in this synapse. For example, by stimulating large sensory myelinated fibers (e.g., Aβ) that mutually connect in the dorsal horn with pain fibers, both noxious and nonnoxious stimuli can have an inhibitory effect on pain transmission (Fig. 62–1).[17] Functionally, the importance of the interplay between these different fibers and various neurotransmitters and neuroreceptors is evident in the analgesic response produced by topical irritants or transcutaneous electrical nerve stimulation. These pain-initiated processes reach the brain through a complex array of at least five ascending spinal cord pathways, which include the spinothalamic tract.[18] Information other than pain is also carried along these pathways. Thus, pain is influenced by many factors supplemental to nociception and precludes simple schematic representation. It is postulated that the thalamus acts as a relay station, as these pathways ascend and passs the impulses to central structures where pain can be processed further.[13]

Pain Perception

At this point in transmission, pain is thought to become a conscious experience that takes place in higher cortical structures. The brain may accommodate only a limited number of pain signals, and cognitive and behavioral functions can modify pain. Relaxation, distraction, meditation, and guided mental imagery may decrease pain by limiting the number of processed pain signals.[13] In contrast, a change in our neurobiochemical makeup that results in states such as depression or anxiety may worsen pain.

Modulation

The body modulates pain through a number of complex processes. One, known as the *endogenous opiate system,* consists of neurotransmitters (e.g., enkephalins, dynorphins, and β-endorphins) and receptors (e.g., μ, δ, and κ) that are found throughout the central nervous system (CNS).[18] Like exogenous opioids, endogenous opioids bind to opioid receptor sites and modulate the transmission of pain impulses.[13] Other receptor types also can influence this system. Activation of *N*-methyl-D-aspartate (NMDA) receptors, found in the dorsal horn, can decrease the μ-receptors' responsiveness to opiates.[18]

The CNS also contains a highly organized descending system for control of pain transmission. This system can inhibit synaptic pain transmission at the dorsal horn and originates in the brain.[13] Important neurotransmitters here include endogenous opioids, serotonin, norepinephrine, γ-aminobutyric acid (GABA), and neurotensin.[13]

Adaptive Inflammation

Inflammatory pain can be thought of as the body's shifting from preventing tissue damage to the promotion of healing (e.g., surgical wounds, traumatic injury). As a result of the inflammatory process, the pain threshold is reduced and the injured area becomes more sensitive to pain. This process decreases our contact with and movement of the injured area, thus promoting the progression of healing.[12] When this course of action outlives its functionality or when it is caused by diseases such as arthritis, it can move from an acute to a chronic problem (maladaptive inflammation).[12] "In response to tissue damage and inflammation, a significant alteration occurs in the chemical composition and properties of the neurons that innervate the inflamed tissues. These alterations reflect the nature and levels of the different proteins expressed by the sensory neurons. Altered production of these proteins may modify the phenotypes of the neurons, changing their transduction and transmission properties. Inflammatory pain is also associated with an increase in the excitability or responsiveness of

neurons within the CNS, referred to as *central sensitization.* This phenomenon, like peripheral sensitization, is a major cause of hypersensitivity to pain after injury."[19]

NEUROPATHIC PAIN/FUNCTIONAL PAIN

Neuropathic and functional pain is distinctly different from nociceptive pain in that it becomes disengaged from noxious stimuli or healing[12] and often is described in terms of chronic pain. Neuropathic pain is a result of nerve damage, whereas functional pain can be thought of as abnormal operation of the nervous system.[12] A number of neuropathic pain syndromes (e.g., postherpetic neuralgia, diabetic neuropathy) and functional pain syndromes (e.g., fibromyalgia, irritable bowel syndrome, sympathetic induced pain, tension-type headaches, and some noncardiac chest pain)[12] exist. They often are underrecognized and difficult to treat.[13] In addition, the pain reported often is not evident by examining physical findings.[13]

The mechanism responsible for neuropathic and functional pain may be the nervous system's endogenous dynamic nature. Nerve damage or certain disease states may evoke changes seen in inflammatory pain, ectopic excitability, enhanced sensory transmission, nerve structure reorganization, and loss of modulatory pain inhibition.[12,19] Pain circuits rewire themselves both anatomically and biochemically.[16] This produces spontaneous nerve stimulation, autonomic neuronal pain stimulation, and a progressive increase in the discharge of dorsal horn neurons.[13,16]

Clinically, patients present with spontaneous pain transmission (often described as burning, tingling, shock-like, or shooting), exaggerated painful response to normally noxious stimuli (hyperalgesia), and/or painful response to normally nonnoxious stimuli (allodynia).[13,20] This change over time may help to explain why this type of pain often manifests long after the actual nerve-related injury or when no actual injury is identified.

CLASSIFICATION OF PAIN

ACUTE PAIN

Acute pain can be a useful physiologic process warning individuals of disease states and potentially harmful situations. Unfortunately, severe, unremitting, undertreated, acute pain, when it outlives its biologic usefulness, can produce many deleterious effects (e.g., psychological problems). Acute pain usually is nociceptive, although it can be neuropathic in nature, with a relatively strong relationship to levels of pathology.[7] Common causes of acute pain include surgery, acute illness, trauma, labor, and medical procedures.[7]

CHRONIC PAIN

Under normal conditions, acute pain subsides quickly as the healing process decreases the pain-producing stimuli; however, in some instances, pain persists for months to years, leading to a chronic pain state with features quite different from those of acute pain (Table 62–1). This type of pain can be nocicpetive, neuropathic/functional, or both.[7] Subtypes include: pain that persists beyond the normal healing time for an acute injury (e.g., complex regional pain syndrome), pain related to a chronic disease (e.g., pain secondary to osteoarthritis), pain without an identifiable organic cause (e.g., fibromyalgia), and a fourth type that many experts believe warrants a discrete classification,[7] pain associated with cancer.[21]

CANCER PAIN

Pain associated with potentially life-threatening conditions is often called malignant pain or simply cancer pain.[7] This type of pain includes both chronic and acute components and often has multiple etiologies. It is pain caused by the disease itself (e.g., tumor invasion, organ obstruction), treatment (e.g., chemotherapy, radiation, surgical incisions), or diagnostic procedures (e.g., biopsy).[7]

TABLE 62-1 Characteristics of Acute and Chronic Pain

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

Data from Stimmel[2] and Jacobson and Mariano.[68]

CLINICAL PRESENTATION

Clinical presentation of pain is best addressed by proper pain assessment. A patient-oriented approach is essential, and evaluation methods should not differ from those used in other medical conditions.[2] Therefore, a comprehensive history and physical examination are imperative to evaluate underlying diseases and possible (1) contributing factors.[2] This includes identifying the source of pain when possible.[2] A baseline characterization of pain can be obtained by assessing PQRST characteristics (Table 62–2).[22] Attention also must be given to mental/emotional factors that alter the pain threshold. Anxiety, depression, fatigue, anger, and fear in particular are noted to lower this threshold, whereas rest, mood elevation, sympathy, diversion, and understanding raise the pain threshold.[22]

Clinicians must evaluate all components of the pain experience, e.g., behavioral (part of our reaction to pain is learned),[23] cognitive (thinking processes alter pain experiences),[24] social (pain expression differs in accordance with social environments),[25] and cultural (cultural background may influence pain tolerance).[25] In addition, separating chronic pain from acute pain allows for improved treatment regimens. Acute pain often is localized, well described, and relieved with conventional analgesic therapy (e.g., opioids, acetaminophen, nonsteroidal antiinflammatory drugs [NSAIDs]), whereas chronic pain many times is not well recognized and is not easily treated with conventional analgesics. (2) Proper patient assessment must include an evaluation of pain management. Pain intensity, pain relief, and medication side effects (e.g., opioid-induced sedation or constipation) must be assessed and reassessed on a regular basis. The timing and regularity of this assessment will depend on the type of pain and the medications administered. Postoperative pain and acute exacerbation of cancer pain may need to be assessed hourly, whereas chronic noncancer pain may require only daily or less frequent assessment. Pain intensity assessment is vital in acute pain,

TABLE 62-2 PQRST Characteristics of Pain

P	Palliative factors Provocative factors	What makes the pain better? What makes the pain worse?
Q	Quality	Describe the pain.
R	Radiation	Where is the pain?
S	Severity/intensity	How does this pain compare with other pain you have experienced?
T	Temporal factors	Does the intensity of the pain change with time?

