36 OPIOIDS

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Morphine

Opioids are among the oldest therapies in our pharmacopeia, and clinicians recognize their universal utility to limit human distress from pain. Although opioids are widely used as potent analgesics, they have the potential for abuse 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 events from excessive dosing are respiratory depression and sedation.

HISTORY AND EPIDEMIOLOGY

The medicinal value of opium, the dried extract of the poppy plant *Papaver somniferum*, was first recorded circa 1500 B.C. in the Ebers papyrus. Raw opium is composed of at least 10% morphine, but extensive variability exists depending on the environment in which the poppy is grown.[109] 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 used 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 benefit from several of the presumed nonanalgesic effects produced by certain opioids. For example, codeine and hydrocodone are widely used as antitussives and loperamide as an antidiarrheal.

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.[193] Subsequently, various xenobiotics with opioidlike effects were marketed, each promoted for its presumed advantages over morphine. However, in general, the purported advantages of such medications have fallen short of expectations, particularly with regard to their potential for abuse and addiction.

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 two 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 overdose in the United States, the Harrison Narcotics Tax Act, enacted in 1914, made nonanalgesic use of opioids illegal. Since that time and despite extensive legislative and other efforts, recreational and habitual use of heroin and other opioids have remained epidemic in the United States and worldwide and currently are one of the leading causes of death in the United States.

Prescription opioids have until recently accounted for approximately 75% of all opioid-related deaths in the US. In 2009, deaths from prescription drugs, mainly opioids, first exceeded those from motor vehicle crashes.[27] From 2000 to 2015, the rate of deaths from drug overdoses increased 137%, including a 200% increase in the rate of overdose deaths involving opioids (opioid analgesics and heroin).[173]

Current data demonstrate that the United States' opioid epidemic includes two distinct but interrelated trends: a 20-year increase in overdose deaths involving prescription opioid analgesics and a recent surge in illicit opioid overdose deaths, driven largely by heroin and other illicit opioids.[173] Beginning around 2013, the rate of drug overdose deaths involving synthetic opioids increased sharply, driven principally by nonpharmaceutical fentanyl, fentanyl analogs, and novel opioid agonists (U47700 and others). All of these opioids are manufactured in illegal laboratories, primarily in China and Mexico, and imported into the United States more readily than heroin. These illicit opioids are either used to adulterate heroin or are, used to create counterfeit prescription opioid pills, which complicates the attribution of the cause of death in heroin decedents.[77,173,174]

Over the past decade, the realization that opioid analgesics are subject to extensive abuse has led to the development of newer formulations of existing opioids that theoretically reduced abuse potential.[32] The use of "tamper-resistant formulations" was emphasized as an approach to reduce the abuser's ability to crush or dissolve the tablet for insufflation or injection, respectively.[177] Although renamed "abuse deterrent formulations" (ADFs), the true clinical benefit of such formulations in reducing abuse is not known. Descriptions of the means to subvert the deterrence mechanism are widely described on the internet. Because the majority of patients who develop addiction or hyperalgesia ingest intact tablets, ADFs are highly unlikely to beneficially impact these adverse outcome. Although primarily a concern with extended-release or long-acting opioid formulations because of their greater content of opioid, abuse-deterrent immediate-release formulations were recently introduced to address this concern.[102]

The terminology used in this chapter recognizes the broad range of xenobiotics commonly considered to be opiumlike. The term *opiate* specifically refers to the 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 opiumlike 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, not derived from an opiate, that is capable of binding to an opioid receptor and producing opioid effects clinically. Synthetic opioids, such as methadone and fentanyl, bear little apparent 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, including, paradoxically, cocaine. 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.[11] In 1963, after studies on the clinical interactions of nalorphine and morphine, the theory of receptor dualism[196] postulated the existence of two classes of opioid receptors. Such opioid binding sites were not demonstrated experimentally until 1973.[159] 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[129] and the subsequent identification of β-endorphin and dynorphin. As a group, these endogenous ligands for the opioid receptors are called *endorphins* (*endo*genous mo*rphine*). Each is a five–amino acid peptide cleaved from a larger precursor peptide: proenkephalin, proopiomelanocortin, and prodynorphin, respectively. Additionally, a minor related endogenous opioid (nociceptin/orphanin FQ) and its receptor ORL are 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.[72]

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 36–1). Even the endogenous opioid peptides exhibit substantial crossover among the 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.[220] In the first new schema, the receptors were denoted by their endogenous ligand (*o*pioid *p*eptide [OP]), with a subscript identifying their chronologic order of discovery.[52] The δ receptor was renamed OP_1, the κ receptor was renamed OP_2, and the μ receptor was renamed OP_3. 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.

TABLE 36–1 Clinical Effects Related to Opioid Receptors

1996 Conventional Name	*Proposed IUPHAR Name*	*IUPHAR Name*	*Important Clinical Effects of Receptor Agonists*
μ_1	OP_{3a}	MOP	Supraspinal analgesia Peripheral analgesia Sedation Euphoria Prolactin release
μ_2	OP_{3b}	MOP	Spinal analgesia Respiratory depression Physical dependence Gastrointestinal dysmotility Pruritus Bradycardia Growth hormone release
κ_1	OP_{2a}	KOP	Spinal analgesia Miosis Diuresis
κ_2	OP_{2b}	KOP	Psychotomimesis Dysphoria
κ_3	OP_{2b}	KOP	Supraspinal analgesia
δ	OP_1	DOP	Spinal and supraspinal analgesia Modulation of μ-receptor function Inhibit release of dopamine
Nociceptin/ orphanin FQ	OP_4	NOP	Anxiolysis Analgesia

IUPHAR = International Union of Pharmacology Committee on Receptor Nomenclature.

Mu Receptor (μ, MOP, OP_3)

The early identification of the μ receptor as the morphine binding site gave this receptor its designation.[135] 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 (μ_1 and μ_2) 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 μ_1 subtype is responsible for supraspinal (brain) analgesia and for the euphoria sometimes engendered by these xenobiotics. Although stimulation of the μ_2 subtype produces spinal-level analgesia, it also produces respiratory depression. 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 later). All of the currently available μ agonists have some activity at the μ_2 receptor and therefore produce some degree of respiratory compromise. This 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 expected.[89]

Kappa Receptor (κ, KOP, OP_2)

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.[135] These 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). κ-receptor stimulation is not associated with significant respiratory depression or constipation. The receptor currently is subclassified into three subtypes. The κ_1 receptor subtype is responsible for spinal analgesia. This analgesia is not reversed by μ-selective antagonists,[143] supporting the role of κ receptors as independent mediators of analgesia. Although the function of the κ_2 receptor subtype is largely unknown, stimulation of cerebral κ_2 receptors by xenobiotics such as pentazocine and salvinorin A produces psychotomimesis in distinction to the euphoria evoked by μ agonists.[186] The κ_3 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 κ_1 and κ_3 agonism, although both nalorphine and nalbuphine are antagonists to morphine at the μ receptor.[161]

Delta Receptor (δ, DOP, OP_1)

Little is known about δ receptors, although the enkephalins are 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 have important in spinal and supraspinal analgesia (probably via a noncompetitive interaction with the μ receptor) and in cough suppression. δ receptors mediate dopamine release from the nigrostriatal pathway, where they modulate the motor activity associated with amphetamine.[90] Conversely these receptors do not modulate dopamine in the mesolimbic tracts and have only a slight behavioral reinforcing role. Subpopulations, specifically δ_1 and δ_2, are postulated based on in vitro studies but presently are not confirmed in vivo.[220]

Nociceptin/Orphanin FQ Receptor (ORL_1, NOP, OP_4)

The ORL_1 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 investigators and *orphanin* FQ by the Swiss investigators, allowed the designation OP_4. A clinical role has not yet been defined, but anxiolytic and analgesic properties are described.[38]

Opioid-Receptor Signal Transduction Mechanisms

Figure 36–1 illustrates opioid-receptor signal transduction mechanisms. Research on the mechanisms by which an opioid receptor induces an effect continues to produce confusing and often contradictory results. Despite the initial theory that each receptor subtype is linked to a specific transduction mechanism, individual receptor subtypes use one or more mechanisms, depending on several factors, including receptor localization (eg, presynaptic versus postsynaptic). As noted, all opioid-receptor subtypes are members of a superfamily of membrane-bound receptors that are coupled to G proteins.[220] 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 G_i or G_o, although coupling to a cholera toxin-sensitive, excitatory G_s subtype is 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 directly affect a channel or transport protein. Guanidine triphosphate 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.

CLINICAL MANIFESTATIONS

Table 36–2 outlines the clinical effects of opioids.

Therapeutic Effects of Opioids

Analgesia and Euphoria

Although classical teaching attributes opioid analgesia solely to the brain, opioids actually 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[167] or iontophoretic application of agonists into these regions results in profound analgesia.[13] 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.[136]

Blockade of the *N*-methyl-D-aspartate (NMDA) receptor, a mediator of excitatory neurotransmission, enhances the analgesic effects of μ-opioid agonists and reduces the development of tolerance (see Dextromethorphan later).[1] Even more intriguing is the finding that low-dose naloxone (0.25 mcg/kg/h) actually improves the efficacy of morphine analgesia.[69] Administration of higher dose, but still low-dose, naloxone (1 mcg/kg/h) obliterated its opioid-sparing effect. Although undefined, the mechanism may be related to selective inhibition of G_s-coupled excitatory opioid receptors by extremely low concentrations of opioid-receptor antagonist.[39,40]

Xenobiotics with strong binding affinity for δ receptors in humans, when given intrathecally, produce significantly more analgesia than morphine administered similarly. 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.

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.[221] Agonism at these receptors reduces afferent pain neurotransmission and inhibits the release of other proinflammatory compounds, such as substance P.[199] Intraarticular morphine (1 mg) administered to patients after arthroscopic knee surgery produces significant, long-lasting analgesia that is prevented with intraarticular naloxone.[198] The clinical analgesic effect of 5 mg of intraarticular morphine is equivalent to 5 mg of morphine given IM.[31] Intraarticular analgesia is mediated by local μ receptors.[63]

Antitussive

Codeine and dextromethorphan are two opioids with a suggestion of cough-suppressant activity. Cough suppression is not likely mediated via the μ_1 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_2 or κ opioid receptors or antagonism of the δ opioid receptor and that the σ or NMDA receptors also are involved.[205]

Nontherapeutic and Adverse Effects of Opioids

Abuse and Addiction

Addiction is defined as a maladaptive pattern of substance use leading to clinically significant impairment or distress. Opioid use disorder (OUD, which replaced the term opioid dependence in the *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition) is defined as a problematic pattern of opioid use leading to clinically significant impairment or distress.[3] Both definitions are determined by a number of diagnostic criteria, including

