INTRODUCTION

Opioids are among the oldest therapies in our armamentarium, and clinicians recognize their universal utility to limit human distress from pain. Opioids enjoy widespread use as potent analgesics, even though they are abused because of their psychoactive properties. Although the therapeutic and toxic doses are difficult to predict because of the development of tolerance with chronic use, the primary adverse event from excessive dosing is respiratory depression.

HISTORY AND EPIDEMIOLOGY

The medicinal value of opium, the dried extract of the poppy plant Papaver somniferum, was first recorded around 1500 b.c. in the Ebers papyrus. Raw opium is typically composed of at least 10% morphine, but extensive variability exists depending on the environment in which the poppy is grown. Although reformulated as laudanum (deodorized tincture of opium; 10 mg morphine/mL) by Paracelsus, paregoric (camphorated tincture of opium; 0.4 mg morphine/mL), Dover’s powder (pulvis Doveri), and Godfrey’s cordial in later centuries, the contents remained largely the same: phenanthrene poppy derivatives, such as morphine and codeine. Over the centuries since the Ebers papyrus, opium and its components have been exploited in two distinct manners: medically to produce profound analgesia and nonmedically to produce psychoactive effects.

Currently, the widest clinical application of opioids is for acute or chronic pain relief. Opioids are available in various formulations that allow administration by virtually any route: epidural, inhalational, intranasal, intrathecal, oral, parenteral (ie, subcutaneous [SC], intravenous [IV], intramuscular [IM]), rectal, transdermal, and transmucosal. Patients also may benefit from several of the nonanalgesic effects engendered by certain opioids. For example, codeine and hydrocodone are widely used as antitussives, and diphenoxylate is used as an antidiarrheal.

Unfortunately, the history of opium and its derivatives is marred by humankind’s endless quest for xenobiotics that produce pleasurable effects. Opium smoking was so problematic in China by the 1830s that the Chinese government attempted to prohibit the importation of opium by the British East India Company. This act led to the Opium Wars between China and Britain. China eventually accepted the importation and sale of the drug and was forced to turn over Hong Kong to British rule. The euphoric and addictive potential of the opioids is immortalized in the works of several famous writers, such as Thomas de Quincey (Confessions of an English Opium Eater, 1821), Samuel Coleridge (The Rime of the Ancient Mariner, 1798), and Elizabeth Barrett Browning (Aurora Leigh, 1856).

Because of mounting concerns of addiction and toxicity in the United States, the Harrison Narcotic Act, enacted in 1914, made nonmedicinal use of opioids illegal. Since that time, recreational and habitual use of heroin and
other opioids have remained epidemic in the United States and worldwide despite extensive and diverse attempts to curb their availability.

Morphine was isolated from opium by Armand Séquin in 1804. Charles Alder Wright synthesized heroin from morphine in 1874. Ironically, the development and marketing of heroin as an antitussive agent by Bayer, the German pharmaceutical company, in 1898 legitimized the medicinal role of heroin. Subsequently, various xenobiotics with opioid-like effects were marketed, each promoted for its presumed advantages over morphine. This assertion proved true for fentanyl because of its pharmacokinetic profile. However, in general, the advantages of such medications have fallen short of expectations, particularly with regard to their potential for abuse.

Prescription drug abuse (use for psychoactive effects) and misuse (eg, use of someone else’s medication) is among the leading causes of death in the United States, and the opioid analgesics account for approximately 80% of these outcomes. Although media reports highlight the abuse of prescription opioids by sports figures and other personalities, such use has reached epidemic levels in regions of the country where heroin is difficult to obtain (thus the term “hillbilly heroin”). In 2009, deaths from prescription drugs, mainly opioids, first exceeded those from motor vehicle crashes. The abuse liabilities of these semisynthetic opioids, based on their subjective profile, are similar. Although many users initially receive oxycodone or hydrocodone as analgesics, the majority of abusers obtain the drugs illicitly or from friends. Regulatory agencies (such as the Food and Drug Administration (FDA) through Risk Evaluation and Mitigation Strategies or REMS) and individual states through prescription drug monitoring programs, law enforcement, and the drug manufacturer have made tremendous efforts to control drug diversion to illicit use. Physicians and pharmacists have been charged criminally with complicity for inappropriate prescribing and dispensing, respectively, for patients with the intent to sell or abuse these drugs. As supplies of the prescription opioids fall, some abusers are turning to heroin, which is easily available and less expensive, as a substitute, but carries distinct risk.

Over the past decade and along with the realization that opioid analgesics are subject to abuse and misuse, newer formulations of existing opioids have attempted to be recognized for their reduced abuse potential. In general, this has been through the use of tamper resistant formulations that reduce the abuser’s ability to crush or dissolve the tablet for insufflation or injection, respectively. However, the true benefit of such formulations is not known, and the majority of abusers ingest their medications whole, suggesting that the overall benefit will be limited.

The terminology used in this chapter recognizes the broad range of xenobiotics commonly considered to be opium-like. The term opiate specifically refers to the relevant alkaloids naturally derived directly from the opium poppy: morphine; codeine; and, to some extent, thebaine and noscapine. Opioids are a much broader class of xenobiotics that are capable of either producing opium-like effects or binding to opioid receptors. A semisynthetic opioid, such as heroin or oxycodone, is created by chemical modification of an opiate. A synthetic opioid is a chemical, that is not derived from an opiate, and is capable of binding to an opioid receptor and producing opioid effects clinically. Synthetic opioids, such as methadone and meperidine, bear little structural similarity to the opiates. Opioids also include the naturally occurring animal derived opioid peptides such as endorphin and nociceptin/orphanin FQ. The term narcotic refers to sleep-inducing xenobiotics and initially was used to connote the opioids. However, law enforcement and the public currently use the term to indicate any illicit psychoactive substance. The term opioid as used hereafter encompasses the opioids and the opiates.

PHARMACOLOGY
Opioid Receptor Subtypes

Despite nearly a century of opioid studies, the existence of specific opioid receptors was not proposed until the mid-20th century. Beckett and Casy noted a pronounced stereospecificity of existing opioids (only the l-isomer is active) and postulated that the drug needed to “fit” into a receptor. In 1963, after studies on the clinical interactions of nalorphine and morphine, the theory of receptor dualism postulated the existence of two classes of opioid receptors. Such opioid binding sites were not demonstrated experimentally until 1973. Intensive experimental scrutiny using selective agonists and antagonists continues to permit refinement of receptor classification. The current, widely accepted schema postulates the coexistence of three major classes of opioid receptors, each with multiple subtypes, and several poorly defined minor classes.

Initially, the reason such an elaborate system of receptors existed was unclear because no endogenous ligand could be identified. However, evidence for the existence of such endogenous ligands was uncovered in 1975 with the discovery of metenkephalin and leuenkephalin and the subsequent identification of β-endorphin and dynorphin. As a group, these endogenous ligands for the opioid receptors are called endorphins (endogenous morphine). Each is a five amino acid peptide cleaved from a larger precursor peptide: proenkephalin, proopiomelanocortin, and prodynorphin, respectively. More recently, a minor related endogenous opioid (nociceptin/orphanin FQ) and its receptor ORL have been described.

All three major opioid receptors have been cloned and sequenced. Each consists of seven transmembrane segments, an amino terminus, and a carboxy terminus. Significant sequence homology exists between the transmembrane regions of opioid receptors and those of other members of the guanosine triphosphate (GTP)–binding protein (G-protein)–binding receptor superfamily. However, the extracellular and intracellular segments differ from one another. These nonhomologous segments probably represent the ligand binding and signal transduction regions, respectively, which would be expected to differ among the three classes of receptors. The individual receptors have distinct distribution patterns within the central nervous system (CNS) and peripherally on nerve endings within various tissues, mediating unique but not entirely understood clinical effects. Until recently, researchers used varying combinations of agonists and antagonists to pharmacologically distinguish between the different receptor subtypes. However, knockout mice (ie, mutant mice lacking the genes for an individual opioid receptor) promise new insights into this complex subject.

Because multiple opioid receptors exist and each elicits a different effect, determining the receptor to which an opioid preferentially binds should allow prediction of the clinical effect of the opioid. However, binding typically is not limited to one receptor type, and the relative affinity of an opioid for differing receptors accounts for the clinical effects (Table 38–1). Even the endogenous opioid peptides exhibit substantial crossover among the receptors.

### TABLE 38–1. Clinical Effects Related to Opioid Receptors

Although the familiar pharmacologic nomenclature derived from the Greek alphabet is used throughout this textbook, the International Union of Pharmacology (IUPHAR) Committee on Receptor Nomenclature has twice recommended a nomenclature change from the original Greek symbol system to make opioid receptor names more consistent with those of other neurotransmitter systems. In the first new schema, the receptors were denoted by their endogenous ligand (opioid peptide (OP)), with a subscript identifying their chronologic order of discovery. The δ receptor was renamed OP₁, the κ receptor was renamed OP₂, and the μ receptor was
renamed OP. However, adoption of this nomenclature met with significant resistance, presumably because of problems that would arise when merging previously published work that had used the Greek symbol nomenclature. The currently proposed nomenclature suggests the addition of a single letter in front of the OP designation and the elimination of the number. In this schema, the μ receptor is identified as MOP. In addition, the latest iteration formally recognizes the nociceptin/orphanin FQ or NOP receptor as a fourth receptor family.

**Mu Receptor (μ, MOP, OP).**

The early identification of the μ receptor as the morphine binding site gave this receptor its designation. Although many exogenous xenobiotics produce supraspinal analgesia via μ receptors, the endogenous ligand is elusive. Nearly all of the recognized endogenous opioids have some affinity for the μ receptor, although none is selective for the receptor. Endomorphin-1 and -2 are nonpeptide ligands present in brain that may represent the endogenous ligand.

Experimentally, two subtypes (μ₁ and μ₂) are well defined, although currently no xenobiotics have sufficient selectivity to make this dichotomy clinically relevant. Experiments with knockout mice suggest that both subtypes derive from the same gene and that either posttranslational changes or local cellular effects subsequently differentiate them. The μ₁ subtype appears to be responsible for supraspinal (brain) analgesia and for the euphoria engendered by these xenobiotics. Although stimulation of the μ₂ subtype produces spinal-level analgesia, it also produces respiratory depression. All of the currently available μ agonists have some activity at the μ₁ receptor and therefore produce some degree of respiratory compromise. Localization of μ receptors to regions of the brain involved in analgesia (periaqueductal gray, nucleus raphe magnus, medial thalamus), euphoria and reward (mesolimbic system), and respiratory function (medulla) is not unexpected. Predictably, μ receptors are found in the medullary cough center; peripherally in the gastrointestinal (GI) tract; and on various sensory nerve endings, including the articular surfaces (see analgesia under Clinical Manifestations below).