Data from Twycross.[22]

CLINICAL PRESENTATION OF PAIN

Acute

General

- Often obvious distress (e.g., trauma)

Symptoms

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

Signs

- Hypertension, tachycardia, diaphoresis, mydriasis, and pallor, but these signs are *not diagnostic*
- In some cases there are no obvious signs
- Comorbid conditions usually not present
- Outcome of treatment generally predictable

Laboratory Tests

- Pain is always subjective
- There are *no* specific laboratory tests for pain
- Pain is best diagnosed based on patient description and history

Chronic

General

- Can appear to have no noticeable suffering

Symptoms

- Can be described as sharp, dull, shock-like, tingling, shooting, radiating, fluctuating in intensity, and varying in location (these often occur *without* a timely relationship with an obvious noxious stimuli)
- Over time, the pain stimulus may cause symptoms that completely change (e.g., sharp to dull, obvious to vague)

Signs

- Hypertension, tachycardia, diaphoresis, mydriasis, and pallor are seldom present
- In most cases there are NO obvious signs
- Comorbid conditions often present (e.g., sleep problems, depression, relationship problems)
- Outcome of treatment often unpredictable

Laboratory Tests

- Pain is always subjective
- Pain is best diagnosed based on patient description and history
- There are *no* specific laboratory tests for pain; however, history and/or diagnostic proof of past trauma (e.g., computed tomography) or present disease state (e.g., autoantibodies) may be helpful in diagnosing etiology

Data from Twycross[22] and the American Pain Society.[26]

whereas functionality becomes more of an issue in chronic pain. Quality of life must be assessed on a regular basis in all patients.

The clinician must remember, however, that "pain is always subjective. Objective observations of grimacing, limping, or tachycardia may be helpful in assessing patients, but these signs are often absent in patients with chronic pain caused by structural lesions. No neurophysiological or chemical test can measure pain. The clinician must accept the patient's report of pain."[26]

TREATMENT

NONPHARMACOLOGIC THERAPY

Stimulation Therapy

Transcutaneous electrical nerve stimulation (TENS) has been used in managing both acute and chronic pain (e.g., surgical, traumatic, low back, arthritis, neuropathy, fibromyalgia, and oral-facial pain).[7,17] However, the studies are contradictory and fail to show any sustained pain relief. As a result, the technique has not gained widespread acceptance.

Psychological Intervention

Even though the cognitive, behavioral, and social aspects of pain are well established, psychological interventions for the treatment of acute pain are not used widely. Simple interventions (e.g., introductory information about sensations to expect after certain procedures) reduce patient distress and greatly reduce postprocedure suffering.[27] Other successful psychological techniques, including relaxation training, imagery, and hypnosis, have proven effective in the management of postprocedure pain and in cancer-related pain.[27,28] Moderate evidence demonstrates that cognitive behavioral therapy and biofeedback also may be useful nonpharmacologic tools in managing chronic pain.[29]

PHARMACOLOGIC TREATMENT

Nonopioid Agents

Analgesia should be initiated with the most effective analgesic agent having the fewest side effects. Acetaminophen, acetylsalicylic acid (aspirin), and NSAIDs often are preferred over opiates in the treatment of mild-to-moderate pain (Table 62–3). These drugs (with the exception of acetaminophen) prevent formation of prostaglandins produced in response to noxious stimuli, thereby decreasing the number of pain impulses received by the CNS.[26] Therapeutic outcomes may be less than desired in those who do not expect "mild" analgesics to relieve pain. NSAIDs may be particularly useful in the management of cancer-related bone pain.[28] Studies comparing the efficacy of these agents have been inconsistent. Therefore, the choice of a particular agent often depends on availability, cost, pharmacokinetics, pharmacologic characteristics, and the side-effect profile. Because of the large interpatient variability with NSAIDS, it is considered rational therapy to switch to another member of this drug group after an adequate therapeutic trial of any single agent.

Opioid Agents

Opioids are often the next logical step in the management of acute pain and cancer-related chronic pain. They also are an effective treatment option in the management of chronic noncancer pain; however, this continues to be somewhat controversial. Many times a trial of opioids is warranted, but such a trial should not be done without a complete assessment of the pain complaint.[30]

TABLE 62-3 Adult FDA-Approved Nonopioid Analgesics (Includes Only FDA Approved Agents for Pain)

Class and Generic Name (Brand Name)	Half-Life (h)	Usual Dosage Range (mg)	Maximal Dose (mg/day)
Salicylates			
Acetylsalicylic acid[a]–aspirin (various)	0.25	325–1,000 every 4–6 h	4,000
Magnesium–anhydrous[a]	Nd/Nd	304–607 every 4 h	3,738
(Doan's, various, various combinations of choline and magnesium are available)		607–934 every 6 h	
Diflunisal (Dolobid, various)	8–12	500–1,000 initial 250–500 every 8–12 h	1,500
para-Aminophenol			
Acetaminophen[a] (Tylenol, various)	2–3	325–1,000 every 4–6 h	4,000[b]
Fenamates			
Meclofenamate (various)	0.8–2.1	50–100 every 4–6 h	400
Mefenamic acid (Ponstel)	2	Initial 500 250 every 6 h (maximum 7 days)	1,000[c]
Pyranocarboxylic acid			
Etodolac (various) (immediate release)	7.3	200–400 every 6–8 h	1,000
Acetic acid			
Diclofenac potassium (Cataflam, various)	1.9	In some patients, initial 100, 50 three times per day	150[d]
Propionicacids			
Ibuprofen[a] (Motrin, various)	2–2.5	200–400 every 4–6 h	3,200[e] 2,400[e] 1,200[f]
Fenoprofen (Nalfon, various)	3	200 every 4–6 h	3,200
Ketoprofen (various)	2	25–50 every 6–8 h	300
Naproxen (Naprosyn, Anaprox, various)	12–17	500 initial 500 every 12 h or 250 every 6–8 h	1,000[c]
Naproxen sodium[a] (Aleve, various)	12–13	In some patients, 440 initial[f] 220 every 8–12 h[f]	660[f]
Pyrrolizine Carboxylic Acid			
Ketorolac–parenteral (various)	5–6	30–60 (single IM dose only)	30–60
		15–30 (single IV dose only)	15–30
		15–30 every 6 h (maximum of 5 days)	60–120
Ketorolac–oral, indicated for continuation with parenteral only (various)	5–6	10 every 4–6 h (maximum of 5 days, which includes parenteral doses) In some patients, initial oral dose of 20	40
Cyclooxygenase-2 inhibitors			
Celecoxib (Celebrex)	11	Initial 400 followed by another 200 on first day, then 200 twice daily	400

[a]Available both as an over-the-counter preparation and as a prescription drug.
[b]Some experts believe 4,000 mg may be too high.
[c]Up to 1,250 mg on the first day.
[d]Up to 200 mg on the first day.
[e]Some individuals may respond better to 3,200 mg as opposed to 2,400 mg, although well-controlled trials show no better response; consider risk versus benefits when using 3,200 mg/day.
[f]Over-the-counter dose.
FDA, Food and Drug Administration; Nd, no data.
Data from American Pain Society,[26] Anonymous,[44,45] and Watkins et al.[66]

CLINICAL CONTROVERSY

Many clinicians believe that some chronic painful conditions (e.g., osteoarthritis) never should be treated with opioids, whereas others believe that when other modalities are not effective or seem to pose more of a risk to that particular patient than does conventional therapy (e.g., NSAIDs), then opioids are necessary.