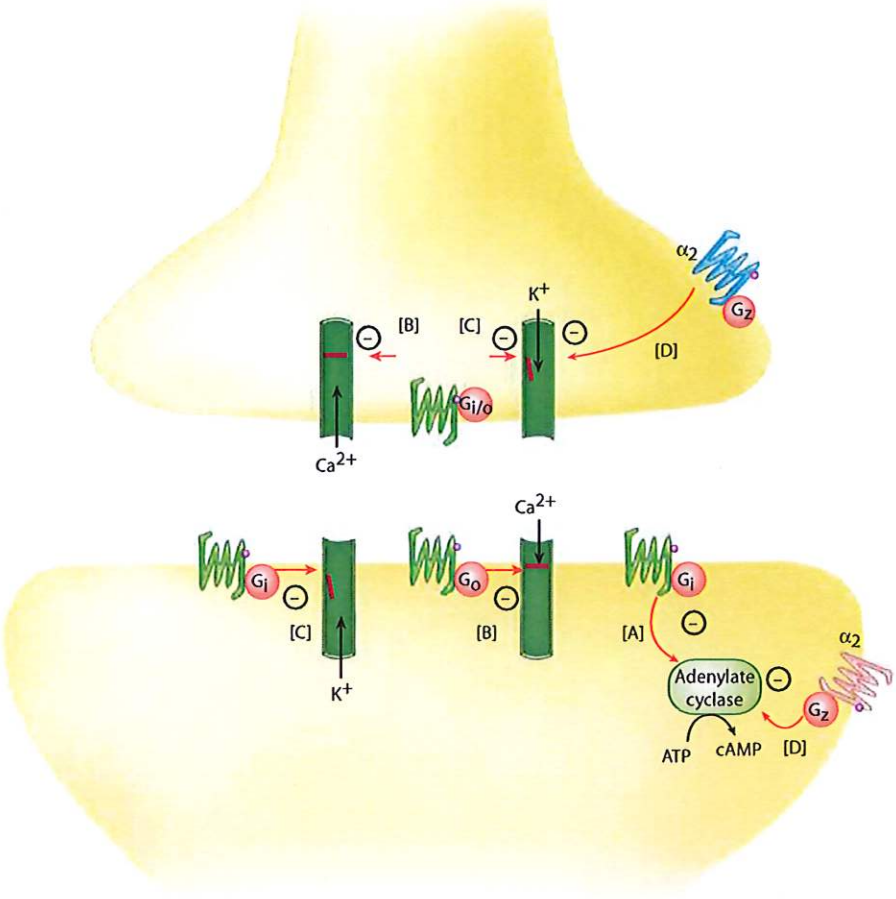


FIGURE 36–1. Opioid-receptor signal transduction mechanisms. Upon binding of an opioid agonist to an opioid receptor, the respective G protein is activated. G proteins (**A**) reduce the capacity of adenylate cyclase to produce cyclic adenosine monophosphate (cAMP); (**B**) close calcium channels that reduce the signal to release neurotransmitters; or (**C**) open potassium channels and hyperpolarize the cell, which indirectly reduces cell activity. Each mechanism is found coupled to each receptor subtype, depending on the location of the receptor (pre- or postsynaptic), and the neuron within the brain (see text). Note that α_2 receptors (**D**) mediate similar effects using a different G protein (G_z).

Adenylate cyclase/cAMP (A). Inhibition of adenylate cyclase activity by G_i or G_o is the classic mechanism for postsynaptic signal transduction invoked by the inhibitory μ receptors. However, this same mechanism is are 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, antianalgesic effects.[44]

Calcium (Ca^{2+}) channels (B). Presynaptic μ receptors inhibit norepinephrine release from the nerve terminals of cells of the rat cerebral cortex. Adenylate cyclase is not 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 concentrations 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_o 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 have an analogous relationship with inhibitory κ receptors, as do acetylcholine-bearing neurons with opioid receptors.

Potassium(K^+) channels (C). Increased conductance through a potassium channel, generally mediated by G_i or G_o, results in membrane hyperpolarization with reduced neuronal excitability. Alternatively, protein kinase A–mediated reduction in membrane potassium conductance enhances neuronal excitability.

tolerance, withdrawal, and deleterious social consequences of opioid use (Table 36–3). Both addiction and OUD share a complicated relationship with, and often overlap, depression and occur in at least 5% of patient using classical definitions and may occur in as many as 40%.[116] This wide range is related to the difficulty of diagnosing misuse, abuse, and OUD in this patient population and inconsistent definitions of misuse and abuse between studies.[30]

Opioid abuse or therapeutic misuse dramatically increases addiction and overdose. Although media reports highlight the abuse of prescription opioids by sports figures and other personalities, such use had simultaneously reached epidemic levels in rural regions of the country where heroin is difficult to obtain. Many of these patients develop an opioid use disorder, particularly addiction, through initial use for therapeutic purposes and then are unable to discontinue their use.

The abuse and addiction liabilities of semisynthetic opioids, based on their subjective profile, are generally similar.[222] Although many users initially receive oxycodone or hydrocodone as analgesics, the majority of abusers obtain the drugs illicitly or from friends.[17,83] Significant efforts by regulatory agencies enhance the understanding and reduce the adverse consequences of opioid use. This includes efforts such as those at the U.S. Food and Drug Administration (FDA) through Risk Evaluation and Mitigation Strategies (REMS), individual states through prescription drug monitoring programs,[158] law enforcement at local and national levels, insurers and pharmacy benefit managers, and the drug manufacturers.[80,216] Physicians and pharmacists have been charged criminally for inappropriate prescribing and dispensing, respectively, for patients with the intent to sell or abuse these drugs.[80]

TABLE 36–2 Clinical Effects of Opioids

Cardiovascular	Bradycardia Orthostatic hypotension Peripheral vasodilation
Dermatologic	Flushing (histamine) Pruritus
Endocrinologic	Reduced antidiuretic hormone release Increased prolactin release Reduced gonadotrophin release
Gastrointestinal	Increased anal sphincter tone Increased biliary tract pressure Reduced gastric acid secretion Reduced motility (constipation)
Neurologic	Analgesia Antitussive Euphoria Sedation, coma Seizures (meperidine, propoxyphene)
Ophthalmic	Miosis
Pulmonary	Acute respiratory distress syndrome Bronchospasm (histamine) Respiratory depression

It is increasingly clear that the prescribing behavior of physicians has been a driver of the widespread misuse of opioids occurring over the past 2 decades. The reasons for such changes are complex but include a mixture of regulatory, sociological, and financial pressures. Data to support the safety and efficacy of opioids for the management of chronic pain are very limited.

TABLE 36–3 Criteria for Opioid Use Disorder[3]

A problematic pattern of opioid use leading to clinically significant impairment or distress, as manifested by at least two of the following, occurring within a 12-month period:

1. Opioids are often taken in larger amounts or over a longer period than was intended.
2. There is a persistent desire or unsuccessful efforts to cut down or control opioid use.
3. A great deal of time is spent in activities necessary to obtain the opioid, use the opioid, or recover from its effects.
4. Craving, or a strong desire or urge to use opioids.
5. Recurrent opioid use resulting in a failure to fulfill major role obligations at work, school, or home.
6. Continued opioid use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of opioids.
7. Important social, occupational, or recreational activities are given up or reduced because of opioid use.
8. Recurrent opioid use in situations in which it is physically hazardous.
9. Continued opioid use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.
10. Tolerance, as defined by either of the following:
    - A need for markedly increased amounts of opioids to achieve intoxication or desired effect
    - A markedly diminished effect with continued use of the same amount of an opioid

Note: This criterion is not considered to be met for those taking opioids solely under appropriate medical supervision.

11. Withdrawal, as manifested by either of the following:
    - The characteristic opioid withdrawal syndrome (refer to Criteria A and B of the criteria set for opioid withdrawal).
    - Opioids (or a closely related substance) are taken to relieve or avoid withdrawal symptoms.

Almost all studies of the long-term use of opioids study periods of use measured in weeks, although in clinical practice patients receive opioid therapy for years. Despite a lack of data, many physicians prescribe opioids for the treatment of chronic nonterminal pain, which results in high rates of OUD. In response to this, the Centers for Disease Control and Prevention has issued guidelines for treatment of chronic pain that encourage alternative medications and therapies initially, discussion of risks of addiction with the patient, use of short-acting opioids, periodic pain and function reassessment, screening for use disorder and diversion, and dispensing of naloxone to patients at risk for overdose.[55]

There is an association between opioids prescribed for acute pain and the development of long-term opioid use.[10,24,33,97,184] Although long-term use reflects ongoing pain, hyperalgesia, dependence, or addiction, the lack of data to support continued beneficial effect compared with harm raises concern. One study suggests the intensity of a physician's opioid prescribing in the emergency department (ED) setting is positively associated with the probability that a patient will become a long-term opioid user over the subsequent 12 months.[10] Another concluded that the likelihood of chronic opioid use after receipt of an opioid prescription increases most sharply in the first days of therapy, particularly after 5 days or 1 month of opioids prescribed.[173] This association was also noted in patients prescribed opioids for postoperative pain with 6% of opioid-naïve patients undergoing both minor and major surgical procedures continuing to use opioids after 90 days after surgery.[21] These studies support the theory that OUD often begins through an initial exposure to a physician-prescribed opioid and that some individuals are "programmed" to have greater reward from and more difficulty discontinuing the use of opioids. The risk of long-term opioid use should be factored into the risk–benefit analysis when considering even short-term opioid therapy.

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 have a direct reinforcing effect on their self-administration through μ receptors within the mesolimbic system.[88]

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.[183] Naloxone reverses euphoria or even produces dysphoria in nonexercising, highly trained athletes.[45,104] Even in normal individuals, high-dose naloxone (4 mg/kg) produces dysphoria.[34]

Exogenous opioids do not induce uniform psychological effects. Some of the exogenous opioids, particularly those that are highly lipophilic such as heroin, are euphorigenic, but morphine is largely devoid of such pleasurable effects.[191] However, morphine administration results in analgesia, anxiolysis, and sedation. Although 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.[155] Chronic users note that fentanyl produces effects that are subjectively similar to those of heroin.[125] This effect offers an explanation of the higher prevalence of fentanyl, as opposed to other accessible opioids, as an abused drug by anesthesiologists,[15,221] as well as the burgeoning appearance of fentanyl and its analogs as a heroin substitute in the community.[174] In distinction, certain opioids, such as pentazocine, produce dysphoria, an effect that is related to their affinity for κ or σ receptors.

Hyperalgesia

Chronic use of opioid analgesics is associated with hyperalgesia, or a heightened sensitivity to pain.[35] This effect was described decades ago in methadone-maintained patients[92] and is again recognized because of the increased use of chronic opioid therapy for pain.[22] Clinically, hyperalgesia manifests as the need for increasing doses of analgesics to mitigate pain, and it occurs as part of or is confused with the development of tolerance. Conceptually, as opposed to tolerance, which is the progressive failure of a drug to adequately

treat the pain, hyperalgesia is the intrinsic increase in the degree of pain in response to an analgesic. The exact mechanisms for the development of opioid-induced hyperalgesia are still not clearly understood. The treatment for hyperalgesia should include weaning from opioids and providing alternative modalities of pain relief.

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,[127] which increases the sensitivity of the light reflex through central reinforcement.[228] Although sectioning of the optic nerve blunts 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 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.[74] Use of opioids with predominantly κ-agonist effects, such as pentazocine, may not result in miosis. Mydriasis occurs in some severely poisoned patients secondary to hypoxic brain injury. Additionally, concomitant drug use or the presence of adulterants will potentially alter pupillary findings. For example, the combination of heroin and cocaine ("speedball") produces 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.[84]

Gastrointestinal

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 D_2 receptor subtypes within the chemoreceptor trigger zone of the medulla. Many opioids, particularly morphine, produce significant nausea and vomiting when used therapeutically.[29] Whether these effects are inhibited by naloxone is not clearly established, but they likely are not.