**Kappa Receptor (κ, KOP, OP).**

Although dynorphins now are known to be the endogenous ligands for these receptors, originally they were identified by their ability to bind ketocyclazocine and thus were labeled κ. Receptors exist predominantly in the spinal cords of higher animals, but they also are found in the antinociceptive regions of the brain and the substantia nigra. Stimulation is responsible for spinal analgesia, miosis, and diuresis (via inhibition of antidiuretic hormone release). Unlike μ-receptor stimulation, κ-receptor stimulation is not associated with significant respiratory depression or constipation. The receptor currently is subclassified into three subtypes. The κ₁ receptor subtype is responsible for spinal analgesia. This analgesia is not reversed by μ-selective antagonists, supporting the role of κ receptors as independent mediators of analgesia. Although the function of the κ₂ receptor subtype is largely unknown, stimulation of cerebral κ₂ receptors by xenobiotics such as pentazocine and salvinorin A produces psychotomimesis in distinction to the euphoria evoked by μ agonists. The κ₃ receptor subtype is found throughout the brain and participates in supraspinal analgesia. This receptor is primarily responsible for the action of nalorphine, an agonist–antagonist opioid. Nalbuphine, another agonist–antagonist, exerts its analgesic effect via both κ₁ and κ₃ agonism, although both nalorphine and nalbuphine are antagonists to morphine at the μ receptor.

**Delta Receptor (δ, DOP, OP).**

Little is known about δ receptors, although the enkephalins are known to be their endogenous ligands. Opioid peptides identified in the skin and brain of *Phyllomedusa* frogs, termed dermorphin and deltorphin, respectively, are potent agonists at the δ receptor. δ Receptors may be important in spinal and supraspinal analgesia (probably via a noncompetitive interaction with the μ receptor) and in cough suppression. δ Receptors may
mediate dopamine release from the nigro-striatal pathway, where they modulate the motor activity associated with amphetamine. Receptors do not modulate dopamine in the mesolimbic tracts and have only a slight behavioral reinforcing role. Subpopulations, specifically δ, and δ2, are postulated based on in vitro studies but presently are not confirmed in vivo.

Nociceptin/Orphanin FQ Receptor (ORL1, NOP, OP1).

The ORL1 receptor was identified in 1994 based on sequence homology during screening for opioid-receptor genes with DNA libraries. It has a similar distribution pattern in the brain and uses similar transduction mechanisms as the other opioid-receptor subtypes. It binds many different opioid agonists and antagonists. Its insensitivity to antagonism by naloxone, often considered the sine qua non of opioid character, delayed its acceptance as an opioid-receptor subtype. Simultaneous identification of an endogenous ligand, called nociceptin by the French discoverers and orphanin FQ by the Swiss investigators, allowed the designation OP1. A clinical role has not yet been defined, but anxiolytic and analgesic properties are described.

Opioid-Receptor Signal Transduction Mechanisms

Figure 38–1 illustrates opioid-receptor signal transduction mechanisms. Continuing research on the mechanisms by which an opioid receptor induces an effect has produced confusing and often contradictory results. Despite the initial theory that each receptor subtype is linked to a specific transduction mechanism, individual receptor subtypes may use one or more mechanisms, depending on several factors, including receptor localization (eg, presynaptic vs postsynaptic). As noted, all opioid-receptor subtypes are members of a superfamily of membrane-bound receptors that are coupled to G proteins. The G proteins are responsible for signaling the cell that the receptor is activated and for initiating the desired cellular effects. The G proteins are generally of the pertussis toxin-sensitive, inhibitory subtype known as Gi or G0, although coupling to a cholera toxin-sensitive, excitatory G protein subtype has been described. Regardless of subsequent effect, the G proteins consist of three conjoined subunits: α, β, and γ. The βγ subunit is liberated upon GTP binding to the subunit. When the α subunit dissociates from the βγ subunit, it modifies specific effector systems, such as phospholipase C or adenylate cyclase, or it may directly affect a channel or transport protein. GTP subsequently is hydrolyzed by a GTPase intrinsic to the α subunit, which prompts its reassociation with the βγ subunit and termination of the receptor-mediated effect.

**FIGURE 38–1.**

Opioid-receptor signal transduction mechanisms. Upon binding of an opioid agonist to an opioid receptor, the respective G protein is activated. G proteins may reduce the capacity of adenylate cyclase to produce cyclic adenosine monophosphate (cAMP) (A); close calcium channels that reduce the signal to release neurotransmitters (B); or open potassium channels and hyperpolarize the cell, which indirectly reduces cell activity (C). Each mechanism has been found coupled to each receptor subtype, depending on the location of the receptor (presynaptic vs postsynaptic), and the neuron within the brain (see text). Note that α receptors (D) mediate similar effects, using a different G protein (G0).

(A) **Adenylate cyclase/cAMP.** Inhibition of adenylate cyclase activity by Gi or G0 is the classic mechanism for postsynaptic signal transduction invoked by the inhibitory µ receptors. However, this same mechanism also has been identified in cells bearing either δ or κ receptors. Activation of cAMP production by adenylate cyclase, with subsequent activation of protein kinase A, occurs after exposure to very-low-dose opioid agonists and produces excitatory, antinociceptive effects.

(B) **Calcium (Ca2+) channels.** Presynaptic µ receptors inhibit norepinephrine release from the nerve terminals of cells of the rat cerebral cortex. Adenylate cyclase does not appear to be the modulator for these receptors because inhibition of norepinephrine release is not enhanced by increasing intracellular cAMP levels by various methods. Opioid-induced blockade is, however, prevented by increased intracellular calcium levels that are induced either by calcium ionophores, which increase membrane permeability to calcium, or by increasing the extracellular calcium concentration. This implies a role for opioid-induced closure of N-type calcium channels, presumably via a G protein. Reduced intraterminal concentrations of calcium prevent the neurotransmitter-
laden vesicles from binding to the terminal membrane and releasing their contents. Nerve terminals containing dopamine appear to have an analogous relationship with inhibitory κ receptors, as do acetylcholine-bearing neurons with opioid receptors.

(C) Potassium (K⁺) channels. Increased conductance through a potassium channel, generally mediated by G, or Gₒ, results in membrane hyperpolarization with reduced neuronal excitability. Alternatively, protein kinase A mediated reduction in membrane potassium conductance enhances neuronal excitability. ATP = adenosine triphosphate.

CLINICAL MANIFESTATIONS

Table 38–2 outlines the clinical effects of opioids.

TABLE 38–2. Clinical Effects of Opioids

Therapeutic Effects

Analgesia.

Although classic teaching attributes opioid analgesia solely to the brain, opioids actually appear to modulate cerebral cortical pain perception at supraspinal, spinal, and peripheral levels. The regional distribution of the opioid receptors confirms that μ receptors are responsible for most of the analgesic effects of morphine within the brain. They are found in highest concentration within areas of the brain classically associated with analgesia—the periaqueductal gray, nucleus raphe magnus, locus ceruleus, and medial thalamus. Microelectrode-induced electrical stimulation of these areas or iontophoretic application of agonists into these regions results in profound analgesia. Specifically, enhancement of inhibitory outflow from these supraspinal areas to the sensory nuclei of the spinal cord (dorsal roots) dampens nociceptive neurotransmission. Additionally, inactivation of the μ opioid receptor gene in embryonic mouse cells results in offspring that are insensitive to morphine analgesia. Interestingly, blockage of the N-methyl-D-aspartate (NMDA) receptor, a mediator of excitatory neurotransmission, enhances the analgesic effects of μ opioid agonists and may reduce the development of tolerance (see dextromethorphan later). Even more intriguing is the finding that low dose naloxone (0.25 μg/kg/h) actually improves the efficacy of morphine analgesia. Administration of higher dose, but still low dose, naloxone (1 μg/kg/h) obliterated its opioid-sparing effect. Although undefined, the mechanism may be related to selective inhibition of Gₛ-coupled excitatory opioid receptors by extremely low concentrations of opioid receptor antagonist.

Xenobiotics with strong binding affinity for δ receptors in humans produce significantly more analgesia than morphine administered intrathecaly. Indeed, the use of spinal and epidural opioid analgesia is predicated on the direct administration of opioid near the κ and δ receptors in the spinal cord. Agonist–antagonist opioids, with agonist affinity for the κ receptor and antagonist effects at the μ receptor, maintain analgesic efficacy.

Interestingly, communication between the immune system and the peripheral sensory nerves occurs in areas of tissue inflammation. In response to inflammatory mediators, such as interleukin-1, immune cells locally release...
opioid peptides, which bind and activate peripheral opioid receptors on sensory nerve terminals. Agonism at these receptors reduces afferent pain neurotransmission and may inhibit the release of other proinflammatory compounds, such as substance P. Of note, intraarticular morphine (1 mg) administered to patients after arthroscopic knee surgery produces significant, long lasting analgesia that can be prevented with intraarticular naloxone. The clinical analgesic effect of 5 mg of intraarticular morphine is equivalent to 5 mg of morphine given IM. Intraarticular analgesia is locally mediated by μ receptors.

The data to support the safety and efficacy of opioids for the management of chronic pain are limited. Addiction and dependence, which share a complicated relationship and often overlap with pain and depression, occur in at least 5% of patients using classical definitions, but other studies suggest it may be as high as 30%. The pleasurable effects of many xenobiotics used by humans are mediated by the release of dopamine in the mesolimbic system. This final common pathway is shared by all opioids that activate the μ–δ receptor complex in the ventral tegmental area, which, in turn, indirectly promotes dopamine release in the mesolimbic region. Opioids also may have a direct reinforcing effect on their self administration through μ receptors within the mesolimbic system.

The sense of well being and euphoria associated with strenuous exercise appears to be mediated by endogenous opioid peptides and μ receptors. This so-called “runner’s high” is reversible with naloxone. Naloxone may also reverse euphoria or even produce dysphoria in nonexercising, highly trained athletes. Even in normal individuals, high dose naloxone (4 mg/kg) may produce dysphoria.