The classification of these agents, their equianalgesic doses, relative histamine-releasing characteristics, pharmacokinetics, and dosing guidelines are outlined in Tables 62–4 and 62–5. The choice of opiate should be based on patient acceptance; analgesic effectiveness; and pharmacokinetic, pharmacodynamic, and side-effect profiles (Tables 62–4 and 62–6).

The pharmacologic activity of opioids depends on their affinity for opiate receptors.[31] Therapeutic activities and side effects range from those exhibited by the opiate agonists (e.g., morphine) to those seen with the opiate antagonists (e.g., naloxone). Partial agonists and antagonists (e.g., pentazocine) compete with agonists for opiate receptor sites and, depending on the inherent agonist and antagonist properties, exhibit mixed agonist–antagonist activity. Mixed agonist–antagonist agents with analgesic activity appear to exhibit selectivity for analgesic receptor sites.[31] This may result in analgesia with fewer undesirable side effects. Efficacy and side effects also may further differ among agents because of receptor subtype variability. Specifically, research has identified multiple

TABLE 62-4 Opioid Analgesics

Class and Generic Name (Brand Name)	Chemical Source	Relative Histamine Release	Route	Equianalgesic Dose in Adults (mg)	Onset (min)/ Half-Life (h)
Phenanthrenes (Morphine-like Agonists)					
Morphine (various)	Naturally occurring	+++	IM	10	10–20/2
			PO	30	
Hydromorphone (Dilaudid, various)	Semisynthetic	+	IM	1.5	10–20/2–3
			PO	7.5	
Oxymorphone (Numorphan, Opana)	Semisynthetic	+	IM	1	10–20/2–3
			R	5[a]	
			PO	10	
Levorphanol (various)	Semisynthetic	+	IM (acute)	2 (acute)	10–20/12–16
			PO	4 (acute)	
			IM	1 (chronic)	
			PO	1 (chronic)	
Codeine (various)	Naturally occurring	+++	IM	15–30[b]	
			PO	15–30[b]	10–30/3
Hydrocodone (available as combination)	Semisynthetic	N/A	PO	5–10[b]	30–60/4
Oxycodone (various)	Semisynthetic	+	PO	20–30[c]	30–60/2–3
Phenylpiperidines (meperidine-like agonists)					
Meperidine (Demerol, various)	Synthetic	+++	IM	75	10–20/3–4
			PO	50–150[b] This drug is not recommended	
Fentanyl (Sublimaze, Duragesic, various)	Synthetic	+	IM	0.1	7–15/3–4
			Transdermal	25 mcg/h[d]	
			Buccal, transmucosal	Variable[e]	
Diphenylheptanes (methadone-like agonists)					
Methadone	Synthetic	+	IM	Variable[f] (acute)	
(Dolophine, various)			PO	Variable[f] (acute)	30–60/12–190
			IM	Variable[f] (chronic)	
			PO	Variable[f] (chronic)	
Propoxyphene (Darvon, various)	Synthetic	N/A	PO	65[b]	30–60/6–12
Agonist–antagonist derivatives					
Pentazocine (Talwin, various)	Synthetic	N/A	IM	Not recommended	
			PO	50[b]	15–30/2–3
Butorphanol (Stadol, various)	Synthetic	+	IM	2	10–20/3–4
			Intranasal	1[b] (one spray)	
Nalbuphine (Nubain, various)	Semisynthetic	N/A	IM	10	<15/5
Buprenorphine (Buprenex, various)	Semisynthetic	N/A	IM	0.4	10–20/2–3
Antagonists					
Naloxone (Narcan, various)	Synthetic	N/A	IV	0.4–2[a]	1–2 (IV), 2–5 (IM)/ 0.5–1.3
Central analgesic					
Tramadol (Ultram, various)	Synthetic	N/A	PO	50–100[b]	<60/5–7

[a]The American Pain Society[26] considers 5 mg rectal morphine = 5 mg rectal oxymorphone.
[b]Starting dose only (equianalgesia not shown).
[c]Starting doses lower (oxycodone 5–10 mg, meperidine 50–150 mg).
[d]Equivalent PO morphine dose = 45–134 mg/day.
[e]For breakthrough pain only.
[f]The equianalgesic dose of methadone when compared with other opioids will decrease progressively the higher the previous opioid dose has been.
[g]Starting doses to be used in cases of opioid overdose.
IM, intramuscular; IV, intravenous; PO, oral.
Data from references 26, 32, 33, 43, 44, 45, and 67.

subtype μ-receptors with varied expression. This μ-receptor subtype variability may explain why some patients respond differently to certain opioids, specifically μ-receptor agonists.[32]

The effects of the opioid analgesics are relatively selective, and at normal therapeutic concentrations, these agents do not affect other sensory modalities,[33] such as sensitivity to touch, sight, or hearing; however, as the dosage increases, so do the undesirable side effects (Table 62–6). Patients in severe pain may receive very high doses of opioids with no unwanted side effects, but as the pain subsides, patients may not tolerate even very low doses.[34] Frequently, when opioids are administered, pain is not eliminated, but its unpleasantness is decreased.[34] Patients report that although their pain is still present, it no longer bothers them.

Opioids share related pharmacologic attributes and exert a profound effect on the CNS and gastrointestinal tract.[33] Mood changes, sedation, nausea, vomiting, decreased gastrointestinal motility, constipation, respiratory depression, dependence, and tolerance are evident in varying degrees with all agents. Constipation, sedation, and nausea/vomiting are the most common side effects of opioids; respiratory depression is less common.[35] Tolerance to side effects (except to constipation) often develops within the first week of therapy. Consideration of efficacy and side-effect profile assists in selection of the most appropriate agent.

3 The route of administration depends on individual patient needs. In patients who have oral access, the oral route is preferred. However, the onset of analgesic effects for oral medications is approximately 45 minutes, and the peak effect usually occurs 1 to 2 hours after administration.26 This delay must be a consideration when immediate relief is needed in the management of acute pain. Therefore, in some scenarios, such as acute severe pain (i.e., pain