Although loperamide is widely used therapeutically to manage diarrhea, opioid-induced constipation is frequently a bothersome side effect of both medical and nonmedical use of opioids. Constipation, mediated by μ_2 receptors within the smooth muscle of the intestinal wall,[96] 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.[142] Methylnaltrexone and naloxegol are bioavailable, "peripherally restricted" opioids that do not cross the blood–brain barrier except in overdose. Although they antagonize the effects of opioids on the GI tract opioid receptor,[17,200] the opioid withdrawal syndrome only occurs rarely (Antidotes in Depth: A4).[141] Lubiprostone is a bicyclic fatty acid derived from prostaglandin E_1 (PGE_1) metabolite that increases fluid secretion in the GI tract. Lubiprostone, methylnaltrexone and naloxegol, are approved by the FDA for treatment of opioid-induced constipation in patients with noncancer pain.[151]

Movement Disorders

Patients infrequently experience acute muscular rigidity with rapid IV injection of certain high-potency opioids, especially fentanyl and its derivatives.[203] This condition is particularly prominent during induction of anesthesia and in neonates.[65] The rigidity primarily involves the trunk and impairs chest wall movement sufficiently to exacerbate hypoventilation. Chest wall rigidity contributes to the lethality associated with epidemics of fentanyl-adulterated or fentanyl-substituted heroin. Although the mechanism of muscle rigidity is unclear, it is likely 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 do produce adverse hemodynamic effects, withdrawal phenomena, or uncontrollable pain, depending on the situation.[65] Also, rapid escalation of methadone doses can result in the development of choreoathetoid movements.[14]

Endocrine

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.[18] Clinical findings include reduced libido, erectile dysfunction, hot flashes, and depression, as well as anemia, hair loss, and osteopenia.[181] 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 occurs.[18] In addition, prolactin concentrations commonly rise and lead to gynecomastia.[166]

Hearing Loss

Although relatively rare, rapidly progressive sensorineural hearing loss occurs in heavy users of opioid analgesics.[93] This effect is 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 reexposure after a period of opioid abstinence.[185] Most patients recover after abstinence, although some are only successfully treated with cochlear implants.[93]

Toxic and Life-Threatening Effects of Opioids

When used appropriately for medical purposes, opioids are generally safe and effective. However, excessive use in terms of dose or duration results in adverse consequences. Most adverse or toxic effects are predictable based on opioid pharmacodynamics (eg, respiratory depression), although several opioids produce unexpected "nonopioid" responses. Determining that a patient has 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 toxic 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_2 receptors in the respiratory depressant effects of morphine.[186] Through these receptors, opioid agonists reduce ventilation by diminishing the sensitivity of the medullary chemoreceptors to hypercapnea.[227] In addition to loss of hypercarbic stimulation, opioids depress the ventilatory response to hypoxia.[126] 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.[59,187] This is supported by experiments in MOR-deficient knockout mice.[171] Patients chronically exposed to opioid agonists, such as those on methadone maintenance, experience chronic hypoventilation, although tolerance to loss of hypercarbic drive develops over several months.[133] However, such patients never develop complete tolerance to loss of hypoxic stimulation.[175] 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, and partial agonists produce only limited agonism at the μ opioid receptor.

It is important to recognize that ventilatory depression results from 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.[157] Large doses of opioids also result in a reduction of respiratory rate.

Respiratory depression is the primary cause of death after therapeutic use or overdose. Common reasons for iatrogenic overdose include a failure to appreciate the importance of genetic polymorphisms (see Codeine), sleep apnea, drug interactions, active metabolites (see Morphine), or the complicated pharmacokinetics of the long-acting and extended-release opioids.[153] In a population-based cohort study, higher doses of opioid analgesics were associated with increased overdose risk, and much of the risk at higher doses appears to be associated with co-prescribed benzodiazepines.[51]

Pulmonary and Acute Respiratory Distress Syndrome

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.[156] Almost all opioids are implicated, and opioid-related acute respiratory distress syndrome (ARDS) 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 crackles on auscultation. 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 nose and mouth.[53] Acute lung injury (currently known as ARDS) was described in 71 (48%) of 149 hospitalized heroin overdose patients in New York City,[57] 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. Acute respiratory distress syndrome occurs as an isolated finding or 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 sometimes unmasks the clinical findings of ARDS that were not apparent because an adequate physical examination could not be performed until breathing was restored. Other evidentiary cases involve surgical patients given naloxone postoperatively who subsequently awoke with clinical signs of ARDS. In addition to presumably receiving the naloxone for ventilatory compromise or hypoxia, these patients received multiple intraoperative medications, further obscuring the etiology.[163] Although naloxone ordinarily is safe when appropriately administered to nonopioid-tolerant individuals, the production of acute opioid withdrawal is often linked with "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 a series of experiments, precipitated opioid withdrawal in nontolerant dogs was associated with dramatic cardiovascular changes and abrupt elevation of serum catecholamine concentrations.[144,145] The effects were more dramatic in dogs with an elevated PCO_2 than in those with a normal or low PCO_2, 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).[62]

Even though abrupt precipitation of withdrawal by naloxone contributes 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.[87,91] In addition, neither naloxone nor any other opioid antagonist was available when Osler and others described their initial cases of pulmonary edema, now termed ARDS. 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 overdose, glottic laxity prevents adequate air entry during inspiration. This effect is especially prominent at the time of naloxone administration, in which case breathing will reinstitute before the return of adequate upper airway function.

Cardiovascular

Arteriolar and venous dilation secondary to opioid use results in a mild reduction in blood pressure.[225] 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. Bradycardia is unusual, although a reduction in heart rate is common as a result of the associated reduction in CNS stimulation. Opioid-induced hypotension is mediated by histamine release, although induction of histamine release does not appear to occur through interaction with an opioid receptor. It is related to the nonspecific ability of certain xenobiotics to activate mast cell G proteins[9] and induce degranulation of histamine-containing vesicles. Many opioids share this ability, which is conferred by the presence of a positive charge on a hydrophobic molecule. Accordingly, not all opioids are equivalent in their ability to release histamine.[9] 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.[67] The combination of H_1 and H_2 antagonists is effective in ameliorating the hemodynamic effects of opioids in humans.[160]

Adulterants and coingestants often produce significant cardiovascular toxicity. For example, quinine-adulterated heroin is associated with dysrhythmias. Cocaine, surreptitiously added to heroin, often causes 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, interfere with normal cardiac repolarization and produce QT interval prolongation, an effect that predisposes to the development of torsade de pointes.[122,152] 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 ms.[122] Methadone prolongs the QT interval via interactions with cardiac K^+ channels.[113]

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 that potentiates the convulsant effect of other xenobiotics.[234] 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,[42] although opioid withdrawal seizures in neonates are more common.

Seizures should be anticipated in patients with meperidine, tapentadol, or tramadol toxicity. 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.[140] However, electroencephalography 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.[192] The rigidity and myoclonus associated with fentanyl use are frequently misinterpreted as a seizure.

SPECIFIC OPIOIDS

The vast majority of opioid-poisoned patients follow predictable clinical courses that can be anticipated based on an understanding of opioid receptor pharmacology. However, certain opioids taken in overdose produce atypical manifestations. Therefore, careful clinical assessment and institution of empiric therapy usually are necessary to ensure proper management (Table 36–4).

TABLE 36–4 Classification, Potency, and Characteristics of Opioids and Opioid Antagonists

Opioid	*Type*[a]	*Derivation*	*Analgesic Dose (mg) (via route, equivalent to 10 mg of morphine SC*[b]*)*	*Comments*[a,c]
Buprenorphine	PA	Semisynthetic	0.3 IM	Medication assisted therapy requires 6–16 mg/day (contains naloxone)
Butorphanol	AA	Semisynthetic	2 IM	
Codeine	Ag	Natural	60 PO	Often combined with acetaminophen; requires demethylation to morphine by CYP2D6
Dextromethorphan	NEC	Semisynthetic	Nonanalgesic (10–30 PO)	Antitussive; psychotomimetic via NMDA receptor
Diphenoxylate	Ag	Synthetic	Nonanalgesic (2.5 PO)	Antidiarrheal, combined with atropine; difenoxin is potent metabolite
Fentanyl	Ag	Synthetic	0.75 IM	Very short acting (<1 h)
Fentanyl analogs	Ag	Synthetic	Variable, but high potency	Examples include furanyl fentanyl and carfentanil
Heroin	Ag	Semisynthetic	5 SC	Used therapeutically in some countries; Schedule I medication in the United States
Hydrocodone	Ag	Semisynthetic	1IM, 2PO	
Hydromorphone	Ag	Semisynthetic	1.3 SC	
Levorphanol	Ag	Semisynthetic	2 SC or IM	
Loperamide	Ag	Synthetic	Nonanalgesic (2 PO)	Antidiarrheal; abuse; P-glycoprotein substrate
Meperidine	Ag	Synthetic	75 SC or IM	Seizures caused by metabolite accumulation
Methadone	Ag	Synthetic	10 IM	Very long acting (24 h)
Methylnaltrexone	Ant	Synthetic	Nonanalgesic (8–12 SC); 15PO	Peripherally acting antagonist; reverses opioid-induced constipation
Morphine	Ag	Natural	10 SC or IM	
Naglexol	Ant	Synthetic	Nonanalgesic (25 PO)	Peripherally acting antagonist; reverses opioid constipation; P-glycoprotein substrate
Nalbuphine	AA	Semisynthetic	10 IM	
Naloxone	Ant	Semisynthetic	Nonanalgesic (0.04 IV or IM)	Short-acting antagonist (0.5 h)
Naltrexone	Ant	Semisynthetic	Nonanalgesic (50 PO)	Very long-acting antagonist (24 h)
Oxycodone	Ag	Semisynthetic	5 PO	Often combined with acetaminophen; OxyContin is extended release
Oxymorphone	Ag	Semisynthetic	1 SC	
Paregoric	Ag	Natural	25 mL PO	Tincture of opium (0.4 mg/mL)
Pentazocine	AA	Semisynthetic	50 SC	Psychotomimetic via receptor
Tapentadol	Ag	Synthetic	50 PO	Seizures
Tramadol	Ag	Synthetic	50–100 PO	Seizures possible with therapeutic dosing

[a]Agonist–antagonists, partial agonists, and antagonists may cause withdrawal in tolerant individuals. [b]Typical dose (mg) for xenobiotics without analgesic effects is given in parentheses. [c]Duration of therapeutic clinical effect 3–6 h unless noted; likely to be exaggerated in overdose.

AA = agonist antagonist (κ agonist, μ antagonist); Ag = full agonist (μ_1, μ_2, κ); Ant = full antagonist (μ_1, μ_2, κ antagonist); IM = intramuscular; IV = intravenous; NEC = not easily classified; NMDA = *N*-methyl-D-aspartate; PA = partial agonist (μ_1, μ_2 agonist, κ antagonist); PO = oral; SC = subcutaneous.

Morphine and Codeine

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.[25] However, M6G administered peripherally is significantly less potent as an analgesic than is morphine.[188] 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.[5] This explains why caution is required when administering morphine to patients with kidney failure.