Exogenous opioids do not induce uniform psychological effects. Some of the exogenous opioids, particularly those that are highly lipophilic such as heroin, are euphorogenic, but morphine is largely devoid of such pleasurable effects. However, morphine administration results in analgesia, anxiolysis, and sedation. Because heroin has little affinity for opioid receptors and must be deacetylated to morphine for effect, these seemingly incompatible properties likely are related to pharmacokinetic differences in blood–brain barrier penetration. Chronic users note that fentanyl produces effects that are subjectively similar to those of heroin. This effect may explain the higher prevalence of fentanyl, as opposed to other accessible opioids, as an abused drug by anesthesiologists. In distinction, certain opioids, such as pentazocine, produce dysphoria, an effect that is related to their affinity for κ or σ receptors.

Chronic use of opioid analgesics is associated with hyperalgesia, or a heightened sensitivity to pain. This effect was described decades ago in methadone maintenance patients and has been revisited as the use of chronic opioid therapy for pain has increased. Hyperalgesia may be part of the development of tolerance or the need for increasing amount of opioid to maintain a stable level of analgesia, but the treatment for hyperalgesia should include attempts at alternative modalities of pain relief.

Antitussive.
Codeine and dextromethorphan are two opioids with cough suppressant activity. Cough suppression is not likely mediated via the μ opioid receptor because the ability of other opioids to suppress the medullary cough centers is not correlated with their analgesic effect. Various models suggest that cough suppression occurs via agonism of the μ or κ opioid receptors or antagonism of the δ opioid receptor and that the σ or NMDA receptors also are involved.

Toxic Effects
When used appropriately for medical purposes, opioids are generally safe and effective. However, excessive dosing for any reason may result in serious toxicity. Most adverse or toxic effects are predictable based on opioid pharmacodynamics (eg, respiratory depression), although several xenobiotics produce unexpected
“nonopioid” or xenobiotic-specific responses. Determining that a patient has an opioid toxicity is generally more important than identifying the specific opioid involved. Notwithstanding some minor variations, patients poisoned by all available opioids predictably develop a constellation of signs, known as the opioid syndrome (Chap. 3). Mental status depression, hypoventilation, miosis, and hypoperistalsis are the classic elements.

**Respiratory Depression.**
Experimental use of various opioid agonists and antagonists consistently implicates μ receptors in the respiratory depressant effects of morphine. Through these receptors, opioid agonists reduce ventilation by diminishing the sensitivity of the medullary chemoreceptors to hypercapnea. In addition to loss of hypercarbic stimulation, opioids depress the ventilatory response to hypoxia. The combined loss of hypercarbic and hypoxic drive leaves virtually no stimulus to breathe, and apnea ensues. Equianalgesic doses of the available opioid agonists produce approximately the same degree of respiratory depression. This reasoning is supported by experiments in MOR deficient knockout mice. Patients chronically exposed to opioid agonists, such as those on methadone maintenance, experience chronic hypoventilation, although tolerance to loss of hypercarbic drive may develop over several months. However, such patients never develop complete tolerance to loss of hypoxic stimulation. Although some opioids, notably the agonist–antagonists and partial agonists, typically demonstrate a ceiling effect on respiratory depression, such sparing generally occurs at the expense of analgesic potency and is incomplete. The different activity profiles likely are a result of differential activities at the opioid-receptor subtypes; that is, agonist–antagonists are predominantly κ-receptor agonists and either partial agonists or antagonists at μ sites.

It is important to recognize that ventilatory depression may be secondary to a reduction in either respiratory rate or tidal volume. Thus, although respiratory rate is more accessible for clinical measurement, it is not an ideal index of ventilatory depression. In fact, morphine-induced respiratory depression in humans initially is related more closely to changes in tidal volume. Large doses of opioids also result in a reduction of respiratory rate.

Respiratory depression is the primary cause of death after therapeutic use or misuse. Common reasons for iatrogenic overdose include not appreciating the importance of genetic polymorphisms (see Codeine), sleep apnea, drug interactions, active metabolites (see Morphine), or the complicated pharmacokinetics of the long-acting and sustained-release opioids.

**Acute Respiratory Distress Syndrome (ARDS).**
Reports linking opioids with the development of acute pulmonary abnormalities became common in the 1960s, although the first report was made by William Osler in 1880. Almost all opioids are implicated, and opioid-related acute respiratory distress syndrome is reported in diverse clinical situations. Typically, the patient regains normal ventilation after a period of profound respiratory depression, either spontaneously or after the administration of an opioid antagonist, and over the subsequent several minutes to hours develops hypoxemia and pulmonary crackles. Occasionally, classic frothy, pink sputum is present in the patient’s airway or in the endotracheal tube of an intubated patient. Decedents often have what is described as a “foam cone” of frothy material extruding from their noses and mouths. Acute lung injury (ALI) was described in 71 (48%) of 149 hospitalized heroin overdose patients in New York City, although the current incidence in this patient group appears to be lower. The outcome generally depends on comorbid conditions and the delay to adequate care. ALI may be an isolated finding or may occur in the setting of multisystem organ damage.

No single mechanism can be consistently invoked in the genesis of opioid associated ARDS. However, several prominent theories are each well supported by experimental data. Rather than causing ARDS, naloxone likely
“uncovers” the clinical findings of ARDS that were not evident because an adequate examination could not be performed until breathing is restored. Other evidentiary cases involve surgical patients given naloxone postoperatively who subsequently awoke with clinical signs of pulmonary edema. In addition to presumably receiving the naloxone for ventilatory compromise or hypoxia, these patients received multiple intraoperative medications, further obscuring the etiology. Although naloxone ordinarily is safe when appropriately administered to nonopioid tolerant individuals, the production of acute opioid withdrawal may be responsible for “naloxone-induced” ARDS. In this situation, as in patients with “neurogenic” pulmonary edema, massive sympathetic discharge from the CNS occurs and produces “cardiogenic” pulmonary edema from the acute effects of catecholamines on the myocardium. In an interesting series of experiments, precipitated opioid withdrawal in nontolerant dogs was associated with dramatic cardiovascular changes and abrupt elevation of serum catecholamine concentrations. The effects were more dramatic in dogs with an elevated PCO₂ than in those with a normal or low PCO₂, suggesting the potential benefit of adequately ventilating patients before opioid reversal with naloxone. Similar effects occur in humans undergoing ultrarapid opioid detoxification (UROD; see later discussion).

Even though abrupt precipitation of withdrawal by naloxone may contribute to the development of ARDS, it cannot be the sole etiology. Alveolar filling was noted in 50% to 90% of the postmortem examinations performed on heroin overdose patients, many of whom were declared dead before arrival to medical care and thus never received naloxone. In addition, neither naloxone nor any other opioid antagonist was available when Osler and others described their initial cases of “pulmonary edema.” Alternatively, the negative intrathoracic pressure generated by attempted inspiration against a closed glottis creates a large pressure gradient across the alveolar membrane and draws fluid into the alveolar space. This mechanical effect, also known as the Müller maneuver, was invoked as the cause of ventilator-associated ARDS before the advent of demand ventilators and neuromuscular blockers. In the setting of opioid poisoning, glottic laxity may prevent adequate air entry during inspiration. This effect may be especially prominent at the time of naloxone administration, in which case breathing may be reinstituted before the return of adequate upper airway function.

**Cardiovascular.**

Arteriolar and venous dilation secondary to opioid use may result in a mild reduction in blood pressure. This effect is clinically useful for treatment of patients with acute cardiogenic pulmonary edema. However, although patients typically do not develop significant supine hypotension, orthostatic changes in blood pressure and pulse routinely occur. A reduction in heart rate is common as a result of the associated reduction in CNS stimulation. Opioid induced hypotension appears to be mediated by histamine release, although induction of histamine release does not appear to occur through interaction with an opioid receptor. It may be related to the nonspecific ability of certain xenobiotics to activate mast cell G-proteins, which induce degranulation of histamine containing vesicles. Many opioids share this ability, which seems to be conferred by the presence of a positive charge on a hydrophobic molecule. Accordingly, not all opioids are equivalent in their ability to release histamine. After administration of one of four different opioids to 60 healthy patients, meperidine produced the most hypotension and elevation of serum histamine concentrations; fentanyl produced the least. The combination of H₁ and H₂ antagonists is effective in ameliorating the hemodynamic effects of opioids in humans.

Adulterants or coingestants may produce significant cardiovascular toxicity. For example, quinine adulterated heroin is associated with dysrhythmias. Cocaine, surreptitiously added to heroin, may cause significant myocardial ischemia or infarction. Similarly, concern that naloxone administration may “unmask” cocaine toxicity in patients simultaneously using cocaine and heroin (“speedball”) probably is warranted but rarely is demonstrated unequivocally.
Certain opioids at therapeutic concentrations, particularly methadone, may interfere with normal cardiac repolarization and produce QT interval prolongation, an effect that predisposes to the development of torsade de pointes. Many patients who receive methadone experience minor increases in QT interval, although a small percentage of patients experience a substantial increase to more than 500 msec. Methadone and levo-α-acetylmethadol (LAAM) both prolong the QT interval via interactions with cardiac K⁺ channels. Additionally, certain opioids, primarily propoxyphene (which was recently removed from the US market), may alter the function of myocardial Na⁺ channels in a manner similar to that of the antidysrhythmics (Chap. 64).

Miosis.
Stimulation of parasympathetic pupilloconstrictor neurons in the Edinger-Westphal nucleus of the oculomotor nerve by morphine produces miosis. Additionally, morphine increases firing of pupilloconstrictor neurons to light, which increases the sensitivity of the light reflex through central reinforcement. Although sectioning of the optic nerve may blunt morphine-induced miosis, the consensual reflex in the denervated eye is enhanced by morphine. Because opioids classically mediate inhibitory neurotransmission, hyperpolarization of sympathetic nerves or of inhibitory neurons to the parasympathetic neurons (removal of inhibition) ultimately may be found to mediate the classic “pinpoint pupil” associated with opioid use.

Not all patients using opioids present with miosis. Meperidine has a lesser miotic effect than other conventional opioids, and propoxyphene use does not result in miosis. Use of opioids with predominantly κ-agonist effects, such as pentazocine, may not result in miosis. Mydriasis may occur in severely poisoned patients secondary to hypoxic brain insult. Additionally, concomitant drug abuse or the presence of adulterants may alter pupillary findings. For example, the combination of heroin and cocaine (“speedball”) may produce virtually any size pupil, depending on the relative contribution by each xenobiotic. Similarly, patients ingesting diphenoxylate and atropine (Lomotil) or those using scopolamine adulterated heroin typically develop mydriasis.