TABLE 62-5 Dosing Guidelines

Agent(s)	Doses (Titrate Up or Down Based on Patient Response)	Notes
NSAIDs/acetaminophen/aspirin	Dose to maximum before switching to another agent (see Table 62–3)	Used in mild-to-moderate pain May use in conjunction with opioid agents to decrease doses of each Regular alcohol use and high doses of acetaminophen may result in liver toxicity Care must be exercised to avoid overdose when combination products containing these agents are used
Morphine	PO 5–30 mg q 3–4 h[a] IM 5–10 mg q 3–4 h[a] IV 1–2.5 mg q 5 min prn[a] SR 15–30 mg q 12 h (may need to be q 8 h in some patients) Rectal 10–20 mg q 4 h[a]	Drug of choice in severe pain Use immediate-release product with SR product to control "breakthrough" pain in cancer patients Every-24-hour product available
Hydromorphone	PO 2–4 mg q 3–6 h[a] IM 1–4 mg q 3–6 h[a] IV 0.1–0.5 mg q 5 min prn[a] Rectal 3 mg q 6–8 h[a]	Use in severe pain More potent than morphine; otherwise, no advantages
Oxymorphone	IM 1–1.5 mg q 4–6 h[a] IV 0.5 mg initially PO immediate release 5–10 mg q 4-6 h[a] PO extended release 10–20 mg q 12 h[a] Rectal 5 mg q 4–6 h[a]	Use in severe pain No advantages over morphine Use immediate-release product with controlled-release product to control "breakthrough" pain in cancer or chronic pain patients
Levorphanol	PO 2–3 mg q 6–8 h[a] (Levo-Dromoran) PO 2–3 mg q 3–6 h[a] (Levorphanol Tartrate) IM 1–2 mg q 6–8 h[a] IV 1 mg q 3–6 h[a]	Use in severe pain Extended half-life useful in cancer patients In chronic pain, wait 3 days between dosage adjustments
Codeine	PO 15–60 mg q 4–6 h[a] IM 15–60 mg q 4–6 h[a]	Use in moderate pain Weak analgesic; use with NSAIDs, aspirin, or acetaminophen
Hydrocodone	PO 5–10 mg q 4–6 h[a]	Use in moderate/severe pain Most effective when used with NSAIDs, aspirin, or acetaminophen Only available as combination product with other ingredients for pain and/or cough
Oxycodone	PO 5–10 mg q 4–6 h[a] Controlled release 10–20 mg q 12 h	Use in moderate/severe pain Most effective when used with NSAIDs, aspirin, or acetaminophen Use immediate-release product with controlled-release product to control "breakthrough" pain in cancer or chronic pain patients
Meperidine	IM 50–150 mg q 3–4 h[a] IV 5–10 mg q 5 min prn[a]	Use in severe pain Oral not recommended Do not use in renal failure May precipitate tremors, myoclonus, and seizures Monoamine oxidase inhibitors can induce hyperpyrexia and/or seizures or opioid overdose symptoms
Fentanyl	IV 25–50 mcg/h IM 50-100 mcg q 1–2 h[a] Transdermal 25 mcg/h q 72 h Transmucosal (Actiq Lozenge) 200 mcg may repeat × 1, 30 min after first dose is started then, titrate Transmucosal (Fentora Buccal Tablet) 100 mcg, may repeat × 1, 30 min after first does is started, then titrate Iontophoretic transdermal system 40 mcg per activation	Used in severe pain Do not use transdermal in acute pain Transmucosal for "breakthrough" cancer pain in patients already receiving or tolerant to opioids Iontophoretic transdermal system used for acute pain and can be reactivated every 10 min
Methadone	PO 2.5–10 mg q 3–4 h (acute)[a] IM 2.5–10 mg q 8–12 h (acute)[a] (more frequent dosing may be needed during initial titration) PO 5–20 mg q 6–8 h (chronic)[a]	Effective in severe chronic pain Sedation can be major problem Some chronic pain patients can be dosed every 12 h Equianalgesic dose of methadone when compared with other opioids will decrease progressively the higher the previous opioid dose
Propoxyphene	PO 100 mg q 4 h[a] (napsylate) PO 65 mg q 4 h[a] (HCl) (maximum 600 mg daily of napsylate, 390 mg HCl)	Use in moderate pain Weak analgesic; most effective when used with NSAIDs, aspirin, or acetaminophen This drug is not recommended in the elderly Will cause carbamazepine levels to increase 100 mg of napsylate salt = 65 mg of HCl salt
Pentazocine	PO 50–100 mg q 3–4 h[b] (maximum 600 mg daily)	Third-line agent for moderate-to-severe pain May precipitate withdrawal in opiate-dependent patients Parenteral doses not recommended
Butorphanol	IM 1–4 mg q 3–4 h[b] IV 0.5–2 mg q 3–4 h[b] Intranasal 1 mg (1 spray) q 3–4 h[b] If inadequate relief after initial spray, may repeat in other nostril ×1 in 60–90 min Max 2 sprays (one per nostril) q 3–4 h[b]	Third-line agent for moderate-to-severe pain May precipitate withdrawal in opiate-dependent patients

(continued)

TABLE 62-5 Dosing Guidelines (continued)

Agent(s)	Doses (Titrate Up or Down Based on Patient Response)	Notes
Nalbuphine	IM/IV 10 mg q 3–6 h[b] (maximum 20 mg dose, 160 mg daily)	Second-line agent for moderate-to-severe pain May precipitate withdrawal in opiate-dependent patients
Buprenorphine	IM 0.3 mg q 6 h[b] Slow IV 0.3 mg q 6 h[b] May repeat ×1, 30–60 min after initial dose	Second-line agent for moderate-to-severe pain May precipitate withdrawal in opiate-dependent patients Naloxone may not be effective in reversing respiratory depression
Naloxone	IV 0.4–2 mg	When reversing opiate side effects in patients needing analgesia, dilute and titrate (0.1–0.2 mg q 2–3 min) so as not to reverse analgesia
Tramadol	PO 50–100 mg q 4–6 h[a] If rapid onset not required, start 25 mg/day and titrate over several days Extended release PO 100 mg q 24 h	Maximum dose for nonextended-release, 400 mg/24 h; maximum for extended release, 300 mg/24 h Decrease dose in patient with renal impairment and in the elderly

[a]May start with an around-the-clock regimen and switch to prn if/when the painful signal subsides or is episodic.
[b]May reach a ceiling analgesic effect.
IM, intramuscular; IV, intravenous; NSAID, nonsteroidal antiinflammatory drug; PO, oral; prn, as needed; SR, sustained release.
Data from American Pain Society,[26] Gutstein and Akil,[33] and Anonymous,[44,45]

crisis) or when the patient is unable to take oral medications, alternative routes of therapy (e.g., intravenous) may be preferred. 4 The opioids differ greatly in equianalgesic dose (Table 62–4), which should be used only as a guide because the nature of pain makes it necessary to individualize pain regimens. True opioid allergies are rare, but Table 62–4 also can be used when treating a patient who is allergic to opiates. Most reactions to opioids, such as itching or rash, are due to the associated histamine release and mast cell degranulation, not to a true allergic or immunoglobulin-E (IgE) response. Although caution is always advised, a decrease in potential cross-sensitivity exists when moving from one opioid structural class to another. The classes are phenanthrenes (morphine-like agonists), phenylpiperidines (meperidine-like agonists), and diphenylheptanes (methadone-like agonists). When considering cross-sensitivity, the mixed agonist–antagonist class acts much like the morphine-like agonists.[36] Reactions due to histamine release may be reduced by choosing agents shown to have less effect on histamine release. Morphine has been associated with the greatest histamine release, whereas agents such as oxycodone and fentanyl typically cause fewer histamine-related reactions (see Table 62–4).

2 5 In the initial stages of acute pain, analgesics should be given around the clock. This should commence after administering a typical starting dose and titrating up or down, depending on the patient's degree of pain and demonstrated side effects (e.g., sedation).[26] As-needed schedules often produce wide swings in analgesic plasma concentrations that create wide swings in pain and sedation. This may initiate a vicious cycle where increasing amounts of pain medications are needed for relief. 5 As the painful state subsides and the need for medication decreases, as-needed schedules may be appropriate. As-needed schedules also may be useful in patients who present with pain that is intermittent or sporadic in nature (Fig. 62–2). The management of chronic pain is also best accomplished by around-the-clock administration schedules that inhibit serum analgesic concentrations from falling below the point at which a patient experiences the suffering of pain. As-needed schedules are to be used in conjunction with around-the-clock regimens and are used when patients experience breakthrough pain.