Codeine itself is an inactive opioid agonist, and it requires metabolic activation by *O*-demethylation to morphine by CYP2D6 (Fig. 36–2). This typically represents a minor metabolic pathway for codeine metabolism. *N*-demethylation into norcodeine by CYP3A4 and glucuronidation is more prevalent but produces 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.[101,121] An increasingly recognized phenomenon is that ultrarapid CYP2D6 metabolizers produce unexpectedly large amounts of morphine from codeine, with resulting life-threatening opioid toxicity.[70,164]

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 μ opioid 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. 36–2).[182] Users claim that heroin has an enhanced euphorigenic effect, often described as a "rush." This effect likely is related to the enhanced blood–brain barrier penetration that results from 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 hCE-1 and hCE-2. This interaction has pharmacokinetic and clinical consequences in patients who "speedball."[12,110]

Heroin is available 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.[108] 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,[103] which improves the sublimation of heroin and enhances the yield.[99]

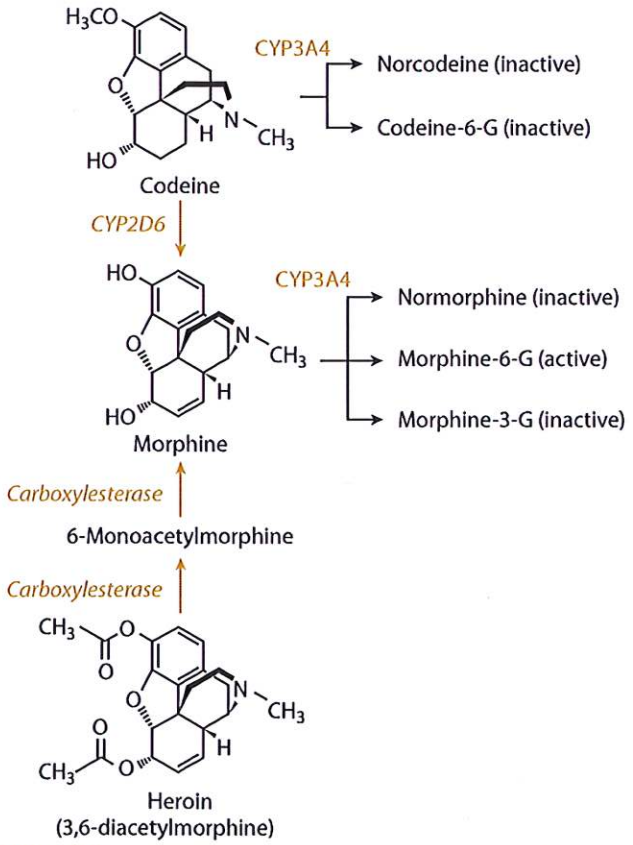


FIGURE 36–2. Opiate and opioid metabolism. Codeine is *O*-methylated to morphine, *N*-demethylated to norcodeine, or glucuronidated to codeine-6-glucuronide (codeine-6-G). Morphine is *N*-demethylated to normorphine or glucuronidated to either morphine-3-glucuronide (morphine-3-G) or morphine-6-glucuronide (morphine-6-G). Heroin is converted to morphine by a two-step process involving plasma cholinesterase and two human liver carboxylesterases known as human carboxylesterase-1 and human carboxylesterase-2.

Widespread IV use has led to many significant direct and indirect medical complications, particularly hepatitis, endocarditis and AIDS, in addition to fatal and nonfatal overdose. Nearly two-thirds of all long-term (longer than 10 years) heroin users in Australia have overdosed on heroin.[47] Among recent-onset heroin users, 23% have overdosed on heroin, and 48% were present when someone else overdosed.[79] Risk factors for fatality after heroin use include the concomitant use of other drugs of abuse, particularly ethanol; recent abstinence, as occurs during incarceration, during which time opioid tolerance has waned;[180] and perhaps unanticipated fluctuations in the concentration or purity of the available heroin.[46,169]

Because most overdoses occur in experienced heroin users and about half occur in the company of other users,[47] the prescribing of naloxone to heroin users for bystander administration is an increasingly available form of harm reduction. Naloxone access for opioid overdose rescue is one of the US Department of Health and Human Services' three priority areas for responding to the opioid crisis,[208] and access to community program-based naloxone distribution for potential overdose bystanders exists in at least 30 states since initial efforts in the late 1990s.[230] Bystanders include people who also use opioids or a friend or family member of a person at risk for overdose. Most community-based naloxone distribution programs provide education on overdose prevention by instructing potential rescuers to recognize known signs of overdose. Naloxone can also be administered by a first responder, such as police or firefighter.

Much of the data proffered to support this practice look at the proportion of those trained that use naloxone within a given time period[137] (maximum potential lives saved) rather than outcomes of overdosed patients with and without bystander intervention. It is possible that many of the patients who receive naloxone did not need the antidote for survival, but that does not mitigate the potential benefit of bystander administration. However, although community-based naloxone distribution programs have gained much momentum in recent years, the cost– and risk–benefit of this practice still remain inadequately understood.[26] 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.[48] 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.[179] The Peltzman effect describes the beneficial effect of a public health intervention is offset by other risk-taking behavior, in this case perhaps using larger doses of opioid (Antidotes in Depth: A4 and Special Considerations: SC6).[162]

Recognition of the efficacy of intranasal heroin administration, or snorting, has fostered a resurgence of heroin use, particularly in suburban communities. The reason for this trend is likely related to falling supplies of the prescription opioids. People already misusing or addicted to prescription opioids are acquiring heroin, which is more available and less expensive, as a substitute, but heroin carries distinct risks.[32] It is also widely suggested that the increasing purity of the available heroin renders 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.[36,172] 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 often change to heroin as the supplies of prescription opioids tighten and prices rise.[106] As such, a component of the recent increase in heroin overdose deaths is likely due to the lack of availability and increased cost of prescription opioids.[173] Celebrities and blogs have popularized intranasal heroin use as a "safe" alternative to IV use. Although intranasal use is less dangerous than IV use from an infectious disease perspective, it is clear that both fatal overdose and drug dependency remain common.[209]

Adulterants, Contaminants, and "Heroin" Substitutes

Retail (street-level) heroin almost always contains adulterants or contaminants, which are differentiated by 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 death. Most heroin overdose decedents do not have serum morphine concentrations that substantially differ from those of living users, raising the possibility that the individual death is related to an adulterant or contaminant.[49]

Historically, alkaloids, such as quinine and strychnine, were used to adulterate heroin to mimic the bitter taste of heroin and to mislead clients. Quinine was initially added in a poorly reasoned attempt to quell an epidemic of malaria among IV heroin users in New York City in the 1930s.[87] 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 (Chap. 55), 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, methaqualone, and phenobarbital all were prevalent adulterants, quinine was not found.[108] Analysis of US heroin samples revealed the presence of procaine, quinine, caffeine, acetaminophen, mannitol lactose, and diphenhydramine in significant quantities.[20] Many other adulterants or contaminants, including thallium, lead, sugars, chalk, brick dust, powdered milk, starch, cocaine, and amphetamines, have been reported.[2]

Poisoning by scopolamine-tainted heroin reached epidemic levels in the northeastern United States in 1995.[84] Exposed patients presented with acute psychosis and anticholinergic signs. Several patients were treated with physostigmine, with excellent therapeutic results.

Clenbuterol, a β_2-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.[93,233] 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"

Intravenous 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.[89] Chasing the dragon is not a new phenomenon, but it has gained acceptance 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 heroin in the Netherlands developed spongiform leukoencephalopathy. Since the initial report, similar cases were reported in other parts of Europe and in the United States.[123,131] Initial findings typically occur within 2 weeks of use and include bradykinesia, ataxia, abulia (inability to make decisions), and speech abnormalities. Of those whose symptoms did not progress, about half recovered. However, in others, progression to spastic paraparesis, pseudobulbar palsy, or hypotonia occurred 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.[116,154]

The syndrome has the characteristics of a point-source toxic exposure, but no culpable contaminants were identified, although aluminum concentrations were frequently elevated.[64] A component or pyrolysis product unique to certain batches of "heroin" is possible.[19] Treatment is largely supportive. Based on the finding of regional mitochondrial dysfunction on functional brain imaging and an elevated brain lactate concentration, supplementation with coenzyme Q 300 mg four times a day has purported benefit and is a reasonable treatment, but it has not undergone controlled study.[123]

Oxycodone, Hydrocodone, Hydromorphone, and Oxymorphone

These semisynthetic opioids are widely used to treat acute and chronic pain. For acute pain, several are sold in fixed combination with acetaminophen (eg, Percocet {oxycodone}, Vicodin {hydrocodone}), raising concerns about the complications of acetaminophen hepatotoxicity as the dose of opioid is escalated. Most are available in extended-release formulations that contain a large quantity of opioid intended to be released over many hours. Up until recently, those intent on abuse were able to crush the tablet, which destroys the controlled-release matrix and liberates large amounts of insufflatable or injectable opioid. New abuse deterrent formulation (ADF) standards required now of all extended release opioids make physical or chemical tampering difficult, limiting but not preventing this practice.[177] Abuse can still occur by ingesting intact pills, which can provide a cumulative amount of opioid.

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" or spray. Fentanyl is widely abused as a heroin substitute (intentionally or unintentionally because of adulteration).[15] Experienced heroin users cannot easily differentiate fentanyl from heroin, although in one study, heroin was noted to provide a more intense "rush."[125] There are thousands of deaths attributed to the illicit use of pharmaceutical fentanyl across North America.

Transdermal fentanyl in the form of a patch 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: SC3)[120] 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-mcg/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, leads 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.[207]

Historically, the largest spontaneous and self-limited fentanyl epidemics, which included more than 1,000 deaths, occurred between 2005 and 2007 primarily in the Philadelphia, Chicago, and Detroit regions because of surreptitiously adulterated or substituted heroin. Fentanyl 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.[28]

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.[121] 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 10,000 times greater than that of morphine), users rapidly developed apnea.

Deaths caused by fentanyl sharply increased in late 2013. During this time period, the fentanyl prescription rate remained relatively stable, suggesting diversion of pharmaceutical fentanyl was not the etiology. Through law enforcement intelligence, it became clear that this increase resulted from the growing availability of nonpharmaceutical (illicitly produced) fentanyl.[77,173,174] In 2015, there was a further sharp increase in opioid fatalities attributable to novel fentanyl analogs, such as acetyl fentanyl, butyryl fentanyl, furanyl fentanyl, and carfentanil (Fig. 36–3). Each of these analogs contains functional groups substituted onto fentanyl that not only changes the pharmacologic effects but also allows the illicit drug to both temporarily skirt controlled substances laws and remain undetectable on traditional opioid immunoassay tests.[148] These highly potent opioids are imported, often through the mail, from synthetic laboratories, primarily in China, in small batches that readily evade detection by law enforcement. Other novel "research" opioids, including compounds such as MT-45, and AH-7921, U-47700, U-50488, which are not fentanyl derivatives, are also associated with significant public health and medical consequences.[148,157,173] Although unconfirmed, the xenobiotic used by Russian authorities to overcome terrorists and subdue a hostage situation in Moscow in October 2002 was carfentanil,[226] a potent μ-receptor agonist that is also 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 is similar to that of clinically equivalent doses of other common opioids.[206] This is because the binding affinity (K_d) of fentanyl at the μ opioid receptor is similar to that of both morphine and naloxone.[128,218] The responsiveness of the fentanyl analogs to reversal by naloxone appears to be pharmacologically similar,[149] but in the clinical setting, it is very difficult to predict. Given the unpredictability of dosing and the extreme potency of the illicit opioids, administration of a large dose, either in absolute or relative terms, should reasonably be expected to require higher than normal doses of naloxone for reversal (Antidotes in Depth: A4).[128]

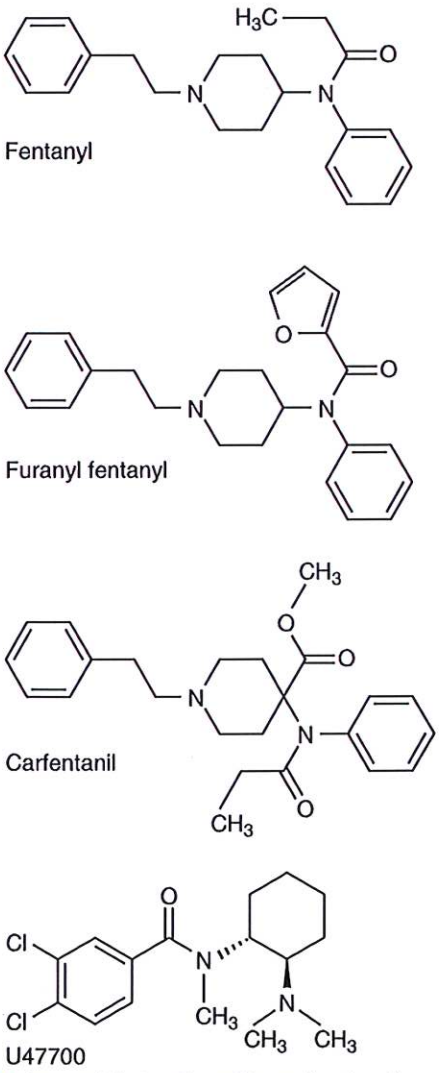


FIGURE 36–3. Structural design of novel fentanyl analogs (furanyl fentanyl and carfentanil) and the novel "research" opioid U-47700.