Seizures.
Seizures are a rare complication of therapeutic use of most opioids. In patients with acute opioid overdose, seizures most likely are caused by hypoxia. However, experimental models demonstrate a proconvulsant effect of morphine in that it potentiates the convulsant effect of other xenobiotics. These effects are variably inhibited by naloxone, suggesting the involvement of a mechanism other than opioid receptor binding. In humans, morphine-induced seizures are reported in neonates and are reversed by naloxone, although opioid withdrawal seizures in neonates are more common.

Seizures should be anticipated in patients with meperidine, propoxyphene, tapentadol, or tramadol toxicity. Naloxone antagonizes the convulsant effects of propoxyphene in mice, although it is only moderately effective in preventing seizures resulting from meperidine or its metabolite normeperidine. Interestingly, naloxone potentiates the anticonvulsant effects of benzodiazepines and barbiturates, but in a single study, it antagonized the effects of phenytoin. The ability of fentanyl and its analogs to induce seizures is controversial. They are used to activate epileptiform activity for localization in patients with temporal lobe epilepsy who are undergoing surgical exploration. However, electroencephalography (EEG) performed on patients undergoing fentanyl anesthesia did not identify seizure activity even though the clinical assessment suggested that approximately one-third of them had seizures. It appears likely that the rigidity and myoclonus associated with fentanyl use are readily misinterpreted as a seizure.

Movement Disorders.
Patients may experience acute muscular rigidity with rapid IV injection of certain high potency opioids, especially fentanyl and its derivatives. This condition is particularly prominent during induction of anesthesia and in neonates. The rigidity primarily involves the trunk and may impair chest wall movement sufficiently to
exacerbate hypoventilation. Chest wall rigidity may have contributed to the lethality associated with epidemics of fentanyl adulterated or fentanyl substituted heroin. Although the mechanism of muscle rigidity is unclear, it may be related to blockade of dopamine receptors in the basal ganglia. Other postulated mechanisms include γ-aminobutyric acid (GABA) antagonism and NMDA agonism. Opioid antagonists generally are therapeutic but may produce adverse hemodynamic effects, withdrawal phenomena, or uncontrollable pain, depending on the situation. Although not a problem for patients taking stable doses of methadone, rapid escalation of methadone doses may produce choreoathetoid movements.

Gastrointestinal Effects.
Historically, the morphine analog apomorphine was used as a rapidly acting emetic whose clinical use was limited by its tendency to depress the patient’s level of consciousness. Emesis induced by apomorphine is mediated through agonism at D₂ receptor subtypes within the chemoreceptor trigger zone of the medulla. Many opioids, particularly morphine, produce significant nausea and vomiting when used therapeutically. Whether these effects are inhibited by naloxone is not clearly established, but they likely are not.

Although diphenoxylate and loperamide are widely used therapeutically to manage diarrhea, opioid-induced constipation is most frequently a bothersome side effect of both medical and nonmedical use of opioids. Constipation, mediated by μ₂ receptors within the smooth muscle of the intestinal wall, is ameliorated by oral naloxone. Provided the first pass hepatic glucuronidative capacity is not exceeded (at doses of ~6 mg), enteral naloxone is poorly bioavailable and thus induces few, if any, opioid withdrawal symptoms. Methylnaltrexone and alvimopan are bioavailable, “peripherally restricted” opioids that cannot cross the blood brain barrier. Although they antagonize the effects of opioids on the GI tract opioid receptor, opioid withdrawal does not occur (Antidotes in Depth: A4).

Endocrine Effects.
Chronic use of opioids is associated with hypofunction of the hypothalamic pituitary gonadal axis by binding to hypothalamic opioid receptors and decreasing the secretion of gonadotropin releasing hormone. Clinical findings include reduced libido, erectile dysfunction, hot flashes, and depression, as well as anemia, hair loss, and osteopenia. Additionally, both men and women may have infertility. Furthermore, opioids reduce the release of corticotropin-releasing hormone from the hypothalamus, leading to a reduction of adrenocorticotropic hormone (ACTH) release from the pituitary. This reduces adrenal function, and clinically relevant adrenal insufficiency may occur. In addition, prolactin concentrations commonly rise and may lead to gynecomastia.

Hearing Loss.
Although relatively rare, rapidly progressive sensorineural hearing loss may occur in heavy users of opioid analgesics. This effect has been associated with most opioids, including hydrocodone, oxycodone, and methadone. The mechanism remains unknown, and suggested causes include ischemia, genetic predisposition, direct cochlear toxicity, and hypersensitization that manifests upon re-exposure after a period of opioid abstinence. Most patients recover after abstinence, although some are only successfully treated with cochlear implants (Chap. 26).

DIAGNOSTIC TESTING
Laboratory Considerations
Opioid-poisoned patients are particularly appropriate for a rapid clinical diagnosis because of the unique characteristics of the opioid toxic syndrome. Additionally, even in situations in which the assay results are available rapidly, the fact that several distinct classes of opioids and nonopioids can produce similar opioid
effects limits the use of laboratory tests, such as immunoassays, that rely on structural features to identify xenobiotics. Furthermore, because opioids may be chemically detectable long after their clinical effects have dissipated, assay results cannot be considered in isolation but rather viewed in the clinical context. Several well-described problems with laboratory testing of opioids are described here and in Chap. 6.

Cross-Reactivity.
Many opioids share significant structural similarities, such as morphine and oxycodone or methadone and propoxyphene, but they do not necessarily share the same clinical characteristics (Fig. 38–2). Because most clinical assays depend on structural features for identification, structurally similar xenobiotics may be detected in lieu of the desired one. Whether a similar xenobiotic is noted by the assay depends on the sensitivity and specificity of the assay and the serum concentration of the xenobiotic. Some cross-reactivities are predictable, such as that of oxycodone with morphine, on a variety of screening tests. Other cross-reactivities are less predictable, as in the case of the cross-reaction of dextromethorphan and the phencyclidine (PCP) component of the fluorescence polarization immunoassay (Abbott TDx), a widely used drug abuse screening test (Chap. 6).

**FIGURE 38–2.**
The figure demonstrates the structural similarities between methadone and propoxyphene and between phencyclidine and dextromethorphan.

Congeners and Adulterants.
Commercial opioid assays, which are specific for morphine, will not readily detect most of the semisynthetic and synthetic opioids. In some cases, epidemic fatalities involving fentanyl derivatives remained unexplained despite obvious opioid toxicity until the ultrapotent fentanyl derivative α-methylfentanyl (although initially misidentified as 3-methylfentanyl) was identified by more sophisticated testing. Oxycodone, hydrocodone, and other common morphine derivatives have variable detectability by different opioid screens and generally only when in high concentrations.

Drug Metabolism.
A fascinating dilemma may arise in patients who ingest moderate to large amounts of poppy seeds. These seeds, which are widely used for culinary purposes, are derived from poppy plants and contain both morphine and codeine. After ingestion of a single poppy seed bagel, patients may develop elevated serum morphine and codeine concentrations and test positive for morphine. Because the presence of morphine on a drug abuse screen may suggest illicit heroin use, the implications are substantial. Federal workplace testing regulations thus require corroboration of a positive morphine assay with assessment of another heroin metabolite, 6-monoacetylmorphine, before reporting a positive result. Humans cannot acetylate morphine and therefore cannot synthesize 6-monoacetylmorphine, but humans can readily deacetylate heroin, which is diacetylmorphine.

A similar problem may occur in patients taking therapeutic doses of codeine. Because codeine is demethylated to morphine by CYP2D6, a morphine screen may be positive as a result of metabolism and not structural cross-reactivity. Thus, determination of the serum codeine or 6-monoacetylmorphine concentration is necessary in these patients. Determination of the serum codeine concentration is not foolproof, however, because codeine is present in the opium preparation used to synthesize heroin.
Forensic Testing.
Decision making regarding the cause of death in the presence of systemic opioids often is complex. Variables that often are incompletely defined contribute substantially to the difficulty in attributing or not attributing the cause of death to the opioid. These variables include the specifics regarding the timing of exposure, the preexisting degree of sensitivity or tolerance, the role of cointoxicants (including parent opioid metabolites), and postmortem redistribution and metabolism. Interesting techniques to help further elucidate the likely cause of death that have been studied include the application of postmortem pharmacogenetic principles and the use of alternative specimens (Chap. 34).

MANAGEMENT
The consequential effects of acute opioid poisoning are CNS and respiratory depression. Although early support of ventilation and oxygenation is generally sufficient to prevent death, prolonged use of bag-valve-mask ventilation and endotracheal intubation may be avoided by cautious administration of an opioid antagonist. Opioid antagonists, such as naloxone, competitively inhibit binding of opioid agonists to opioid receptors, allowing the patient to resume spontaneous respiration. Naloxone competes at all receptor subtypes, although not equally, and is effective at reversing almost all adverse effects mediated through opioid receptors (Antidotes in Depth: A4).

Because many clinical findings associated with opioid poisoning are nonspecific, the diagnosis requires clinical acumen. Differentiating acute opioid poisoning from other etiologies with similar clinical presentations may be challenging. Patients manifesting opioid toxicity, those found in an appropriate environment, or those with characteristic physical clues such as fresh needle marks require little corroborating evidence. However, subtle presentations of opioid poisoning may be encountered, and other entities superficially resembling opioid poisoning may occur. Hypoglycemia, hypoxia, and hypothermia may result in clinical manifestations that share features with opioid poisoning and may exist concomitantly. Each can be rapidly diagnosed with routinely available, point-of-care testing, but their existence does not exclude opioid toxicity. Other xenobiotics responsible for similar clinical presentations include clonidine, PCP, phenothiazines, and sedative–hypnotics (primarily benzodiazepines). In such patients, clinical evidence usually is available to assist in diagnosis. For example, nystagmus nearly always is noted in PCP toxic patients, hypotension or electrocardiographic (ECG) abnormalities in phenothiazine-poisoned patients, and coma with virtually normal vital signs in patients poisoned by benzodiazepines. Most difficult to differentiate on clinical grounds may be toxicity produced by the centrally acting antihypertensive agents such as clonidine (see Clonidine later and Chap. 63). Additionally, myriad traumatic, metabolic, and infectious etiologies may occur simultaneously and must always be considered and evaluated appropriately.