Continuous intravenous and subcutaneous methods of opioid infusion are effective for some postoperative pain, but the probability of unwanted side effects is high.[26] An alternative method is patient-controlled analgesia (PCA). With this technique, patients can self-administer a preset dose of an intravenous opioid via a pump electronically interfaced with a timing device. Compared to traditional as-needed opioid dosing, PCA yields better pain control, improved patient satisfaction, and relatively few differences in side effects.[37]

Administration of opiates directly into the CNS (e.g., epidural and intrathecal/subarachnoid routes) has shown considerable promise in the control of acute, chronic noncancer, and cancer pain (Table 62–7)[13,38,39] and is common in both large and small institutions throughout the United States. Because of reports of marked sedation, respiratory depression, pruritus, nausea, vomiting, urinary retention, and hypotension,[40] these methods of analgesia require careful monitoring and are best used by experienced practitioners. Respiratory depression is of concern and can occur within the first half hour or manifest as late as 12 hours after a single dose of epidural morphine.[40] Naloxone is used to antagonize this effect, but continuous infusion may be required.[40] Analgesia and side effects are evident at lower doses when the opioids are administered intrathecally instead of epidurally. Intrathecally, single morphine doses of 0.1 to 0.3 mg are common, whereas epidurally, doses of 1 to 6 mg are the norm.[38] These intrathecal and epidural opioids often are administered on a continuous-infusion and/or patient-controlled basis, and, when given simultaneously with intrathecal or epidural local anesthetics such as bupivacaine, they have been proven safe and effective.[41] All agents administered directly into the CNS should be preservative-free.

TABLE 62-6 Major Adverse Effects of the Opioid Analgesic

Effect	Manifestation
Mood changes	Dysphoria, euphoria
Somnolence	Lethargy, drowsiness, apathy, inability to concentrate
Stimulation of chemoreceptor trigger zone	Nausea, vomiting
Respiratory depression	Decreased respiratory rate
Decreased gastrointestinal motility	Constipation
Increase in sphincter tone	Biliary spasm, urinary retention (varies among agents)
Histamine release	Urticaria, pruritus, rarely exacerbation of asthma (varies among agents)
Tolerance	Larger doses for same effect
Dependence	Withdrawal symptoms upon abrupt discontinuation

Data from Stimmel,[2] Miyoshi and Leckband,[31] and Reisine and Pasternak.[34]

Tolerance, Dependence, Addiction, and Pseudoaddiction

A barrier that consistently causes clinicians to misjudge and mistreat pain is the misunderstanding of opioid tolerance, physical dependence, addiction, and pseudoaddiction. "Tolerance is the diminution of drug effect over time as a consequence of exposure to the drug."[42] It develops at different rates and with tremendous patient variability. However, with stable disease, opioid use often stabilizes, and tolerance does not lead to addiction.[42] "Physical dependence is defined by

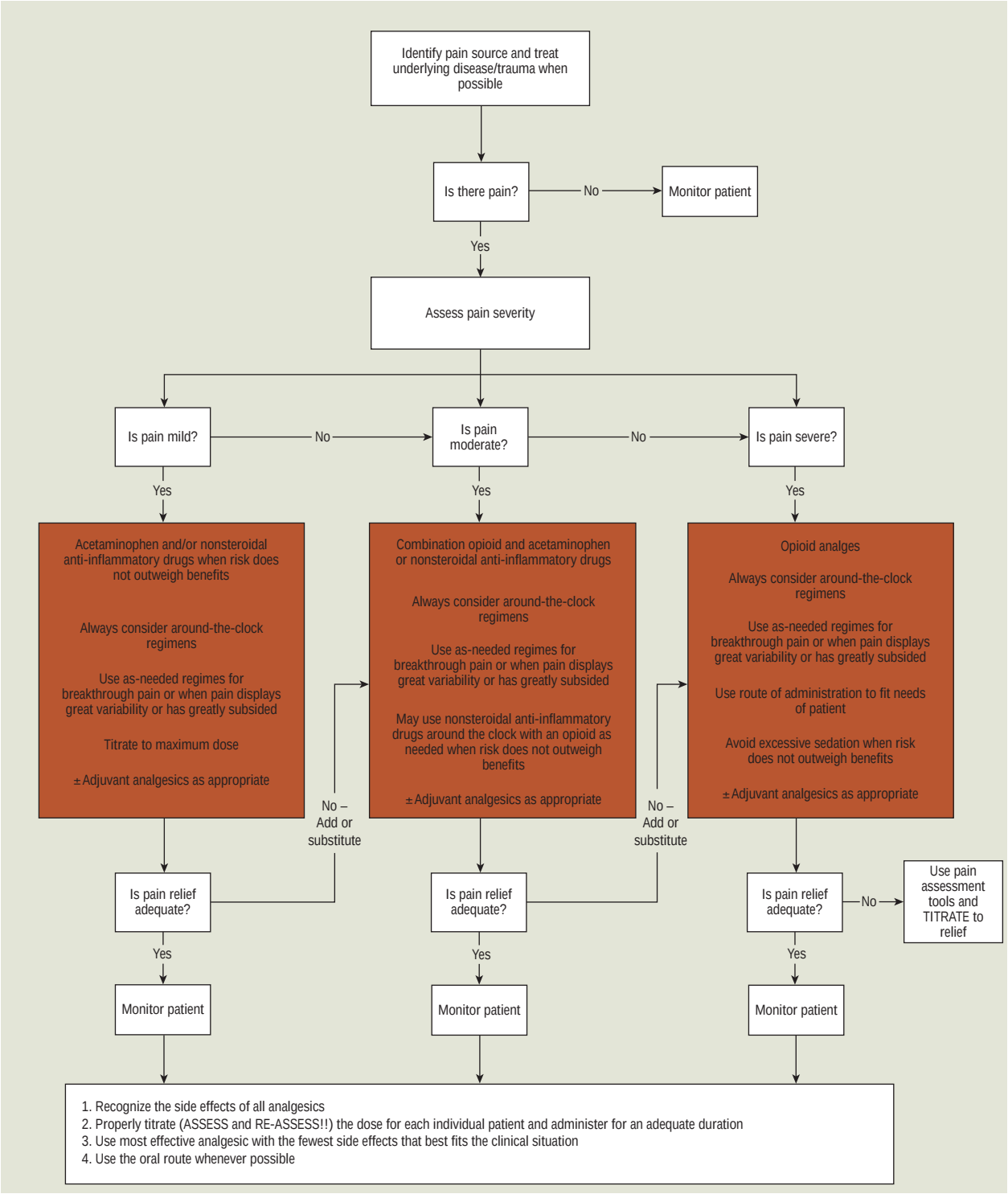

FIGURE 62-2. Algorithm for acute pain. *(Data modified from Omnicare, Inc., Acute Pain Pathway.)*

the occurrence of an abstinence syndrome following administration of an antagonist drug or abrupt dose reduction or discontinuation."[42] Clinicians must understand that physical dependence and tolerance are not equivalent to addiction; however, with chronic opioid use, they are likely to develop.[26] "Addiction is best defined as a behavioral pattern characterized as loss of control over drug use, compulsive drug use, and continued use of a drug despite harm."[42] When opioids are being used, these behaviors must be evaluated continually, but extreme caution is advised when using the term *addiction* because of its many negative connotations, which can lead to a compromised clinician–patient relationship and ineffective pain control.[26,42] In addition, clinicians must be aware that an individual's behaviors may suggest addiction, when in reality the behaviors noted are a reflection of unrelieved pain or pseudoaddiction.[26] The incidence of addiction varies depending on the patient population. In patients with no history of addiction, the risk of addiction is relatively small. "Drug exposure appears to be only one etiologic factor in the development of addiction, and genetics, social, and psychologic factors may be more significant determinants."[7]

Morphine and Congeners Despite the availability of several newer agents, morphine remains the prototype opiate analgesic. As

TABLE 62-7 Intraspinal Opioids

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

Data from American Pain Society[26] and Ready.[38]

new opioid and nonopioid compounds are developed, their efficacy and side-effect profiles are compared against morphine as the standard. Many clinicians consider morphine the first-line agent when treating moderate-to-severe pain. Morphine can be given parenterally, orally, or rectally.