Xenobiotics Used in Medication Assisted Therapy: Methadone and Buprenorphine

Two contrasting approaches to the management of patients with chronic opioid use exist: (1) detoxification and abstinence and (2) maintenance therapy. Detoxification probably is most appropriate for patients motivated or compelled to discontinue opioid use and remain abstinent. It is usually performed by tapered withdrawal of an opioid agonist. Maintenance therapy includes use of a long-acting opioid antagonist, such as naltrexone, to pharmacologically block the effects of additional opioid use. Greater success in reducing recurrent opioid use is achieved through medication-assisted therapy (MAT), which is essentially maintenance therapy using opioid substitution.[25]

Methadone

Methadone is a synthetic μ-opioid–receptor agonist used both for treatment of chronic pain and as MAT for opioid dependence. Although therapeutic use of methadone, whether for pain or MAT, is generally safe, rapid dose escalation during induction of therapy rarely unintentionally result in toxicity and fatal respiratory depression.[25] 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.

Methadone has been routinely available in many cities for MAT since the 1960s through methadone maintenance treatment programs (MMTPs).[51] In MMTPs, the abused opioid (historically heroin) is replaced by methadone, which is legal, pure, oral, and long acting. Methadone 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.[112]

Primarily because of its low cost compared with other extended-release opioids, until about 2007, methadone was increasingly used in the treatment of chronic pain.[66] Because such policies led to disproportionate adverse effects in patients receiving Medicaid and a safety warning about methadone issued by the FDA in 2006,[66] many such practices were abandoned. Despite accounting for only 1% of opioid prescriptions in 2014, methadone was implicated in approximately 23% of prescription opioid deaths that year.[66] The majority of methadone-related decedents used methadone for pain indications not as part of MAT.[107]

Methadone is administered as a chiral mixture of (*R,S*)-methadone. In humans, methadone metabolism is mediated by several cytochrome P450 (CYP) isozymes, mainly CYP3A4 and CYP2B6 and to a lesser extent CYP2D6. CYP2B6 demonstrates stereoselectivity toward *(S)*-methadone.[73] In vivo data show that CYP2B6 slow metabolizer status is associated with high *(S)*-, but not serum *(R)*-methadone concentrations.[41] *(R)*-methadone is used in Germany and is both more effective and safer than the chiral mixture or the *(S)* enantiomer because the former is largely devoid of QT effects and is the enantiomer that binds to opioid receptors, but it is not available in the United States at the present time.

Methadone predictably and in a concentration-dependent fashion produces QT interval prolongation because of blockade of the hERG (human *ether-a-gogo* related gene) channel.[134] In the human heart, the hERG voltage-gated potassium channel mediates the rapidly activating delayed rectifier current (Chap. 15). 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. Genetic factors in the metabolism of methadone[58] and baseline QT status at the initiation of methadone therapy underlie and potentially predict adverse effects. In clinical trials, QT interval prolongation was greater in individuals who were CYP2B6 slow metabolizers, and this population had higher *(S)*-methadone concentrations.[58] *(S)*-methadone binding to hERG is twofold greater than that of *(R)*-methadone.[103]

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 electrocardiogram (ECG) and a follow-up ECG at 30 days and yearly.[122] Patients who receive methadone doses of greater than 100 mg/day necessitate more frequent ECGs, particularly after dose escalation or change in comorbid disease staus.[122] 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, we agree with the guideline recommendations.[111]

Methadone abuse and unintentional overdose is often related to the manner in which MMTPs dispense the drug.[107] Most patients attending MMTPs are given doses of methadone greater than needed to simply prevent withdrawal and to prevent surreptitious heroin or other opioid use.[201] Additionally, most 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 permits 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,[85] is a cause of unintentional methadone ingestion by children. Such events should be anticipated because methadone is frequently formulated as a palatable liquid, and it is not always stored 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 while being dispensed at the MMTP. Unfortunately, death is frequent in children who overdose.[129] Since 2007, the overdose death rate has declined and is associated with actions aimed at reducing methadone use for pain. In 2006, the FDA issued warnings about the risks of prescribing methadone for pain.[107]

Buprenorphine

Because prescription of methadone for medication assisted therapy is restricted to federally licensed MMTPs, it is inaccessible and inconvenient for many patients. Buprenorphine was approved in 2000 for MAT for office-based prescribing in patients with opioid addiction. It is administered daily at home, providing a more attractive alternative for patients than daily MMTP visits, and it substantially broadened the potential for obtaining outpatient MAT. However, because of the initial limitations on patient volume (which was subsequently expanded), the requirement for physician certification, and possibly the hesitation on the part of community physicians to welcome patients with substance use disorder into their practices, many of the benefits of office-based buprenorphine therapy over methadone are not yet 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 abused, 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. Because there is no reported effect on the QT interval, patients on methadone with concerning QT interval prolongation are offered the opportunity to switch to buprenorphine. Reasons for refusal are multifactorial and include the potential to precipitate withdrawal symptoms at induction, loss of the pleasant effects of methadone, and the reluctance of prescribers to escalate dosing regimens.[98]

Buprenorphine competes with the extant opioid for the μ receptor; thus, administration of initial doses of buprenorphine in patients taking methadone for medication assisted therapy or who are dependent on any other opioid can be complicated by opioid withdrawal. For this reason, the initial dose of buprenorphine is often administered in the presence of a physician and only when the patient is in mild to moderate withdrawal. Buprenorphine cessation results in a mild withdrawal syndrome and for this reason should be an advantage in opioid detoxification programs.[6] Buprenorphine is available as a sublingual (SL) tablets or sublingual or buccal films containing both buprenorphine and naloxone (Suboxone), which is added to prevent 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.[82] Although naloxone prevents the clinical effects of buprenorphine, 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.[176,215] 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.[215] Further increasing the naloxone dose to 5 to 7 mg caused a decline in reversal activity and increased the degree of respiratory depression. The reasons for this are unclear. Therefore, it is recommended that the reversal of respiratory depression 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 1 mg in an adult, is a reasonable initial dose. The dose is then increased incrementally, not to exceed a dose of about 5 mg for concern of decreasing efficacy of naloxone. Because of the difficulty in prediction of naloxone's effect in treatment of buprenorphine-induced respiratory depression, all patients should be closely monitored. Furthermore, because sedation and respiratory depression from buprenorphine may outlast the reversal effects of naloxone, boluses or short infusions or a continuous infusion of naloxone is recommended to maintain respiratory function.[78]

As a partial agonist, buprenorphine has a ceiling effect on respiratory depression in healthy volunteers, with a similar plateau in analgesic effect.[43] However, in some patients, despite the ceiling effect, clinically consequential respiratory depression does occur.[210] 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.[210] Children are at particularly high risk.[23]

The higher affinity (lower K_d) 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,[229] there is not enough evidence to recommend this practice at this time. In fact, some reported deaths involved patients given buprenorphine tablets intravenously by fellow drug abusers for the treatment of heroin-induced respiratory depression.[16]

Other Unique Opioids

Tramadol and Tapentadol

Tramadol and tapentadol are 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, O-desmethyltramadol catalyzed by CYP2D6, which is a μ opioid receptor agonist.[165] The expression of CYP2D6 is extremely variable. Thus, the analgesic effect of tramadol is inconsistent among individual patients. Tapentadol, which does not require activation, has relatively strong μ-opioid receptor agonism and inhibits the reuptake of norepinephrine but not serotonin.[86] Both are available in immediate- and extended-release formulations.

A large number of spontaneous reports to the FDA describe therapeutic use of tramadol resulting in seizures, particularly on the first day of therapy. However, epidemiologic studies have not confirmed this association.[71] Tramadol-related seizures are not responsive to naloxone but are suppressed with benzodiazepines. In fact, the prescribing information cautions against using naloxone in patients with tramadol overdose because the risk of seizure is increased in animal models. Correspondingly, one patient in a prospective series had a seizure that was temporally related to naloxone administration.[196] Acute overdose of tramadol is generally considered non–life threatening, and most fatalities were associated with polysubstance overdose. Ultrarapid metabolizers at CYP2D6 will develop complications at conventional doses.[61] Patients using monoamine oxidase inhibitors (MAOIs) are at risk for development of serotonin toxicity after use of tramadol.

Tramadol abuse is reported. Data indicate an increase in tramadol inquires in recent years, and tramadol was the second most common drug inquired about on a user-based website next to oxycodone.[232] In August 2014, tramadol was moved to Schedule IV of the US Controlled Substances Act, reflecting its potential for abuse and diversion. In a review of physician drug abuse in several states, tramadol was the second most frequent opioid reported.[190,212] Opioid abusers recognized tramadol as an opioid only when given in an amount that was six times the therapeutic dose, but at this dose, they did not develop opioidlike clinical effects such as miosis. Patients develop typical opioid manifestations after a large overdose. Significant respiratory depression is uncommon and should respond to naloxone.[196] Hypoglycemia is associated with therapeutic use of tramadol, and it is reasonable to admit all patients with tramadol-induced hypoglycemia because of the uncertainty of continuing risk.[68] Generally, urine drug screening for drugs of abuse is negative for opioids in tramadol-using patients. Tapentadol is relatively new to the market, and although its abuse potential remains concerning and case reports exist,[115] there are insufficient epidemiologic data to identify diversion or abuse.[50]

Diphenoxylate

Although diphenoxylate is structurally similar to meperidine, its extreme insolubility limits absorption from the GI tract. This factor enhances its use as an antidiarrheal, which presumably occurs via a local opioid effect at the GI μ receptor. However, there is significant systemic absorption of the standard adult formulation with resulting toxicity in children, and all such exposures in children 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 are absorbed and their pharmacokinetic profiles differ somewhat, a biphasic clinical syndrome is occasionally noted.[138] Patients typically 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 postingestion.

A review of 36 pediatric reports of diphenoxylate overdoses found that although naloxone was effective in reversing the opioid toxicity, recurrence of CNS and respiratory depression was common.[138] This series included a patient with an asymptomatic presentation 8 hours postingestion who was observed for several hours and then discharged. This patient returned to the ED 18 hours postingestion 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 postingestion. Naloxone infusion is indicated for patients with recurrent signs of opioid toxicity. Because of the delayed and possibly severe consequences, all individuals with potentially significant ingestions should be admitted for monitored observation in the hospital.

Loperamide

Loperamide is another insoluble meperidine analog that is used to treat diarrhea and is available over the counter as a nonprescription medication. At therapeutic doses, it inhibits peristaltic activity through agonism of μ opioid receptors, calcium channel blockade, calmodulin inhibition, and decreasing paracellular permeability in the large intestine.[8,197] At therapeutic dosing (< 16 mg/day), loperamide is essentially devoid of central opioid effects because transporter protein P-glycoprotein actively facilitates removal of the drug from the gut and the CNS.[213,217] However, larger than recommended doses overcome these mechanisms, enabling CNS penetration and affording relief of opioid withdrawal symptoms or even opioidlike euphoria and psychotropic effects. These effects are facilitated by coingestion of a P-glycoprotein inhibitor. Central nervous system and respiratory depression are reported after therapeutic oral dosing in infants.[130] Since 2010, loperamide exposures misuse and abuse continue to increase in the United States because prescription opioids are costly and becoming less accessible.[214] Loperamide was initially placed in Schedule II, down scheduled to Schedule V in 1977, and descheduled in 1982.[212] Because it is not tracked as a controlled substance, the true extent of use, diversion, and abuse are largely unavailable. As people with OUD search for alternatives to self-treat opioid dependence and withdrawal symptoms, loperamide is becoming more popular as an easily available inexpensive option.