Antidote Administration
The goal of naloxone therapy is not necessarily complete arousal; rather, the goal is reinstitution of adequate spontaneous ventilation. Because precipitation of withdrawal is potentially detrimental and often unpredictable, the lowest practical naloxone dose should be administered initially, with rapid escalation as warranted by the clinical situation. Most patients respond to 0.04 to 0.05 mg of naloxone administered IV, although the requirement for ventilatory assistance may be slightly prolonged because the onset may be slower than with larger doses. Administration in this fashion effectively avoids endotracheal intubation and allows timely identification of patients with nonopioid causes of their clinical condition yet diminishes the risk of precipitation of acute opioid withdrawal. SC administration may allow for smoother arousal than the high-dose IV route but is unpredictable in onset and likely prolonged in offset. Prolonged effectiveness of naloxone by the SC route
can be a considerable disadvantage if the therapeutic goal is exceeded and the withdrawal syndrome develops.

In the absence of a confirmatory history or diagnostic clinical findings, the cautious empiric administration of naloxone may be both diagnostic and therapeutic. Naloxone, even at extremely high doses, has an excellent safety profile in opioid-naïve patients receiving the medication for nonopioid-related indications, such as spinal cord injury or acute ischemic stroke. However, administration of naloxone to opioid-dependent patients may result in adverse effects; specifically, precipitation of an acute withdrawal syndrome should be anticipated. The resultant agitation, hypertension, and tachycardia may produce significant distress for the patient and complicate management for the clinical staff and occasionally may be life threatening. Additionally, emesis, a common feature of acute opioid withdrawal, may be particularly hazardous in patients who do not rapidly regain consciousness after naloxone administration. For example, patients with concomitant ethanol or sedative–hypnotic exposure and those with head trauma are at substantial risk for pulmonary aspiration of vomitus if their airways are unprotected.

Identification of patients likely to respond to naloxone conceivably would reduce the unnecessary and potentially dangerous precipitation of withdrawal in opioid-dependent patients. Routine prehospital administration of naloxone to all patients with subjectively assessed altered mental status or respiratory depression was not beneficial in 92% of patients. Alternatively, although not perfectly sensitive, a respiratory rate of 12 breaths/min or less in an unconscious patient presenting via emergency medical services best predicted a response to naloxone. Interestingly, neither respiratory rate below 8 breaths/min nor coma was able to predict a response to naloxone in hospitalized patients. It is unclear whether the discrepancy between the latter two studies is a result of the demographics of the patient groups or whether patients with prehospital opioid overdose present differently than patients with iatrogenic poisoning. Regardless, relying on the respiratory rate to assess the need for ventilatory support or naloxone administration is not ideal because hypoventilation secondary to hypopnea may precede that caused by bradypnea.

The decision to discharge a patient who awakens appropriately after naloxone administration is based on practical considerations. Patients presenting with profound hypoventilation or hypoxia are at risk for development of ARDS or posthypoxic encephalopathy. Thus, it seems prudent to observe these patients for at least 24 hours in a medical setting. Patients manifesting only moderate signs of poisoning who remain normal for at least several hours after parenteral naloxone likely are safe to discharge. However, the need for psychosocial intervention in patients with uncontrolled drug use or after a suicide attempt may prevent discharge from the emergency department (ED).

Patients with recurrent or profound poisoning by long acting opioids, such as methadone, or patients with large GI burdens (e.g., "body packers" or those taking sustained release preparations) may require continuous infusion of naloxone to ensure continued adequate ventilation. An hourly infusion rate of two thirds of the initial reversal dose of naloxone is sufficient to prevent recurrence. Titration of the dose may be necessary as indicated by the clinical situation. Although repetitive bolus dosing of naloxone may be effective, it is labor intensive and subject to error.

**TABLE 38–3. How to Use Naloxone**

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Despite the availability of long-acting opioid antagonists (eg, naltrexone) that theoretically permit single-dose reversal of methadone poisoning, the attendant risk of precipitating an unrelenting withdrawal syndrome hinders their use as antidotes for initial opioid reversal. However, these long acting opioid antagonists may have a clinical role in the maintenance of consciousness and ventilation in opioid-poisoned patients already awakened by naloxone. Prolonged observation and perhaps antidote readministration may be required to match the pharmacokinetic parameters of the two antagonists. Otherwise well children who ingest short-acting opioids may be given a long-acting opioid antagonist initially because they are not expected to develop a prolonged, potentially hazardous withdrawal. However, the same caveats remain regarding the need for extended hospital observation periods if ingestion of methadone or other long-acting opioids is suspected.

Rapid and Ultrarapid Opioid Detoxification
The concept of antagonist-precipitated opioid withdrawal is promoted extensively as a “cure” for opioid dependency, particularly heroin and oxycodone, but has fallen out of favor in recent years. Rather than slow, deliberate withdrawal or detoxification from opioids over several weeks, antagonist-precipitated withdrawal occurs over several hours or days. The purported advantage of this technique is a reduced risk of relapse to opioid use because the duration of discomfort is reduced and a more rapid transition to naltrexone maintenance can be achieved. Although most studies find some beneficial short-term results, relapse to drug use is very common. Rapid opioid detoxification techniques are usually offered by outpatient clinics and typically consist of naloxone- or naltrexone-precipitated opioid withdrawal tempered with varying amounts of clonidine, benzodiazepines, antiemetics, or other drugs. UROD uses a similar concept but involves the use of deep sedation or general anesthesia for greater patient control and comfort. The risks of these techniques are not fully defined but are of substantial concern. Massive catecholamine release, ARDS, kidney injury, and thyroid hormone suppression have been reported after UROD, and many patients still manifest opioid withdrawal 48 hours after the procedure. As with other forms of opioid detoxification, the loss of tolerance after successful completion of the program paradoxically increases the likelihood of death from heroin overdose if these individuals relapse. Both techniques are costly; UROD under anesthesia commonly costs thousands of dollars. Professional medical organizations involved in addiction management have publicly expressed concern for this form of detoxification.

SPECIFIC OPIOIDS
The vast majority of opioid-poisoned patients follow predictable clinical courses that can be anticipated based on our understanding of opioid receptor pharmacology. However, certain opioids taken in overdose may produce atypical manifestations. Therefore, careful clinical assessment and institution of empiric therapy usually are necessary to ensure proper management (Table 38–4).

<table>
<thead>
<tr>
<th>TABLE 38–4. Classification, Potency, and Characteristics of Opioids and Opioid Antagonists</th>
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<td>Morphine and Codeine</td>
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Morphine is poorly bioavailable by the oral route because of extensive first-pass elimination. Morphine is hepatically metabolized primarily to morphine-3-glucuronide (M3G) and, to a lesser extent, to morphine-6-glucuronide (M6G), both of which are cleared renally. Unlike M3G, which is essentially devoid of activity, M6G
has μ-agonist effects in the CNS. However, M6G administered peripherally is significantly less potent as an analgesic than is morphine. The polar glucuronide has a limited ability to cross the blood–brain barrier, and P-glycoprotein is capable of expelling M6G from the cerebrospinal fluid. The relative potency of morphine and M6G in the brain is incompletely defined, but the metabolite is generally considered to be several-fold more potent.

Codeine itself is an inactive opioid agonist, and it requires metabolic activation by O-demethylation to morphine by CYP2D6 (Fig. 38–3). This typically represents a minor metabolic pathway for codeine metabolism. N-Demethylation into norcodeine by CYP3A4 and glucuronidation are more prevalent but produce inactive metabolites. The need for conversion to morphine explains why approximately 5% to 7% of white patients, who are devoid of CYP2D6 function, cannot derive an analgesic response from codeine. An increasingly recognized phenomenon is that ultrarapid CYP2D6 metabolizers produce unexpectedly large amounts of morphine from codeine, with resulting life-threatening opioid toxicity.

Heroin
Heroin is 3,6-diacetylmorphine, and its exogenous synthesis is performed relatively easily from morphine and acetic anhydride. Heroin has a lower affinity for the receptor than does morphine, but it is rapidly metabolized by plasma cholinesterase and liver human carboxylesterase (hCE)-2 to 6-monoacetylmorphine, a more potent μ agonist than morphine (Fig. 38–3). Users claim that heroin has an enhanced euphorogenic effect, often described as a “rush.” This effect likely is related to the enhanced blood–brain barrier penetration occasioned by the additional organic functional groups of heroin and its subsequent metabolic activation within the CNS. Interestingly, cocaine and heroin compete for metabolism by plasma cholinesterase and the two human liver carboxylesterases known as human carboxylesterase-1 and human carboxylesterase-2.

Heroin can be obtained in two distinct chemical forms: base or salt. The hydrochloride salt form typically is a white or beige powder and was the common form of heroin available before the 1980s. Its high water solubility allows simple IV administration. Heroin base, on the other hand, now is the more prevalent form of heroin in most regions of the world. It often is brown or black. “Black tar heroin” is one appellation referring to an impure South American import available in the United States. Because heroin base is virtually insoluble in water, IV administration requires either heating the heroin until it liquefies or mixing it with acid. Alternatively, because the alkaloidal form is heat stable, smoking or “chasing the dragon” is sometimes used as an alternative route. Street-level heroin base frequently contains caffeine or barbiturates, which improves the sublimation of heroin and enhances the yield.

Widespread IV use has led to many significant direct and indirect medical complications, particularly endocarditis and AIDS, in addition to fatal and nonfatal overdose. Nearly two-thirds of all long-term (>10 years)
heroin users in Australia had overdosed on heroin. Among recent-onset heroin users, 23% had overdosed on heroin, and 48% had been present when someone else overdosed. Risk factors for fatality after heroin use include the concomitant use of other drugs of abuse, particularly ethanol; recent abstinence, as occurs during incarceration; and perhaps unanticipated fluctuations in the purity of available heroin. Because most overdoses occur in seasoned heroin users and about half occur in the company of other users, the prescribing of naloxone to heroin users for companion administration has become increasingly available but remains poorly studied. Although earlier administration of antidote could be beneficial, certain issues make this approach controversial. For example, despite the acknowledged injection skills of the other users in the “shooting gallery,” their judgment likely is impaired. In one survey, summoning an ambulance was the initial response to overdose of a companion in only 14% of cases. A survey of heroin users suggested they lacked an understanding of the pharmacology of naloxone, which might lead to inappropriate behaviors regarding both heroin and naloxone administration.