Side effects can be numerous, particularly when morphine is first initiated or when doses are significantly increased. Morphine causes nausea and vomiting through direct stimulation of the chemoreceptor trigger zone.[33] Opioid-induced nausea is observed most frequently after the initial dose and often subsides with subsequent doses.[43] Although euphoria and dysphoria have been reported, morphine's unpleasant effects are more prominent when administered to patients not experiencing pain.[33] As doses of morphine are increased, the respiratory center becomes less responsive to carbon dioxide, causing progressive respiratory depression. This effect is less pronounced in patients being treated for severe or chronic pain. Respiratory depression often manifests as a decrease in respiratory rate (although minute volume and tidal volume also are affected) and is further compounded because the cough reflex is also depressed. Morphine-induced respiratory depression can be reversed by pure opioid antagonists, such as naloxone.[34] In patients with underlying pulmonary dysfunction, caution must be used as these patients are already using compensatory breathing mechanisms and are at risk for further respiratory compromise.[34] Caution is also urged when combining opiate analgesics with alcohol or other CNS depressants because this combination is potentially harmful and possibly lethal.

Therapeutic doses of morphine have minimal effects on blood pressure, cardiac rate, or cardiac rhythm when patients are supine; however, morphine does produce venous and arteriolar vessel dilation, and orthostatic hypotension may result. Hypovolemic patients are more susceptible to morphine-induced cardiovascular changes (e.g., decreases in blood pressure).[34] Because morphine prompts a decrease in myocardial oxygen demand in ischemic cardiac patients, it is often considered the drug of choice when using opioids to treat pain associated with myocardial infarction.

Morphine decreases the propulsive contractions of the gastrointestinal tract and reduces biliary and pancreatic secretions,[34] resulting in constipation. Morphine-induced spasms of the sphincter of Oddi have been observed.[34] However, the clinical significance of such an occurrence is unclear. Urinary retention is another potential side effect of morphine; tolerance develops to this effect over time.[34] Morphine-induced histamine release often manifests as pruritus, and although not seen often, it may exacerbate bronchospasm in patients with a history of asthma.[34] Therapeutic doses of morphine do not directly affect cerebral circulation, but drug-induced respiratory depression can increase intracranial pressure. Thus, caution is advised in head trauma patients who are not ventilated because morphine may exaggerate this pressure[34] and cloud the neurologic examination results.

Morphine is metabolized to two important metabolites, morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G). One metabolite, M6G, contributes to analgesia, whereas the other, M3G, may contribute to side effects if allowed to accumulate. The metabolites are renally cleared and can accumulate in patients with renal impairment, contributing to greater side effects.[33]

Hydromorphone is more potent, has better oral absorption characteristics, and is more soluble than morphine, but its overall pharmacologic profile parallels that of morphine. Some clinicians believe hydromorphone is associated with fewer side effects, especially pruritus, compared to other opioids. However, the research is limited and does not conclusively demonstrate a difference in side effects between morphine and hydromorphone. Oxymorphone can be administered orally, rectally, and by injection. Although extended-release and immediate-release oral products have become available, making oxymorphone useful in chronic and acute pain, it offers no pharmacologic advantage over morphine. Levorphanol has an extended half-life, but its overall therapeutic effects are similar to the other agents in this class.

Codeine is a commonly used opiate in the treatment of mild-to-moderate pain. It often is combined with other analgesic products (e.g., acetaminophen). Unfortunately, it has the same propensity to produce side effects as morphine and may produce more nausea and constipation.[26] Hydrocodone is another commonly prescribed opiate and is available for pain only in combination products with other analgesic agents (e.g., acetaminophen, ibuprofen). Its pharmacologic properties are similar to those of morphine. Oxycodone is a useful oral analgesic for moderate-to-severe pain. This is especially true when the product is used in combination with nonopioids. Although oxycodone shares basic morphine characteristics, the availability of an immediate-release and controlled-release oral dosage form also makes it very useful in persistent pain as well as acute pain.

Meperidine and Congeners (Phenylpiperidines) The prototype phenylpiperidine, meperidine, has a pharmacologic profile comparable with that of morphine; however, it is not as potent and has a shorter analgesic duration. This necessitates larger doses that often must be administered more frequently for satisfactory pain relief. Meperidine is metabolized to the toxic metabolite normeperidine, which can cause CNS excitability, manifested as tremor, muscle twitching, and possible seizures.[33] Normeperidine is renally cleared, so the risk of accumulation and toxicity is greatest in patients with renal dysfunction or the elderly.[44] The combination of monoamine oxidase inhibitors and meperidine should not be used because this mixture can produce severe respiratory depression or excitation, delirium, hyperpyrexia, and convulsions.[34] Meperidine is not recommended for long-term use because of its relatively short duration of action and the CNS hyperirritability of normeperidine.[28] Meperidine offers no analgesic advantage over morphine, has greater toxicity, and should be limited in use. In particular, its use should be avoided in patients at greatest risk for toxicity (e.g., elderly, patients with renal dysfunction).

Fentanyl is a synthetic opioid structurally related to meperidine that is used often in anesthesiology as an adjunct to general anesthesia.[44] This agent is more potent, more lipophilic, and shorter acting than meperidine (Table 62–4). It can be administered parenterally, transmucosally, and transdermally. The fentanyl patch may provide a more convenient dosing alternative in patients on stable regimens. The transdermal patch can provide analgesia for up to 72 hours, but takes 12 to 24 hours for full onset and up to 6 days to reach steady state after dose adjustments. Therefore, the transdermal patch should be limited to patients with chronic pain; it is not appropriate for the management of acute pain.[45] A fentanyl lozenge and a buccal dosage form also are available for treatment of breakthrough cancer pain.[45] Caution should be used when fentanyl is administered to patients who have a very small body habitus, always starting with the

smallest expected effective dose and carefully titrating to effect. Most recently an iontophoretic patient controlled transdermal system has been developed for use in acute postoperative pain.[45]

Methadone and Congeners Methadone has gained considerable popularity because of its oral efficacy, extended duration of action, and low cost. Although methadone is effective in acute pain,[45] it has gained particular prominence in treating cancer pain[39] and has increasingly been used in the management of chronic noncancer pain.[46] This despite the fact that, with repeated doses, the analgesic duration of action is prolonged,[45] resulting in an unpredictable half-life, possible excessive sedation, and difficulty in titration. Properties unique to methadone, compared with other opioids, include the D-isomer's ability to antagonize NMDA receptors, agonist effects at κ- and δ-opioid receptors, and blockade of serotonin and norepinephrine reuptake.[46–49] These properties may prove useful in the treatment of neuropathic and chronic pain or in patients with a maladaptive inflammatory component to their pain. The equianalgesic dose of methadone may decrease with higher doses of the previous opioid,[47] complicating conversions from other opioids to methadone.

CLINICAL CONTROVERSY

Some clinicians believe that methadone should be tried before other opioids in many chronic pain conditions where an opioid is warranted because they believe that neuropathic pain is often a component. Other clinicians believe that sustained-released morphine or oxycodone are better first choices.

Propoxyphene usually is used in combination with acetaminophen for treatment of moderate pain. Propoxyphene is metabolized to norpropoxyphene, a potentially toxic metabolite.[26] Elderly patients and those with renal dysfunction are at greatest risk for toxicity; therefore, propoxyphene use is discouraged in these patients.[26,50]

Opioid Agonist–Antagonist Derivatives

Analgesic agents that stimulate the analgesic portion of opioid receptors while blocking or having no effect on the toxicity portion would be considered ideal. The agonist–antagonist derivatives were developed with this in mind. The analgesic class produces analgesia and has a ceiling effect on respiratory depression.[31] These agents also have a lower abuse potential than does morphine, but psychotomimetic responses (e.g., hallucinations and dysphoria, as seen with pentazocine), a ceiling analgesic effect, and a propensity to initiate withdrawal in opioid-dependent populations[31] have diminished their widespread clinical use.