Deaths are reported at the high doses required for CNS effects (70–400 mg) and are associated with respiratory depression cardiotoxicity.[60,197] Loperamide inhibits human cardiac sodium channels and inhibits delayed-rectifier potassium currents in vitro. Correspondingly, both QRS prolongation and polymorphic ventricular tachycardia are reported after overdose.[60,197] Inhibition of calcium channel function likely contributes to its cardiac toxicity in overdose. Naloxone should be administered to reverse consequential respiratory depression associated with loperamide overdose.[60] In patients who present with wide complex dysrhythmias and polymorphic ventricular tachycardia, it is reasonable to use sodium bicarbonate and magnesium sulfate, as potentially preventive measures but primary treatment is electrical cardioversion. However, data on the optimal treatment of cardiotoxicity associated with loperamide overdose are very limited.

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. At high doses, dextromethorphan binds to opioid receptors to produce miosis, respiratory depression, and CNS depression, which are at least partially reversed by naloxone. Binding to the phencyclidine (PCP) site on the NMDA receptor, with subsequent inhibition of calcium influx through this receptor-linked ion channel, causes sedation. This same activity accounts for its antiepileptic properties and for its neuroprotective effects in ischemic brain injury. Because NMDA receptor blockade both reduces hyperalgesia and enhances the analgesic effects of μ-opioid agonists, combination therapy with morphine and dextromethorphan is increasingly studied and used.[114,119]

Blockade of presynaptic serotonin reuptake by dextromethorphan causes the serotonin toxicity in patients receiving MAOIs or other serotonergics.[194] Movement disorders, described as choreoathetoid or dystonialike, occasionally occur and presumably result from alteration of dopaminergic neurotransmission. Dextrorphan, the active *O*-demethylation metabolite of dextromethorphan, is produced by CYP2D6, an enzyme with a well-described genetic polymorphism.[7] 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.[237]

Dextromethorphan is available without prescription in cold preparations, primarily because of its presumed lack of significant addictive potential. Despite this, the prevalence of use among high school students

was high but decreased recently.[195] 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 concerns, including acetaminophen poisoning, opioid dependency, and bromide toxicity.[100] This last concern relates to the common formulation of dextromethorphan as the hydrobromide salt. At times, the first clue is an elevated serum chloride concentration when measured on certain autoanalyzers (Chaps. 7 and 12).

Meperidine

Meperidine was previously widely used for treatment of chronic and acute pain syndromes. Its use was dramatically reduced and is either closely monitored in many institutions or eliminated because of its adverse risk–benefit profile. Meperidine produces clinical manifestations typical of the other opioids and may lead to greater euphoria caused by its blockade of presynaptic serotonin reuptake.[236] This most consequential nonopioid-receptor effect causes serotonin toxicity, characterized by muscle rigidity, hyperthermia, and altered mental status, particularly in patients using MAOIs (Chap. 71). 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 or in those with chronic kidney disease.[204] Normeperidine causes excitatory neurotoxicity, which manifests as delirium, tremor, myoclonus, or seizures. Based on animal studies and human evidence, the seizures do not respond to naloxone.[75]

DIAGNOSTIC TESTING

Laboratory Considerations

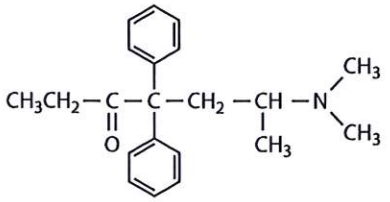
Opioid-poisoned patients are particularly appropriate for a rapid clinical diagnosis because of the unique characteristics of the opioid toxic syndrome. Additionally, even in situations in which the assay results are available rapidly, the fact that several distinct classes of opioids and nonopioids produce similar opioid effects limits the use of laboratory tests, such as immunoassays, that rely on structural features to identify xenobiotics. Furthermore, because opioids are 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 later and in Chap. 7.

Cross-Reactivity

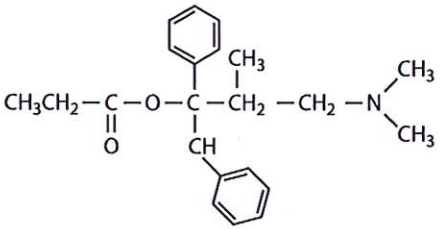
Many opioids share significant structural similarities, such as morphine and oxycodone or methadone and propoxyphene (Fig. 36–4). Because most clinical assays depend on structural features for identification, structurally similar xenobiotics are frequently detected in lieu of the desired one. Whether 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 hydrocodone 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 PCP component of the fluorescence polarization immunoassay (Abbott TDx),[178] a widely used drug abuse screening test (Chap. 7).[200]

Congeners and Adulterants

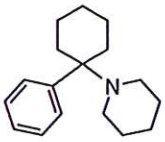
Commercial opiate assays, which are usually specific for morphine (a metabolite of heroin), do not readily detect most of the semisynthetic and synthetic opioids. Epidemic fatalities involving fentanyl derivatives remained unexplained despite obvious opioid toxicity until the ultrapotent fentanyl analog α-methylfentanyl (although initially misidentified as 3-methylfentanyl) was identified by more sophisticated testing.[121,135] Oxycodone, hydrocodone, and other common morphine derivatives have variable detectability by different opioid screens and generally only when in high concentrations.[132] Currently, because of the public health threat of fentanyl analogs and other potent opioids, reference and forensic laboratories have markedly expanded their detection capabilities by using advanced technologies such as tandem mass spectroscopy.[148]



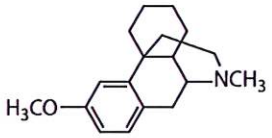
Methadone



Propoxyphene



Phencyclidine



Dextromethorphan

FIGURE 36–4. Structural similarity between methadone and propoxyphene and between phencyclidine and dextromethorphan.

Drug Metabolism

A fascinating dilemma often arises in patients who ingest moderate to large amounts of poppy seeds.[118] 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 infrequently develop elevated serum morphine and codeine concentrations and test positive for morphine.[147,170] Because the presence of morphine on a drug abuse screen supports 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.[150,219] Humans readily deacetylate heroin, which is diacetylmorphine but cannot acetylate morphine and therefore cannot synthesize 6-monoacetylmorphine.

Similar problems occur in patients taking therapeutic doses of codeine. Because codeine is demethylated to morphine by CYP2D6, a morphine screen will be positive as a result of metabolism and not structural cross-reactivity.[71] 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 opium, which is used to synthesize heroin.

Forensic Testing

Decision making regarding the cause of death in the presence of systemic opioids often is complex.[41] 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.[56,112] Techniques to help further elucidate the likely cause of death include the application of postmortem pharmacogenetic principles[105] and the use of alternative specimens (Chap. 140).

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 can often 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 is challenging. Patients manifesting findings of opioid poisoning, found in an appropriate environment, or with characteristic physical clues such as fresh needle marks require little corroborating evidence. However, subtle presentations of opioid poisoning are encountered, and other xenobiotics can simulate opioid poisoning. Hypoglycemia, hypoxia, and hypothermia result in clinical manifestations that share features with opioid poisoning and often exist concomitantly. Many other xenobiotics are rapidly identifiable with routinely available, point-of-care testing, but their existence does not exclude opioid poisoning. 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 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 is toxicity produced by the centrally acting antihypertensives such as clonidine (see later and Chap. 61). Additionally, myriad traumatic, metabolic, and infectious etiologies may occur simultaneously and must always be evaluated appropriately.

Antidote Administration

The goal of naloxone therapy is not necessarily complete restoration of normal consciousness; rather, the goal is reinstitution of adequate spontaneous ventilation. Because precipitation of withdrawal is potentially detrimental and often unpredictable, we recommend administering the lowest practical naloxone dose initially, with rapid escalation as warranted by the clinical situation. Most patients respond to 0.04 of naloxone administered IV,[117] although the requirement for ventilatory assistance is often slightly prolonged because the onset will be slower than with larger doses. We recommend repeating this dose for several doses at 3-minute intervals, as needed for persistent findings, with escalation up to 0.4-mg and 2-mg doses.[37] Infrequently if the presumption of opioid overdose persists repetitive bolus doses of naloxone of 2 mg up to a total of 10 mg is indicated. In patients who do not respond to high doses, opioid-induced hypoventilation is excluded (Antidotes in Depth: A4). Administration in this fashion usually avoids endotracheal intubation and allows for timely identification of patients with nonopioid causes of their clinical condition yet diminishes the risk of precipitation of acute opioid withdrawal. Subcutaneous administration allows for smoother arousal than the high-dose IV route, but is unpredictable in onset and prolonged in offset.[223] Prolonged effectiveness of naloxone by the SC route can be a considerable disadvantage if a withdrawal syndrome develops or if discharge from the ED is dependent on the duration of effect of the antagonist, so we recommend IV dosing and titration to effect whenever feasible (Antidotes in Depth: A4).

In the absence of a confirmatory history or diagnostic clinical findings, the cautious empiric and titrated administration of naloxone will 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 often results in adverse effects; specifically, precipitation of an acute withdrawal syndrome should be anticipated. The resultant agitation, hypertension, and tachycardia produce significant distress for the patient and complicate management for the clinical staff and occasionally is life threatening. Additionally, emesis, a common feature of acute opioid withdrawal, is 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.[235] 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.[91] In contrast, neither respiratory rate below 8 breaths/min nor coma was able to predict a response to naloxone in hospitalized patients.[231] 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.[168,189]

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. We recommend observing these patients for at least 24 hours in a medical setting. Based on the pharmacokinetics of naloxone, patients manifesting only moderate signs of opioid poisoning who remain normal for at least 2 hours after a standard parenteral dose of naloxone are likely safe to discharge (Antidotes in Depth: A4). Patients requiring larger doses of naloxone should be observed longer, although 6 hours should generally be sufficient. Patients with uncontrolled drug use or after a suicide attempt often need psychosocial interventions before discharge from the ED. Patients who have used methadone or an extended-release opioid formulation often require continuous infusion of naloxone or administration of a long-acting opioid antagonist is indicated to maintain adequate ventilation. Patients receiving a naloxone infusion should be maintained for 12 to 24 hours and then observed an additional 4 to 6 hours after discontinuation of the naloxone infusion (Antidotes in Depth: A4).

Patients with recurrent or profound poisoning by long-acting opioids, such as methadone, or patients with large GI burdens (eg, "body packers" or those taking extended-release preparations) often require continuous infusion of naloxone to ensure continued adequate ventilation (Table 36–5). An hourly infusion rate of two-thirds of the initial reversal dose of naloxone is usually sufficient to prevent recurrence.[78] Titration of the dose is often necessary as indicated by the clinical situation. Although repetitive bolus dosing of naloxone is effective, it is labor intensive and subject to error.