Recognition of the efficacy of intranasal heroin administration, or snorting, has fostered a resurgence of heroin use, particularly in suburban communities. The reasons for this trend are unclear, although it is widely suggested that the increasing purity of the available heroin has rendered it more suitable for intranasal use. However, because intranasal administration of a mixture of 3% heroin in lactose produces clinical and pharmacokinetic effects similar to an equivalent dose administered IM, the relationship between heroin purity and price and intranasal use is uncertain. Needle avoidance certainly is important, reducing the risk of transmission of various infectious diseases, including HIV. Heroin smoking has also increased in popularity in the United States, albeit not to the extent in other countries (see Chasing the Dragon later). In addition, users of prescription drugs such as oxycodone or hydrocodone may change to heroin as the supplies of prescription opioids tighten and prices rise. Celebrities and blogs have popularized intranasal heroin use as a “safe” alternative to IV use. This usage is occurring despite a concomitantly reported rise in heroin deaths in regions of the country where its use is prevalent. Although intranasal use may be less dangerous than IV use from an infectious disease perspective, it is clear that both fatal overdose and drug dependency remain common.

Adulterants, Contaminants, and “Heroin” Substitutes.
The history of heroin adulteration and contamination has been extensively described. Retail (street-level) heroin almost always contains adulterants or contaminants. What differentiates the two is the intent of their admixture. Adulterants typically are benign because inflicting harm on the consumer with their addition would be economically and socially unwise, although adulterants occasionally are responsible for epidemic deaths. Interestingly, most heroin overdose fatalities do not have serum morphine concentrations that substantially differ from those of living users, raising the unlikely possibility that the individual death is related to an adulterant or contaminant.

Historically, alkaloids, such as quinine and strychnine, were used to adulterate heroin to mimic the bitter taste of heroin and to mislead clients. Quinine may have first been added in a poorly reasoned attempt to quell an epidemic of malaria among IV heroin users in New York City in the 1930s. That quinine adulteration was common is demonstrated by the common practice of urine screening for quinine as a surrogate marker for heroin use. However, quinine was implicated as a causative factor in an epidemic of heroin-related deaths in the District of Columbia between 1979 and 1982. Toxicity attributed to quinine in heroin users includes cardiac dysrhythmias, amblyopia, and thrombocytopenia. Quinine adulteration currently is much less common than it was in the past. Trend analysis of illicit wholesale and street-level heroin adulteration over a 12-year period in Denmark revealed that although caffeine, acetaminophen (APAP), methaqualone, and phenobarbital all were prevalent adulterants, quinine was not found. Recent data on adulteration in the United
States are unavailable. Many other adulterants or contaminants, including thallium, lead, cocaine, and amphetamines, are reported.

Poisoning by scopolamine-tainted heroin reached epidemic levels in the northeastern United States in 1995. Exposed patients presented with acute psychosis and anticholinergic signs. Several patients were treated with physostigmine, with excellent therapeutic results.

Clenbuterol, a β2-adrenergic agonist with a rapid onset and long duration of action, was found to be a contaminant in street heroin in the Eastern United States in early 2005. Users rapidly developed nausea, chest pain, palpitations, dyspnea, and tremor. Physical findings included significant tachycardia and hypotension, as well as hyperglycemia, hypokalemia, and increased lactate concentrations on laboratory evaluation, and a few fatalities occurred. The initial patients were thought to be cyanide poisoned. Several patients were treated with β-adrenergic antagonists or calcium channel blockers and potassium supplementation with good results.

“Chasing the Dragon.”

IV injection and insufflation are the preferred means of heroin self-administration in the United States. In other countries, including the Netherlands, the United Kingdom, and Spain, a prevalent method is “chasing the dragon” whereby users inhale the white pyrolysate that is generated by heating heroin base on aluminum foil using a handheld flame. This means of administration produces heroin pharmacokinetics similar to those observed after IV administration. Chasing the dragon is not a new phenomenon, but it has gained acceptance recently among both IV heroin users and drug-naïve individuals. The reasons for this shift are diverse but probably are related to the avoidance of injection drug use with its concomitant infectious risks.

In the early 1980s, a group of individuals who smoked and inhaled heroin in the Netherlands developed spongiform leukoencephalopathy. Other causes of this rare clinicopathologic entity include prion-related infections such as bovine spongiform leukoencephalopathy, hexachlorophene, pentachlorophenol, and metal poisoning, although none appeared responsible for this phenomenon. Since the initial report, similar cases have been reported in other parts of Europe and in the United States. Initial findings may occur within 2 weeks of use and include bradykinesia, ataxia, abulia, and speech abnormalities. Of those whose symptoms do not progress, half may recover. However, in others, progression to spastic paraparesis, pseudobulbar palsy, or hypotonia may occur over several weeks. Approximately half of individuals in this group do not develop further deficits or improve, but death occurs in approximately 25% of reported cases. The prominent symmetric cerebellar and cerebral white matter destruction noted on brain computed tomography and magnetic resonance imaging corresponds to that noted at necropsy.

The syndrome has the characteristics of a point-source toxic exposure, but no culpable contaminants have been identified, although aluminum concentrations may be elevated. A component or pyrolysis product unique to certain batches of “heroin” is possible. Treatment is largely supportive. Based on the finding of regional mitochondrial dysfunction on functional brain imaging and an elevated brain lactate concentration, supplementation with 300 mg four times a day of coenzyme Q has purported benefit but has not undergone controlled study.

Other Opioids

Fentanyl and Its Analogs.

Fentanyl is a short-acting opioid agonist that has approximately 50 to 100 times the potency of morphine. It is well absorbed by the transmucosal route, accounting for its use in the form of a “lozenge.” Fentanyl is widely abused as a heroin substitute (intentionally or because of adulteration) and is the controlled substance most often abused by anesthesiologists.
Transdermal fentanyl in the form of a patch (Duragesic) was approved in 1991 and is widely used by patients with chronic pain syndromes. Fentanyl has adequate solubility in both lipid and water for transdermal delivery (Special Considerations: SC1). A single patch contains an amount of drug to provide a transdermal gradient sufficient to maintain a steady-state plasma concentration for approximately 3 days (eg, a 50 μg/h patch contains 5 mg). However, even after the patch is considered exhausted, approximately 50% of the total initial fentanyl dose remains. Interindividual variation in dermal drug penetration and errors in proper use, such as use of excessive patches or warming of the skin, may lead to an iatrogenic fentanyl overdose. Fentanyl patch misuse and abuse occur either by application of one or more patches to the skin or by withdrawal or extraction of the fentanyl from the reservoir for subsequent administration.

Regional epidemics of heroin substitutes with “superpotent” activity occasionally produce a dramatic increase in “heroin-related” fatalities. Epidemic deaths among heroin users first appeared in Orange County, California, in 1979 and were traced to α-methylfentanyl sold under the brand name China White. Similar epidemics of China White poisoning occurred in Pittsburgh in 1988 and in Philadelphia in 1992, although the adulterant in these cases was 3-methylfentanyl, another potent analog. A later epidemic in New York City marked the reappearance of 3-methylfentanyl under the brand name Tango and Cash. Typically, patients present comatose and apneic, with no opioids detected on routine blood and urine analysis. In such cases, unsuspecting users had administered their usual “dose of heroin,” measured in 25-mg “bags” that contained variable amounts of the fentanyl analog. Because of the exceptional potency of this fentanyl analog (as much as 6000 times greater than that of morphine), users rapidly developed apnea.

The largest epidemic of more than 1000 fentanyl-related deaths occurred between 2005 and 2007 primarily in the Philadelphia, Chicago, and Detroit regions because of surreptitiously adulterated or substituted heroin. Fentanyl use was identified by postmortem urine and blood testing or through analysis of unused drug found on either the decedent or persons with whom the decedent shared drugs. In response to this large epidemic, drug users and others were counseled in overdose prevention and cardiopulmonary resuscitation and provided with “take-home” parenteral or intranasal naloxone.

Sufentanil and alfentanil are anesthetic opioids with increased potency compared with fentanyl. In some regions of the country, fentanyl and both licit and illicit fentanyl analogs (eg, 3-methylfentanyl and para-fluorofentanyl) are common drugs of abuse. Experienced heroin users could not easily differentiate fentanyl from heroin, although in one study, heroin was noted to provide a more intense “rush.” Although unconfirmed, the xenobiotic used by Russian authorities to overcome terrorists and subdue a hostage situation in Moscow in October 2002 may have been carfentanil, a potent μ-receptor agonist that is commonly used as a positron emission tomography scan radioligand.

Although fentanyl is a more potent opioid agonist than heroin, the dose of naloxone required to reverse respiratory depression appears to be similar to that of other common opioids. This is because the binding affinity (K_d) of fentanyl at the μ opioid receptor is similar to that of both morphine and naloxone. In a typical overdose, the quantity of fentanyl is likely to be equipotent to typical heroin. However, if large quantities of fentanyl are involved in the poisoning, higher than normal doses of naloxone may be required for reversal. Use of other opioids, such as sufentanil and buprenorphine, which have higher affinity for opioid receptors (lower K_d), may lead to the need for larger doses of naloxone to reverse the patient’s respiratory depression (Antidotes in Depth: A4).

Oxycodone and Hydrocodone.
Both oxycodone and hydrocodone are sold in fixed combination with APAP (eg, Percocet, Vicodin), raising concerns about the complications of APAP hepatotoxicity as the dose of opioid is
escalated. Several opioids, including oxycodone and oxymorphone, can be obtained in a controlled-release form that contains a large quantity of opioid intended to be released over many hours. Up until recently, abusers were able to crush the tablet, which destroys the sustained-release matrix and liberates large amounts of insufflatable or injectable opioid. New tamper-resistant formulations, required of most extended release opioids, make physical or chemical release of the opioid difficult limiting this practice. Users can still ingest intact large dose pills. The psychoactive effects of these opioids are similar to each other and to other μ receptor agonists and often are used as a substitute for heroin. Opioid dependence, overdose, and death are common sequelae of oxycodone abuse.

**Body Packers.**

In an attempt to transport illicit drugs from one country to another, “mules,” or body packers, ingest large numbers of multiple-wrapped packages of concentrated cocaine or heroin. When the authorities discover such individuals or when individuals in custody become ill, they may be brought to a hospital for evaluation and management. Although these patients generally are asymptomatic on arrival, they are at risk for delayed, prolonged, or lethal poisoning as a consequence of packet rupture. In the past, determining the country of origin of the current journey was nearly diagnostic of packet content. However, because most of the heroin imported into the United States now originates from South America, which is also the major source of imported cocaine, the discernment from cocaine on this basis is impossible. Given the current greater revenue potential of heroin, the majority of body packers carry heroin. Details of diagnosis and management are discussed in Special Considerations: SC5.