Opioid Antagonists

The pure opioid antagonist naloxone binds competitively to opioid receptors but does not produce an analgesic or opioid side-effect response. Therefore, it is used most often to reverse the toxic effects of agonist- and agonist–antagonist-derived opioids.

Central Analgesic

Tramadol has two basic modes of action: μ-opiate receptor binding and inhibition of norepinephrine and serotonin reuptake. It is indicated for the relief of moderate to moderately severe pain.[51]

Tramadol has a side-effect profile similar to that of the previously mentioned opioid analgesics (e.g., dizziness, euphoria, hallucinations, cognitive dysfunction, and constipation).[44] Tramadol alone may enhance the risk of seizures. In addition, concomitant use with serotonin reuptake inhibitors, opioids, tricyclic antidepressants, monoamine oxidase inhibitors, neuroleptics, or other drugs that can reduce the seizure threshold and use in patients with seizure disorders may increase the risk of seizures.[51] Tramadol may have a place in treating patients with chronic pain, especially neuropathic pain.[52]

Adjuvant Analgesics

Adjuvant analgesics are pharmacologic agents with individual characteristics that make them useful in the management of pain but that typically are not classified as analgesics. Examples of adjuvant analgesics include antidepressants and anticonvulsants. 6 Chronic pain that has a maladaptive inflammatory (e.g., low back pain) and/or neuropathic component (e.g., diabetic neuropathy) may require such agents (Table 62–8). Anticonvulsants (e.g., gabapentin, which may decrease neuronal excitability), tricyclic antidepressants, serotonin and norepinephrine reuptake inhibitor antidepressants (which block the reuptake of serotonin and norepinephrine, thus enhancing pain inhibition), and topically applied local anesthetics (which decrease nerve stimulation) all have been effective in managing chronic pain.[53,54]

In cancer patients, bone pain can be treated with radiopharmaceuticals. Both strontium 89 and samarium Sm 153 lexidronam have been shown to provide pain relief.[45] Although antihistamines, amphetamines, and steroids have been used as adjuvant pain medications,[28] they have demonstrated only limited success as pain relievers.

Combination Therapy

The combination of opioid and nonopioid analgesics often results in analgesia superior to that produced by either agent alone.[27] This facilitates the use of lower doses and a more favorable side-effect profile, and, when needed, this approach is encouraged.

REGIONAL ANALGESIA

Regional analgesia with properly administered local anesthetics can provide relief of both acute and chronic pain (Table 62–9).[41] These agents can be positioned by injection (e.g., in joints, in the epidural or intrathecal space, along nerve roots, or in a nerve plexus) or topically. Lidocaine in the form of a patch has proven effective in treating focal

TABLE 62-8 Pharmacologic Management of Chronic Noncancer Pain

Type of Pain	Nonopioids	Opioids	Other Medications	Comments
Chronic low back pain	Acetaminophen, NSAIDs	Short-term use for mild-to-moderate flare-ups	TCAs, AEDs	Acetaminophen and NSAIDS first; opioids in selected patients; AEDs or TCAs if neuropathic symptoms
Fibromyalgia	Acetaminophen, NSAIDs	Long-term use not recommended	Tramadol, TCAs; AEDs	Acetaminophen and NSAIDs considered first; tramadol may be better alternative than opioids
Neuropathic pain	Acetaminophen or NSAIDs are rarely effective	Considered first-line therapy but usually are tried after AEDs and/or TCAs, tramadol, lidocaine 5% patch	TCAs, AEDs, SNRIs, tramadol, topical (e.g., 5% lidocaine patch, capsaicin)	Gabapentin, 5% lidocaine patch, tramadol, nortriptyline, desipramine, all considered first-line agents; opioids considered first-line agents but usually are tried after above

AED, antiepileptic drug; NSAIDs, nonsteroidal antiinflammatory drugs; SNRI, serotonin–norepinephrine reuptake inhibitor; TCA, tricyclic antidepressant.
Data from references 7, 19, 53, 54, and 65.

TABLE 62-9 Local Anesthetics[a]

Agent (Brand Name)	Onset (min)	Duration (h)
Esters		
Procaine (Novocain, various)	2–5	0.25–1
Chloroprocaine (Nesacaine)	6–12	0.5
Tetracaine (Pontocaine)	≤15	2–3
Amides		
Mepivacaine (Polocaine, various)	3–5	0.75–1.5
Bupivacaine (Marcaine, various)	5	2–4
Lidocaine (Xylocaine, various)	<2	0.5–1
Prilocaine (Citanest)	<2	≥1
Levobupivacaine[b] (Chirocaine)	≈10	≈8
Articaine with epinephrine[c] (Septodont)	1–6	1
Ropivacaine[d] (Naropin)	11–26	1.7–3.2

[a]Unless otherwise indicated, values are for infiltrative anesthesia.
[b]Epidural administration in cesarean section.
[c]Dental anesthesia.
[d]Epidural administration.
Data from Anonymous.[44,45]

neuropathic pain.[54] Regional anesthetics relieve pain by blocking nociceptive transmission and interrupting sympathetic reflexes.[41] Their lipid solubility, pK_a, percentage of un-ionized drug, drug concentration, vasodilator behavior, and amount of vasoconstrictor (commonly epinephrine) used concomitantly determine the mechanism of action.[41] High plasma concentrations can cause signs of CNS excitation and depression, including dizziness, tinnitus, drowsiness, disorientation, muscle twitching, seizures, and respiratory arrest.[44] Cardiovascular effects include myocardial depression, hypotension, decreased cardiac output, heart block, bradycardia, ventricular arrhythmia, and cardiac arrest.[45] Disadvantages of such methods include the need for skillful technical application, need for frequent administration, and highly specialized followup procedures.

SPECIAL CONSIDERATIONS IN ACUTE PAIN

1 2 3 5 The World Health Organization (WHO) recommends a three-step ladder approach using the simplest dosage schedules and medications with the least amount of potential harm based on pain intensity ratings from mild to moderate-to-severe.[28] An acute pain algorithm outlining how to use these principles is given in Fig. 62–2. The importance of reassessment and titration during this process cannot be overemphasized.

SPECIAL CONSIDERATIONS IN CANCER PAIN

Managing the pain of cancer encompasses both acute and chronic management techniques. 7 Thus, pharmacologic treatment and psychological therapies are best combined with surgical methods, anesthetic procedures, and supportive care measures in a multidisciplinary approach to pain relief.[55] The goal is to provide patients with enough pain amelioration to tolerate diagnostic and therapeutic manipulation and permit the patient to function at a level that will allow freedom of movement and choice.[28] Assessment of the factors given in Table 62–2 also applies to cancer patients. Special attention must be given to continual reassessment of the painful state, adverse effects with medications, and aberrant behaviors. 5 Individualization of therapy is always required.[28] Supportive care, in and outside the hospital, using programs such as hospice, is one of the cancer patient's greatest allies, not only in coping with pain but also in accepting the disease. The positive effect this has on the patient cannot be overstated. Pharmacologic management is the mainstay of therapy, and a typical progression of analgesic use in oncology patients is outlined in Fig. 62–3.