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. We recommend against their use for opioid overdose in almost all circumstances. However, these opioid antagonists have a clinical role in the maintenance of consciousness and ventilation in opioid-poisoned patients already awakened by naloxone who are not experiencing opioid withdrawal. Prolonged observation and perhaps antidote readministration will be required to match the pharmacokinetic

TABLE 36–5 Recommended Use of a Naloxone Infusion

1. If a naloxone bolus (start with 0.04 mg IV and titrate) is successful, for those determined to need an infusion administer two-thirds of the effective bolus dose per hour by IV infusion; frequently reassess the patient's respiratory status.
2. If respiratory depression is not reversed after the initial bolus dose:
   Increase dose slowly and titrate to reversal of respiratory depression. Administer up to 10 mg of naloxone as an IV bolus.
   If the patient does not respond, do not initiate an infusion.
   AND prepare for
   Intubation of the patient, as clinically indicated.
3. If the patient develops withdrawal after the bolus dose:
   Allow the effects of the bolus to abate.
   If respiratory depression recurs, administer half of the initial bolus dose and begin an IV infusion at two-thirds of the new bolus dose per hour. Frequently reassess the patient's respiratory status.
4. If the patient develops withdrawal signs or symptoms during the infusion:
   Stop the infusion until the withdrawal symptoms abate.
   Restart the infusion at half the initial rate; frequently reassess the patient's respiratory status.
   Exclude withdrawal from other xenobiotics.
5. If the patient develops respiratory depression during the infusion:
   Readminister half of the initial bolus and repeat until reversal occurs.
   Increase the infusion by half of the initial rate; frequently reassess the patient's respiratory status.
   Exclude continued absorption, readministration of opioid, and other etiologies as the cause of the respiratory depression.

IV = intravenous.

parameters of the agonist and antagonist. For example, it is reasonable to give well children who ingest short-acting opioids a long-acting opioid antagonist such as naltrexone because they are not expected to develop delayed opioid toxicity beyond the duration of the antagonist. However, the same caveats remain regarding the need for extended hospital observation periods if ingestion of methadone or other long-acting opioids is suspected.

Body Packers

In an attempt to transport illicit drugs from one country to another, 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.[211] 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 (Special Considerations: SC5).[76]

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.[81] 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.[139] 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. Ultrarapid opioid detoxification 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, acute kidney injury, and thyroid hormone suppression does occur 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. That is, recrudescence of opioid use in predetoxification quantities is likely to result in overdose.[202] Both techniques are costly; UROD under anesthesia commonly costs thousands of dollars. We agree with the professional medical organizations involved in addiction management that have publicly expressed concern for this form of detoxification.[4]

SUMMARY

- Opioid poisonings, both intentional and unintentional, remain major causes of drug-related morbidity and mortality.
- 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.
- Mechanical ventilation, or administration of a short-acting opioid antagonist such as naloxone, are adequate initial therapies. Naloxone dosing requires cautious escalation.
- An appreciation of the pharmacologic differences among the various opioids allows for the identification and appropriate management of patients poisoned or otherwise adversely affected by these xenobiotics.

REFERENCES

1. Aicher SA, et al. Co-localization of mu opioid receptor and N-methyl-D-aspartate receptor in the trigeminal dorsal horn. *J Pain.* 2002;3:203-210.
2. Akhgari M, et al. Street level heroin, an overview on its components and adulterants. In: Preedy V, ed. *Neuropathology of Drug Addictions and Substance misuse.* Vol 3. 1st ed. New York, NY: Elsevier; 2016:863-877.
3. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders.* 5th ed. Arlington, VA: American Psychiatric Publishing; 2013.
4. American Society of Addiction Medicine. Public Policy Statement on Rapid and Ultra Rapid Opioid Detoxification. http://www.asam.org/advocacy/find-a-policy-statement/view-policy-statement/public-policy-statements/2011/12/15/rapid-and-ultra-rapid-opioid-detoxification.
5. Andersen G, et al. Relationships among morphine metabolism, pain and side effects during long-term treatment: An update. *J Pain Symptom Manage.* 2003;25:74-91.
6. Assadi SM, et al. Opioid detoxification using high doses of buprenorphine in 24 hours: a randomized, double blind, controlled clinical trial. *J Subst Abuse Treat.* 2004;27:75-82.
7. Bailey B, et al. Discrepancy between CYP2D6 phenotype and genotype derived from post-mortem dextromethorphan blood level. *Forensic Sci Int.* 2000;110:61-70.
8. Baker DE. Loperamide: A pharmacological review. *Rev Gastroenterol Disord.* 2007;7(suppl 3):S11-S18.
9. Barke KE, Hough LB. Opiates, mast cells and histamine release. *Life Sci.* 1993;53:1391-1399.
10. Barnett ML, et al. Opioid-prescribing patterns of emergency physicians and risk of long-term use. *N Engl J Med.* 2017;376:663-673.
11. Beckett AH, Casy AF. Synthetic analgesics: stereochemical considerations. *J Pharm Pharmacol.* 1954;6:986-1001.
12. Bencharit S, et al. Structural basis of heroin and cocaine metabolism by a promiscuous human drug-processing enzyme. *Nat Struct Biol.* 2003;10:349-356.
13. Bodnar RJ, et al. Role of mu 1-opiate receptors in supraspinal opiate analgesia: a microinjection study. *Brain Res.* 1988;447:25-34.
14. Bonnet U, et al. Choreoathetoid movements associated with rapid adjustment to methadone. *Pharmacopsychiatry.* 1998;31:143-145.
15. Booth JV, et al. Substance abuse among physicians: a survey of academic anesthesiology programs. *Anesth Analg.* 2002;95:1024-1030.
16. Boyd J, et al. Serious overdoses involving buprenorphine in Helsinki. *Acta Anaesthesiol Scand.* 2003;47:1031-1033.
17. Brands B, et al. Prescription opioid abuse in patients presenting for methadone maintenance treatment. *Drug Alcohol Depend.* 2004;73:199-207.
18. Brennan MJ. The effect of opioid therapy on endocrine function. *Am J Med.* 2013;126 (3 suppl 1):S12-S18.
19. Brenneisen R, Hasler F. GC/MS determination of pyrolysis products from diacetylmorphine and adulterants of street heroin samples. *J Forensic Sci.* 2002;47:885-888.
20. Broseus J, et al. The cutting of cocaine and heroin: a critical review. *Forensic Sci Int.* 2016;262:73-83.
21. Brummett CM, et al. New persistent opioid use after minor and major surgical procedures in US adults. *JAMA Surg.* 2017:e170504.