**Agonist–Antagonists.**

The opioid agonists in common clinical use tend to have specific binding affinity toward the μ opioid receptor subtype. The agonist–antagonists differ in that they interact with multiple receptor types and may have different effects at each receptor. Thus, although most opioids typically produce either agonist or antagonist effects, the agonist–antagonists generally have agonist effects at the κ-receptor subtype and antagonistic effects at the μ receptor subtype. Therefore, opioids such as pentazocine (Talwin) may elicit a withdrawal syndrome in a μ-opioid–tolerant individual because of antagonist effects at the μ receptor. This effect forms the basis of the claim offered by many methadone-dependent patients that they are “allergic to Talwin.” However, this same drug may act as an analgesic in nonopioid-using patients through its agonist effects at the κ-receptor subtype. Although the clinical effects of agonist–antagonists after overdose resemble those of the other opioids, including lethal respiratory depression, they are less likely than the full agonists to produce severe morbidity or mortality (see Respiratory Depression above).

**Pentazocine.**

Historically, patients abusing pentazocine (Talwin) administered it with tripelennamine, a blue capsule, accounting for the appellation “T’s and Blues.” Although this mixture has largely fallen out of favor, pentazocine abuse occurs occasionally. The psychotomimetic effects noted with high doses of pentazocine likely are mediated by κ or perhaps σ receptors. Because pentazocine can be readily dissolved, IV injection was a preferred route for its abuse until the commercial formulation was altered to include 0.5 mg naloxone (Talwin NX), which is not orally bioavailable but fully active parenterally.

**Xenobiotics Used in Opioid Substitution Therapy: Methadone and Buprenorphine**

Two contrasting approaches to the management of patients with chronic opioid use exist, detoxification and maintenance therapy. Detoxification probably is most appropriate for patients motivated or compelled to discontinue opioid use. It can be performed either by tapered withdrawal of an opioid agonist or with the assistance of opioid antagonists. Maintenance therapy may include use of a long-acting opioid antagonist, such
as naltrexone, to pharmacologically block the effects of additional opioid use. Alternatively, and more commonly, maintenance therapy involves opioid substitution therapy.¹⁹

**Methadone.**

Methadone is a synthetic μ opioid receptor agonist used both for treatment of chronic pain and as a maintenance substitute for opioid dependence. Methadone has been available for the latter use for more than 40 years through methadone maintenance treatment programs (MMTPs).² In MMTPs, the opioid in use is replaced by methadone, which is legal, oral, and long acting. This opioid allows patients to abstain from activities associated with procurement and administration of the abused opioid and eliminates much of the morbidity and mortality associated with illicit drug use. Although often successful in achieving opioid abstinence, some methadone users continue to use heroin, other opioids, and other xenobiotics.³³

Methadone is administered as a chiral mixture of (R,S)-methadone. In humans, methadone metabolism is mediated by several cytochrome P450 (CYP) isoenzymes, mainly CYP3A4 and CYP2B6, and to a lesser extent CYP2D6. CYP2B6 demonstrates stereoselectivity toward (S)-methadone, and in vivo data show that CYP2B6 slow metabolizer status is associated with high (S)- but not serum (R)-methadone concentrations.⁴ In clinical trials, QT prolongation was exacerbated in individuals who were CYP2B6 slow metabolizers, and this population had higher (S)-methadone concentrations.⁵ (R)-methadone is used in Germany and is both more effective and safer than the chiral mixture or the (S) enantiomer, but it is not available in the United States at the present time.

Methadone predictably produces QT interval prolongation because of blockade of the hERG (human ether-a-go-go related gene) channel. In the human heart, the hERG voltage-gated potassium channel mediates the rapidly activating delayed rectifier current (Chap. 16). Blocking potassium efflux from the cardiac myocyte prolongs cellular repolarization, prolonging the QT interval. Syncope and sudden death caused by ventricular dysrhythmias (eg, torsade de pointes) are the result. Initially described in case reports of patients on high doses of methadone, clinical trials now reveal that methadone can prolong the QT interval in a concentration-dependent fashion.⁶ Genetic factors in the metabolism of methadone⁷ and probably baseline QT status at the initiation of methadone therapy may underlie and potentially predict adverse effects. (S)-methadone binding to hERG is greater than twofold than that of (R)-methadone and accounts for the cardiotoxicity.⁸

A major difficulty is identification of individuals who are at risk for life-threatening dysrhythmias from methadone-induced QT interval prolongation. Expert-derived guidelines recommend questioning patients about intrinsic heart disease or dysrhythmias, counseling patients initiating methadone therapy, and obtaining a pretreatment ECG and a follow-up ECG at 30 days and yearly.⁹ Patients who receive methadone doses of greater than 100 mg/day might warrant more frequent ECGs, particularly after dose escalation or change in comorbid disease status.⁹ Although these guidelines are disputed by some and limited data exist on the utility of the ECG as a screening test for persons at risk for torsade de pointes from methadone, given its low cost, easy availability, and minimal invasiveness, the guideline recommendations seem practical and appropriate.¹⁰ Although therapeutic methadone is generally safe, rapid dose escalation during induction of therapy may unintentionally produce toxicity and, rarely, fatal respiratory depression.¹¹ This adverse effect is generally the result of the combination of variable pharmacokinetics (unpredictable but generally long half-life) and the time lag for the development of tolerance.

After a successful therapeutic response to the administration of naloxone, recurrence should be expected because the duration of effect of naloxone is only approximately 30 to 60 minutes. In many cases, continuous infusion of naloxone or possibly administration of a long-acting opioid antagonist is indicated to maintain adequate ventilation (Table 38–3).
Unintentional methadone overdose may be related to the manner in which MMTPs dispense the drug. Most patients attending MMTPs are given doses of methadone greater than needed to simply prevent withdrawal and in order to prevent surreptitious heroin or other opioid use. Additionally, many MMTPs provide their established patients with sufficient methadone to last through a weekend or holiday without the need to revisit the program. This combination of dose and quantity may allow diversion of portions of the dose without the attendant risk of opioid withdrawal. Furthermore, home storage of this surplus drug in inappropriate containers, such as juice containers or baby bottles, is a cause of unintentional methadone ingestion by children. Such events can be anticipated because methadone is frequently formulated as a palatable liquid and may not be distributed in child-resistant containers. The primary reason for distribution as a liquid, as opposed to the pill form given to patients with chronic pain syndromes, is to ensure dosing compliance at the MMTP. Unfortunately, death is frequent in children who overdose.

**Buprenorphine.**

Because prescription of methadone for maintenance therapy is restricted to federally licensed programs, it is inaccessible and inconvenient for many patients. Buprenorphine was approved in 2000 as a schedule III medication for office-based prescription, administered three times weekly, providing an attractive alternative for patients with substantially broader potential for obtaining outpatient therapy. However, because of the initial limitations on patient volume (subsequently expanded), the requirement for physician certification, and possibly the hesitation on the part of community physicians to welcome patients with substance use problems into their practices, many of the perceived benefits of buprenorphine therapy over methadone have not been realized.

Buprenorphine, a partial μ-opioid agonist, in doses of 8 to 16 mg sublingually, is effective at suppressing both opioid withdrawal symptoms and the covert use of illicit drugs. Buprenorphine, although still abused and misused, has a substantially better safety profile than methadone. That is, buprenorphine overdose is associated with markedly less respiratory depression than full agonists such as methadone, and there is no reported effect on the QT interval.

Buprenorphine competes with the extant opioid for the μ receptor; thus, administration of initial doses of buprenorphine in patients taking methadone for opioid substitution therapy can be complicated by opioid withdrawal, particularly in patients on higher doses of methadone. For this reason, the initial dose of buprenorphine is administered in the presence of a physician and when the patient is in mild withdrawal. Buprenorphine cessation results in a mild withdrawal syndrome and for this reason may prove efficacious in opioid detoxification programs. After the initial doses of buprenorphine, sublingual film containing both buprenorphine and naloxone (Suboxone) are prescribed to prevent their IV use.

At therapeutic doses, buprenorphine produces nearly complete occupancy of the μ opioid receptors, and its receptor affinity is sufficiently strong that it prevents other opioids from binding. Interestingly, naloxone may prevent the clinical effects of buprenorphine, but the reversal of respiratory effects by naloxone appears to be related in a nonlinear fashion. Relatively low bolus doses of IV naloxone have no effect on the respiratory depression induced by buprenorphine, but high doses (5–10 mg) caused only partial reversal of the respiratory effects of buprenorphine. More recently, data in healthy volunteers suggest a bell-shaped dose response to naloxone. Although doses that would reverse other opioids were ineffective (0.2–0.4 mg), increasing the dose of naloxone to 2 to 4 mg caused full reversal of buprenorphine respiratory depression. However, the onset of reversal is usually slower than occurs when antagonizing other opioids. Further increasing the naloxone dose to 5 to 7 mg caused a decline in reversal activity and actually increased the degree of respiratory depression. The reasons for this are unclear. Therefore, reversal of respiratory depression should be treated with a starting dose that is slightly higher than that used to reverse other opioids and increased slowly and
Titrated to reversal of respiratory depression. For example, a starting dose of naloxone of 0.02 mg/kg, or between 1 and 2 mg, is reasonable, and upward titration should not provide doses in excess of about 5 mg without careful consideration and monitoring. Furthermore, because respiratory depression from buprenorphine may outlast the reversal effects of naloxone boluses or short infusions, a continuous infusion of naloxone may be required to maintain respiratory function.

As a partial agonist, buprenorphine has a ceiling effect on respiratory depression in healthy volunteers, with minimal plateau in analgesic effect. However, in some patients, despite the ceiling effect, clinically consequential respiratory depression may occur. Data from multiple case series indicate that most buprenorphine-related deaths are associated with concomitant use of other drugs, most often benzodiazepines, or to the IV injection of crushed tablets.

The higher affinity (lower Kd) and partial agonism of buprenorphine should allow it to function as an antagonist to the respiratory depressant effects of heroin and improve spontaneous respiration. Although administration of sublingual buprenorphine for opioid overdose is reportedly successful in some case reports, this practice is largely unstudied and not recommended at this time. Interestingly, some reported deaths involved patients given buprenorphine tablets intravenously by fellow drug users for the treatment of heroin-induced respiratory depression.