SPECIAL CONSIDERATIONS IN CHRONIC NONCANCER PAIN

7 The numerous etiologies that produce chronic noncancer pain make treatment complex, and overall management should be multidisciplinary. As pain becomes gradually more chronic, acute symptoms such as hypertension, tachycardia, and diaphoresis become less evident, and symptoms such as depression, sleep disturbances, anxiety, irritability, work problems, and family instability tend to dominate. Patients should not be told that the pain they are feeling is "psychosomatic" or is in their head. In most cases, etiology is not as important as symptomatic relief. Evaluation objectives include establishing an accurate diagnosis, identifying iatrogenic factors, obtaining a comprehensive psychiatric and psychosocial assessment, paying special attention to family and social problems, and obtaining a description of factors that alleviate or exacerbate pain.[2] 8 Given these objectives, placebos should never be used to diagnose pain.[2]

7 In all cases of chronic noncancer pain, an integrated systematic approach (such as that often provided by pain clinics), with a strong emphasis on patient–clinician relationships, is essential. The goal is to improve or maintain the patient's level of functioning, decrease the rate of physical deterioration, decrease pain perception, improve the patient's sense of well-being, improve family and social relationships, and decrease dependency on drug therapy.[2] Patients and clinicians must realize that maximum effective treatment may take months or even years.

SPECIAL POPULATIONS

The elderly and the young are at a higher risk for undertreatment because of misunderstandings regarding the pathophysiology of their pain. 5 In addition, those living with chronic, debilitating, and life-threatening illnesses need specialized pain control and care that is palliative in nature.[56] Although care must be taken in these populations to ensure that proper individualized treatment plans follow accepted guidelines,[56–59] the key concepts in pain management as outlined in this chapter are the guiding tenets in maximizing pain control.

PHARMACOECONOMIC CONSIDERATIONS

The *suffering* component of pain cannot be overemphasized. Most of us know how devastating pain can be to our daily lives. Swift relief from acute and cancer pain and well-planned treatment regimens in chronic nonmalignant pain will allow patients to concentrate on recovery and regaining control of their lives. Although few well-designed pharmacoeconomic studies have been performed,[60–62] most pain clinicians believe that this approach minimizes time in the hospital and time away from work while maximizing quality of life.

EVALUATION OF THERAPEUTIC OUTCOMES

2 5 The key to treating pain effectively is consistent monitoring for effectiveness (pain relief) versus side effects (e.g., sedation) and titrating treatment accordingly. In acute pain, this often must be done several times per day (in the early stages, hourly), whereas in chronic pain this may occur daily or even weekly. The frequency of evaluation also depends on the drug, the administration route, and other therapies being used. When patients cannot be asked about their pain (e.g., coma), monitoring agitation and heart rate is appropriate. Given the subjective nature of pain, the most successful therapies involve not only frequent patient assessment but also a large degree of patient control (as with PCA). With chronic pain, tools such as the Brief Pain Inventory, Initial Pain Assessment

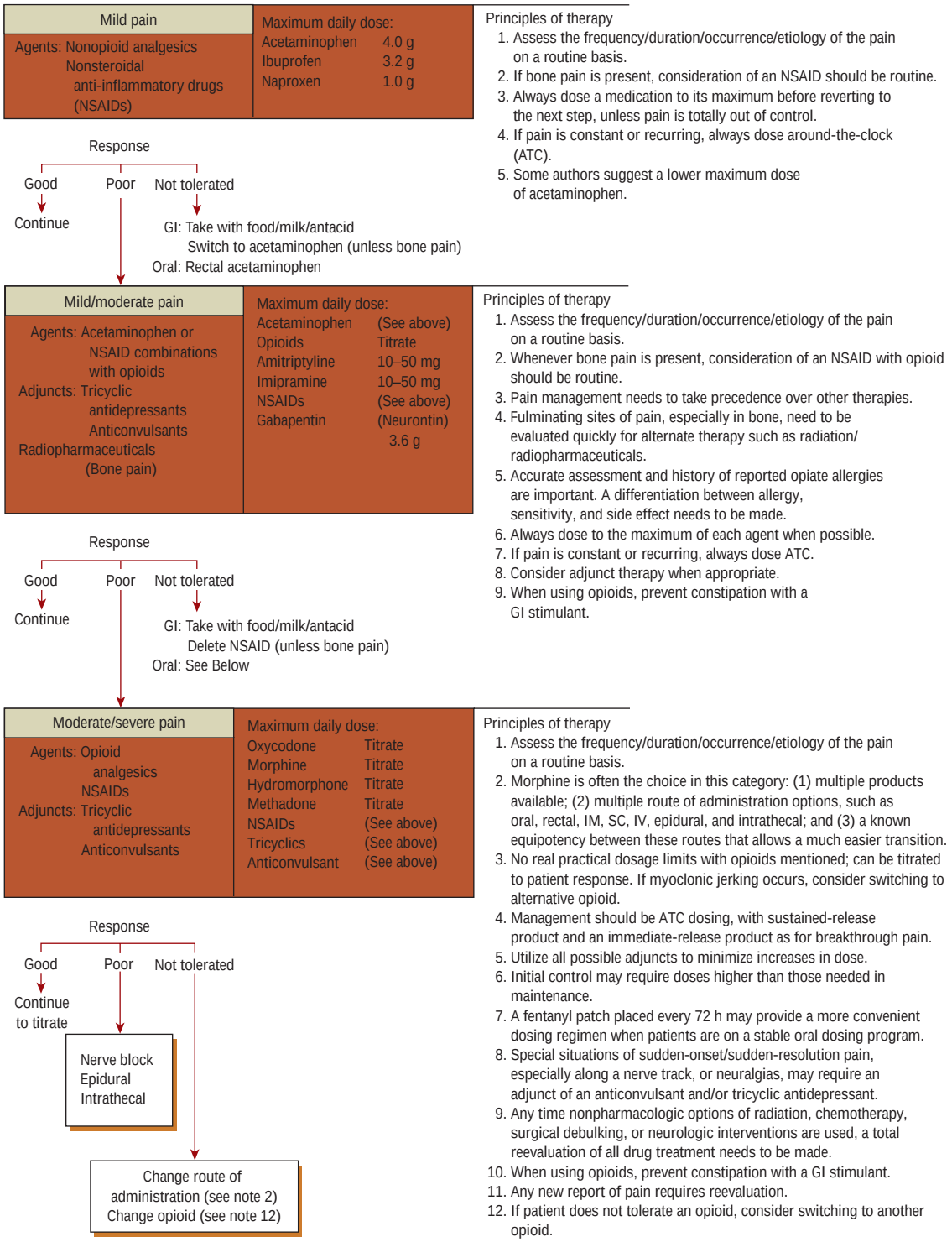

FIGURE 62-3 Algorithm for pain management in oncology patients. *(Data modified from the Kaiser Permanente Algorithm for Pain Management in Patients with Advanced Malignant Disease and reference 28.)*

Inventory, McGill Pain Questionnaire, or pain drawings may be helpful.[7]

2 All opioids can cause constipation. The best management of constipation is prevention. Patients should be counseled on the proper intake of fluids and fiber. A stimulating laxative should be added with chronic opioid use. As noted earlier, CNS depressants (e.g., alcohol, benzodiazepines) amplify CNS depression when used with opioid analgesics, and use of these combinations should be discouraged when possible. When the combinations are used, patients should be monitored closely.

CONCLUSIONS

Poor training of healthcare practitioners in pain assessment and management, improper patient education, and inadequate communication among healthcare professionals are some of the reasons for inadequate pain relief.[63,64] The use of an integrated approach, incorporating the expertise of many disciplines, may well be the most overlooked principle of pain pharmacotherapy. It is the responsibility of all healthcare professionals who deal with pain to work together to ensure proper management.

ABBREVIATIONS

CNS: Central nervous system

FDA: Food and Drug Administration

GABA: γ-Aminobutyric acid

IM: Intramuscular

IV: Intravenous

K^+: Potassium ion

NMDA: *N*-methyl-D-aspartate

NSAIDs: Nonsteroidal antiinflammatory drugs

PCA: Patient-controlled analgesia

PO: Oral

TENS: Transcutaneous electrical nerve stimulation

WHO: World Health Organization

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