Unique Opioids
Meperidine.
Meperidine, called pethidine outside of the United States, was previously widely used for treatment of chronic and acute pain syndromes. Meperidine produces clinical manifestations typical of the other opioids and may lead to greater euphoria. Pupillary constriction is less pronounced and, if it occurs, is less persistent than that associated with morphine. However, normeperidine, a toxic, renally eliminated hepatic metabolite, accumulates in patients receiving chronic high-dose meperidine therapy, such as those with sickle cell disease or cancer. A similar accumulation occurs in patients with kidney disease, in whom the elimination half-life increases from a normal of 14 to 21 hours to 35 hours. Normeperidine causes excitatory neurotoxicity, which manifests as delirium, tremor, myoclonus, or seizures. Based on animal studies, the seizures should not be expected to respond to naloxone. In fact, experimental evidence suggests that naloxone may potentiate normeperidine-induced seizures, presumably by inhibiting an anticonvulsant effect of meperidine. Hemodialysis using a high-efficiency membrane may be of limited clinical benefit but rarely, if ever, is indicated because the toxicity generally is self-limited.

Although primarily an opioid, meperidine is capable of exerting effects at other types of receptors. The most consequential nonopioid-receptor effects occur through the serotonin receptor. Blockade of the presynaptic reuptake of released serotonin may produce serotonin toxicity, which is characterized by muscle rigidity, hyperthermia, and altered mental status, particularly in patients using monoamine oxidase inhibitors (MAOIs) (Chap. 73). However, dextromethorphan (see Dextromethorphan later) also may produce toxicity. Conversely, the simultaneous use of MAOIs and morphine, fentanyl, or methadone is not expected to produce serotonin toxicity based on the currently appreciated pharmacology of these drugs. Despite its purported (and likely overstated) beneficial effects on biliary tract physiology, meperidine offers little to support its clinical use and has significant disadvantages. Meperidine use has been dramatically reduced or is closely monitored in many institutions and has been eliminated in other centers because of its adverse risk–benefit profile.

MPTP.
In 1982, several cases of acute, severe parkinsonian symptoms were identified in IV drug users. The patients were labeled “frozen addicts” because of the severe bradykinesia, and extensive investigations into the etiology
of the problem ensued. This ultimately led to the discovery of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), an inadvertent product of presumed errors in the attempted synthesis of the illicit meperidine analog MPPP (1-methyl-4-phenyl-4-propionoxy-piperidine). MPTP is metabolized to the ultimate toxicant MPP⁺ by monoamine oxidase-B in glial cells. Toxicity is inhibited by pretreatment with deprenyl, a monoamine oxidase-B inhibitor. MPP⁺ is a paraquatlike xenobiotic capable of selectively destroying the dopamine-containing cells of the substantia nigra by inhibiting mitochondrial oxidative phosphorylation. The index cases initially responded to standard antiparkinsonian therapy, but none improved substantially, and the effects of the medications waned. Although calamitous for exposed patients, MPTP has proved to be invaluable in the development of experimental models for the study of Parkinson disease. Several of the original “frozen” patients subsequently underwent stereotactic implantation of fetal adrenal tissue grafts into their basal ganglia, with significant clinical improvement.

**Dextromethorphan.**

Dextromethorphan is devoid of analgesic properties altogether even though it is the optical isomer of levorphanol, a potent opioid analgesic. Based on this structural relationship, dextromethorphan is commonly considered an opioid, although its receptor pharmacology is much more complex and diversified. At high doses, dextromethorphan does bind to opioid receptors to produce miosis, respiratory depression, and CNS depression. Reversal of these opioid effects by naloxone is reported. Binding to the PCP site on the NMDA receptor and subsequent inhibition of calcium influx through this receptor-linked ion channel causes sedation. This same activity may account for its antiepileptic properties and for its neuroprotective effects in ischemic brain injury. Because NMDA receptor blockade also enhances the analgesic effects of μ-opioid agonists, combination therapy with morphine and dextromethorphan (MorphiDex) has been introduced.

Blockade of presynaptic serotonin reuptake by dextromethorphan may elicit serotonin toxicity in patients receiving MAOIs. Movement disorders, described as choreothetoid or dystonialike, occasionally occur and presumably result from alteration of dopaminergic neurotransmission. Dextorphan, the active O-demethylation metabolite of dextromethorphan, is produced by CYP2D6, an enzyme with a well-described genetic polymorphism. Whereas patients with the “extensive metabolizer” polymorphism appear to experience more drug-related psychoactive effects, poor metabolizers experience more adverse effects related to the parent compound.

Dextromethorphan is available without prescription in cold preparations, primarily because of its presumed lack of significant addictive potential. However, abuse of dextromethorphan is increasing, particularly among high school students. This increase in use likely is related to the easy availability of dextromethorphan and its perceived limited toxicity. Common street names include “DXM,” “dex,” and “roboshots.” Users often have expectations of euphoria and hallucinations, but a dysphoria comparable to that of PCP commonly ensues. Reports of substantial cold medicine consumption raise several concerns, including APAP poisoning, opioid dependency, and bromide toxicity. This last concern relates to the common formulation of dextromethorphan as the hydrobromide salt. At times, the first clue may be an elevated serum chloride concentration when measured on certain autoanalyzers (Chaps. 6 and 19).

**Tramadol and Tapentadol.**

Tramadol (Ultram) and tapentadol (Nucynta) are novel synthetic analgesics with both opioid and nonopioid mechanisms responsible for their clinical effects. Tramadol is a reuptake inhibitor of norepinephrine and 5-HT, and it has an active metabolite, formed via CYP2D6, that is a weak μ opioid receptor agonist. Tapentadol, which does not require activation, has relatively strong μ-opioid receptor agonism and inhibits the reuptake of norepinephrine but not serotonin. Both are available in immediate-release and extended-release formulations.
A large number of spontaneous reports to the FDA suggest that therapeutic use of **tramadol** may cause seizures, particularly on the first day of therapy. However, epidemiologic studies have not confirmed this association. Tramadol-related seizures are not responsive to naloxone but are suppressed with benzodiazepines. In fact, the package insert cautions against using naloxone in patients with **tramadol** overdoses because in animals treated with naloxone, the risk of seizure is increased. Correspondingly, one patient in a prospective series had a seizure that was temporarily related to naloxone administration. Acute overdose of **tramadol** is generally considered non–life threatening, and most fatalities were associated with polysubstance overdose. Ultrarapid metabolizers at CYP2D6 may experience complications at conventional doses. Patients using MAOIs may be at risk for development of serotonin toxicity after taking **tramadol**.

**Tramadol** abuse is reported, but its extent is undefined. In a review of physician drug abuse in several states, **tramadol** was the second most frequent opioid reported. Opioid users recognized **tramadol** as an opioid only when given in an amount that was six times the therapeutic dose, but at this dose, the users did not develop opioid-like clinical effects such as miosis. Patients may develop typical opioid manifestations after a large overdose. Significant respiratory depression is uncommon and should respond to naloxone. Generally, urine drug screening for drugs of abuse is negative for opioids in **tramadol**-exposed patients. Tapentadol is relatively new to the market, and although its abuse potential remains concerning and case reports exist, there are insufficient epidemiologic data to identify diversion or abuse.

**Propoxyphene.**

Propoxyphene is a weak analgesic with limited efficacy data and serious safety concerns. Similar to its structural analog methadone, propoxyphene binds μ-opioid receptors and produces the expected opioid clinical findings. However, unanticipated properties of propoxyphene manifest after overdose. Propoxyphene and its hepatic metabolite, norpropoxyphene, produce myocardial sodium channel blockade identical to the type IA antidysrhythmics. This process results in QRS complex widening and negative inotropy. **Diphenoxylate and Loperamide.**

Although diphenoxylate is structurally similar to meperidine, its extreme insolubility limits absorption from the GI tract. This factor may enhance its use as an antidiarrheal agent, which presumably occurs via a local opioid effect at the GI μ receptor. However, the standard adult formulation may result in significant systemic absorption and toxicity in children, and all such ingestions should be deemed consequential. Diphenoxylate is formulated with a small dose (0.025 mg) of **atropine** (as Lomotil), both to enhance its antidiarrheal effect and to discourage illicit use. Because both components of Lomotil may be absorbed and their pharmacokinetic profiles differ somewhat, a biphasic clinical syndrome is occasionally noted. Patients may manifest **atropine** poisoning (anticholinergic syndrome), either independently or concomitantly with the opioid effects of diphenoxylate. Delayed, prolonged, or recurrent toxicity is common and is classically related to the delayed gastric emptying effects inherent to both opioids and anticholinergics. However, these effects are more likely explained by the accumulation of the hepatic metabolite difenoxin, which is a significantly more potent opioid than diphenoxylate and possesses a longer serum half-life. Still, the relevance of gastroparesis is highlighted by the retrieval of Lomotil pills by gastric lavage as late as 27 hours after ingestion.

A review of 36 pediatric reports of Lomotil overdoses found that although naloxone was effective in reversing the opioid toxicity, recurrence of CNS and respiratory depression was common. This series included a patient with an asymptomatic presentation 8 hours after ingestion who was observed for several hours and then discharged. This patient returned to the ED 18 hours after ingestion with marked signs of atropinism. In this
same series, children with delayed onset of respiratory depression and other opioid effects were reported, and others describe cardiopulmonary arrest 12 hours after ingestion. Naloxone infusion may be appropriate for patients with recurrent signs of opioid toxicity. Because of the delayed and possibly severe consequences, all children and all adult patients with potentially significant ingestions should be admitted for monitored observation in the hospital.

Loperamide (Imodium) is another insoluble meperidine analog that is used to treat diarrhea. This medication is available without a prescription, and the paucity of adverse patient outcomes reported in the medical literature suggests that the safety profile of this agent is good.

SUMMARY

- Opioid overdose and toxicity remain major causes of drug-related morbidity and mortality.
- Although the therapeutic and toxic doses of opioids are difficult to predict because of the development of tolerance with chronic use, the primary adverse event from excessive dosing is respiratory depression.
- Thus ventilatory support, or administration of a short-acting opioid antagonist such as naloxone, should be adequate initial therapy.
- An appreciation of the pharmacologic differences between the various opioids allows for the identification and appropriate management of patients poisoned or otherwise adversely affected by these xenobiotics.

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