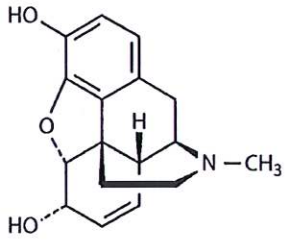
22. Brush DE. Complications of long-term opioid therapy for management of chronic pain: the paradox of opioid-induced hyperalgesia. *J Med Toxicol.* 2012;8:387-392.
23. Budnitz DS, et al. Notes from the field: pediatric emergency department visits for buprenorphine/naloxone ingestion—United States, 2008-2015. *MMWR Morb Mortal Wkly Rep.* 2016;65:1148-1149.
24. Butler MM, et al. Emergency department prescription opioids as an initial exposure preceding addiction. *Ann Emerg Med.* 2016;68:202-208.
25. Center for Substance Abuse Prevention. *Methadone-Associated Mortality: Report of a National Assessment.* Rockville, MD: US Department of Health and Human Services, Substance Abuse and Mental Health Services Administration, Center for Substance Abuse Treatment; 2004.
26. Centers for Disease Control and Prevention (CDC). Community-based opioid overdose prevention programs providing naloxone—United States, 2010. *MMWR Morb Mortal Wkly Rep.* 2012;61:101-105.
27. Centers for Disease Control and Prevention (CDC). Drug overdose deaths—Florida, 2003-2009. *MMWR Morb Mortal Wkly Rep.* 2011;60:869-872.
28. Centers for Disease Control and Prevention (CDC). Nonpharmaceutical fentanyl-related deaths—multiple states, April 2005-March 2007. *MMWR Morb Mortal Wkly Rep.* 2008;57:793-796.
29. Cepeda MS, et al. Incidence of nausea and vomiting in outpatients undergoing general anesthesia in relation to selection of intraoperative opioid. *J Clin Anesth.* 1996;8:324-328.
30. Cheatle MD. Prescription opioid misuse, abuse, morbidity, and mortality: balancing effective pain management and safety. *Pain Med.* 2015;16(suppl 1):S3-S8.
31. Christensen O, et al. Analgesic effect of intraarticular morphine. A controlled, randomised and double-blind study. *Acta Anaesthesiol Scand.* 1996;40:842-846.
32. Cicero TJ, et al. Effect of abuse-deterrent formulation of OxyContin. *N Engl J Med.* 2012;367:187-189.
33. Clarke H, et al. Rates and risk factors for prolonged opioid use after major surgery: population based cohort study. *BMJ.* 2014;348:g1251.
34. Cohen MR, et al. Behavioural effects after high dose naloxone administration to normal volunteers. *Lancet.* 1981;2:1110-1110.
35. Compton P, et al. Hyperalgesia in heroin dependent patients and the effects of opioid substitution therapy. *J Pain.* 2012;13:401-409.
36. Cone EJ, et al. Pharmacokinetics and pharmacodynamics of intranasal snorted heroin. *J Anal Toxicol.* 1993;17:327-337.
37. Connors NJ, Nelson LS. The evolution of recommended naloxone dosing for opioid overdose by medical specialty. *J Med Toxicol.* 2016;12:276-281.
38. Courteix C, et al. Evidence for an exclusive antinociceptive effect of nociceptin/orphanin FQ, an endogenous ligand for the ORL1 receptor, in two animal models of neuropathic pain. *Pain.* 2004;110:236-245.
39. Crain SM, Shen KF. Antagonists of excitatory opioid receptor functions enhance morphine's analgesic potency and attenuate opioid tolerance/dependence liability. *Pain.* 2000;84:121-131.
40. Crain SM, Shen KF. Modulation of opioid analgesia, tolerance and dependence by gs-coupled, GM1 ganglioside-regulated opioid receptor functions. *Trends Pharmacol Sci.* 1998;19:358-365.
41. Crettol S, et al. Methadone enantiomer plasma levels, CYP2B6, CYP2C19, and CYP2C9 genotypes, and response to treatment. *Clin Pharmacol Ther.* 2005;78:593-604.
42. da Silva O, et al. Seizure and electroencephalographic changes in the newborn period induced by opiates and corrected by naloxone infusion. *J Perinatol.* 1999;19:120-123.
43. Dahan A, et al. Buprenorphine induces ceiling in respiratory depression but not in analgesia. *Br J Anaesth.* 2006;96:627-632.
44. Daldrup T. A forensic toxicological dilemma: the interpretation of post-mortem concentrations of central acting analgesics. *Forensic Sci Int.* 2004;142:157-160.
45. Daniel M, et al. Opiate receptor blockade by naltrexone and mood state after acute physical activity. *Br J Sports Med.* 1992;26:111-115.
46. Darke S, et al. Fluctuations in heroin purity and the incidence of fatal heroin overdose. *Drug Alcohol Depend.* 1999;54:155-161.
47. Darke S, et al. Overdose among heroin users in Sydney, Australia: I. prevalence and correlates of non-fatal overdose. *Addiction.* 1996;91:405-411.
48. Darke S, et al. Overdose among heroin users in Sydney, Australia: II. Responses to overdose. *Addiction.* 1996;91:413-417.
49. Darke S, et al. A comparison of blood toxicology of heroin-related deaths and current heroin users in Sydney, Australia. *Drug Alcohol Depend.* 1997;47:45-53.
50. Dart RC, et al. Assessment of the abuse of tapentadol immediate release: the first 24 months. *J Opioid Manag.* 2012;8:395-402.
51. Dasgupta N, et al. Cohort study of the impact of high-dose opioid analgesics on overdose mortality. *Pain Med.* 2016;17:85-98.
52. Dhawan BN, et al. International union of pharmacology. XII. Classification of opioid receptors. *Pharmacol Rev.* 1996;48:567-592.
53. Dinis-Oliveira RJ, et al. "Foam cone" exuding from the mouth and nostrils following heroin overdose. *Toxicol Mech Methods.* 2012;22:159-160.
54. Dole VP, Nyswander M. A medical treatment for diacetylmorphine (heroin) addiction. A clinical trial with methadone hydrochloride. *JAMA.* 1965;193:646-650.
55. Dowell D, et al. CDC guideline for prescribing opioids for chronic pain—United States, 2016. *MMWR Recomm Rep.* 2016;65:1-49.
56. Drummer OH. Postmortem toxicology of drugs of abuse. *Forensic Sci Int.* 2004;142:101-113.
57. Duberstein JL, Kaufman DM. A clinical study of an epidemic of heroin intoxication and heroin-induced pulmonary edema. *Am J Med.* 1971;51:704-714.
58. Eap CB, et al. Stereoselective block of hERG channel by (S)-methadone and QT interval prolongation in CYP2B6 slow metabolizers. *Clin Pharmacol Ther.* 2007;81:719-728.
59. Eckenhoff JE, Oech SR. The effects of narcotics and antagonists upon respiration and circulation in man. A review. *Clin Pharmacol Ther.* 1960;1:483-524.
60. Eggleston W, et al. Loperamide abuse associated with cardiac dysrhythmia and death. *Ann Emerg Med.* 2017;69:83-86.
61. Elkalioubie A, et al. Near-fatal tramadol cardiotoxicity in a CYP2D6 ultrarapid metabolizer. *Eur J Clin Pharmacol.* 2011;67:855-858.
62. Elman I, et al. Ultrarapid opioid detoxification: effects on cardiopulmonary physiology, stress hormones and clinical outcomes. *Drug Alcohol Depend.* 2001;61:163-172.
63. Elvenes J, et al. Expression of functional mu-opioid receptors in human osteoarthritic cartilage and chondrocytes. *Biochem Biophys Res Commun.* 2003;311:202-207.
64. Exley C, et al. Elevated urinary aluminium in current and past users of illicit heroin. *Addict Biol.* 2007;12:197-199.
65. Fahnenstich H, et al. Fentanyl-induced chest wall rigidity and laryngospasm in preterm and term infants. *Crit Care Med.* 2000;28:836-839.
66. Faul M, et al. Methadone prescribing and overdose and the association with medicaid preferred drug list policies—United States, 2007-2014. *MMWR Morb Mortal Wkly Rep.* 2017;66:320-323.
67. Flacke JW, et al. Histamine release by four narcotics: a double-blind study in humans. *Anesth Analg.* 1987;66:723-730.
68. Fournier JP, et al. Tramadol use and the risk of hospitalization for hypoglycemia in patients with noncancer pain. *JAMA Intern Med.* 2015;175:186-193.
69. Gan TJ, et al. Opioid-sparing effects of a low-dose infusion of naloxone in patient-administered morphine sulfate. *Anesthesiology.* 1997;87:1075-1081.
70. Gasche Y, et al. Codeine intoxication associated with ultrarapid CYP2D6 metabolism. *N Engl J Med.* 2004;351:2827-2831.
71. Gasse C, et al. Incidence of first-time idiopathic seizures in users of tramadol. *Pharmacotherapy.* 2000;20:629-634.
72. Gavériaux-Ruff C, Kieffer BL. Opioid receptor genes inactivated in mice: the highlights. *Neuropeptides.* 2002;36:62-71.
73. Gerber JG, et al. Stereoselective metabolism of methadone N-demethylation by cytochrome P4502B6 and 2C19. *Chirality.* 2004;16:36-44.
74. Ghoneim MM, et al. Comparison of four opioid analgesics as supplements to nitrous oxide anesthesia. *Anesth Analg.* 1984;63:405-412.
75. Gilbert PE, Martin WR. Antagonism of the convulsant effects of heroin, d-propoxyphene, meperidine, normeperidine and thebaine by naloxone in mice. *J Pharmacol Exp Ther.* 1975;192:538-541.
76. Gill JR, Graham SM. Ten years of "body packers" in New York City: 50 deaths. *J Forensic Sci.* 2002;47:843-846.
77. Gladden RM, et al. Fentanyl law enforcement submissions and increases in synthetic opioid-involved overdose deaths - 27 states, 2013-2014. *MMWR Morb Mortal Wkly Rep.* 2016;65:837-843.
78. Goldfrank L, et al. A dosing nomogram for continuous infusion intravenous naloxone. *Ann Emerg Med.* 1986;15:566-570.
79. Gossop M, et al. Frequency of non-fatal heroin overdose: survey of heroin users recruited in non-clinical settings. *BMJ.* 1996;313:402.
80. Government Accounting Office. OxyContin abuse and diversion and efforts to address the problem: highlights of a government report. *J Pain Palliat Care Pharmacother.* 2004;18:109-113.
81. Gowing L, et al. Opioid antagonists under heavy sedation or anaesthesia for opioid withdrawal. *Cochrane Database Syst Rev.* 2006;(2):CD002022.
82. Greenwald MK, et al. Effects of buprenorphine maintenance dose on mu-opioid receptor availability, plasma concentrations, and antagonist blockade in heroin-dependent volunteers. *Neuropsychopharmacology.* 2003;28:2000-2009.
83. Gugelmann HM, Nelson LS. The prescription opioid epidemic: repercussions on pediatric emergency medicine. *Pediatr Emerg Med.* 2012;13:260-268.
84. Hamilton RJ, et al. A descriptive study of an epidemic of poisoning caused by heroin adulterated with scopolamine. *J Toxicol Clin Toxicol.* 2000;38:597-608.
85. Harkin K, et al. Storing methadone in babies' bottles puts young children at risk. *BMJ.* 1999;318:329-330.
86. Hartrick CT, Rozek RJ. Tapentadol in pain management: a mu-opioid receptor agonist and noradrenaline reuptake inhibitor. *CNS Drugs.* 2011;25:359-370.
87. Helpern M, Rho YM. Deaths from narcotism in New York City. Incidence, circumstances, and postmortem findings. *N Y State J Med.* 1966;66:2391-2408.
88. Hemby SE, et al. The effects of intravenous heroin administration on extracellular nucleus accumbens dopamine concentrations as determined by in vivo microdialysis. *J Pharmacol Exp Ther.* 1995;273:591-598.
89. Hendriks VM, et al. Heroin self-administration by means of "chasing the dragon": pharmacodynamics and bioavailability of inhaled heroin. *Eur Neuropsychopharmacol.* 2001;11:241-252.
90. Henriksen G, Willoch F. Imaging of opioid receptors in the central nervous system. *Brain.* 2008;131(Pt 5):1171-1196.
91. Hine CH, et al. Analysis of fatalities from acute narcotism in a major urban area. *J Forensic Sci.* 1982;27:372-384.

92. Ho A, Dole VP. Pain perception in drug-free and in methadone-maintained human ex-addicts. *Proc Soc Exp Biol Med.* 1979;162:392-395.
93. Ho T, et al. Hydrocodone use and sensorineural hearing loss. *Pain Physician.* 2007;10:467-472.
94. Hoffman JR, et al. The empiric use of naloxone in patients with altered mental status: a reappraisal. *Ann Emerg Med.* 1991;20:246-252.
95. Hoffman RS, et al; Clenbuterol Study Investigators. A descriptive study of an outbreak of clenbuterol-containing heroin. *Ann Emerg Med.* 2008;52:548-553.
96. Holzer P. Opioids and opioid receptors in the enteric nervous system: from a problem in opioid analgesia to a possible new prokinetic therapy in humans. *Neurosci Lett.* 2004;361:192-195.
97. Hoppe JA, et al. Association of emergency department opioid initiation with recurrent opioid use. *Ann Emerg Med.* 2015;65:493-499.e4.
98. Hser YI, et al. Treatment retention among patients randomized to buprenorphine/naloxone compared to methadone in a multi-site trial. *Addiction.* 2014;109:79-87.
99. Huizer H. Analytical studies on illicit heroin. V. efficacy of volatilization during heroin smoking. *Pharm Weekbl Sci.* 1987;9:203-211.
100. Hung YM. Bromide intoxication by the combination of bromide-containing over-the-counter drug and dextromethorphan hydrobromide. *Hum Exp Toxicol.* 2003;22:459-461.
101. Ingelman-Sundberg M. Genetic polymorphisms of cytochrome P450 2D6 (CYP2D6): clinical consequences, evolutionary aspects and functional diversity. *Pharmacogenomics J.* 2005;5:6-13.
102. Inspirion Delivery Sciences L, ed. Roxybound package insert. Valley Cottage, NY; 2017.
103. Inturrisi CE. Pharmacology of methadone and its isomers. *Minerva Anestesiol.* 2005;71:435-437.
104. Janal MN, et al. Pain sensitivity, mood and plasma endocrine levels in man following long-distance running: effects of naloxone. *Pain.* 1984;19:13-25.
105. Jannetto PJ, et al. Pharmacogenomics as molecular autopsy for postmortem forensic toxicology: genotyping cytochrome P450 2D6 for oxycodone cases. *J Anal Toxicol.* 2002;26:438-447.
106. Jones CM. Heroin use and heroin use risk behaviors among nonmedical users of prescription opioid pain relievers—United States, 2002-2004 and 2008-2010. *Drug Alcohol Depend.* 2013;132:95-100.
107. Jones CM, et al. Trends in methadone distribution for pain treatment, methadone diversion, and overdose deaths—United States, 2002-2014. *MMWR Morb Mortal Wkly Rep.* 2016;65:667-671.
108. Kaa E. Impurities, adulterants and diluents of illicit heroin. changes during a 12-year period. *Forensic Sci Int.* 1994;64:171-179.
109. Kalant H. Opium revisited: a brief review of its nature, composition, non-medical use and relative risks. *Addiction.* 1997;92:267-277.
110. Kamendulis LM, et al. Metabolism of cocaine and heroin is catalyzed by the same human liver carboxylesterases. *J Pharmacol Exp Ther.* 1996;279:713-717.
111. Kao D, et al. Trends in reporting methadone-associated cardiac arrhythmia, 1997-2011: an analysis of registry data. *Ann Intern Med.* 2013;158:735-740.
112. Karch SB, Stephens BG. Toxicology and pathology of deaths related to methadone: retrospective review. *West J Med.* 2000;172:11-14.
113. Katchman AN, et al. Influence of opioid agonists on cardiac human ether-a-go-go-related gene K(+) currents. *J Pharmacol Exp Ther.* 2002;303:688-694.
114. Katz NP. MorphiDex (MS:DM) double-blind, multiple-dose studies in chronic pain patients. *J Pain Symptom Manage.* 2000;19(1 suppl):S37-41.
115. Kemp W, et al. Death due to apparent intravenous injection of tapentadol. *J Forensic Sci.* 2013;58:288-291.
116. Keogh CF, et al. Neuroimaging features of heroin inhalation toxicity: "chasing the dragon." *AJR Am J Roentgenol.* 2003;180:847-850.
117. Kim HK, Nelson LS. Reversal of opioid-induced ventilatory depression using low-dose naloxone (0.04 mg): a case series. *J Med Toxicol.* 2016;12:107-110.
118. King MA, et al. Poppy tea and the baker's first seizure. *Lancet.* 1997;350:716-716.
119. King MR, et al. Perioperative dextromethorphan as an adjunct for postoperative pain: a meta-analysis of randomized controlled trials. *Anesthesiology.* 2016;124:696-705.
120. Kornick CA, et al. Benefit-risk assessment of transdermal fentanyl for the treatment of chronic pain. *Drug Saf.* 2003;26:951-973.
121. Kram TC, et al. Behind the identification of china white. *Anal Chem.* 1981;53:1386.
122. Krantz MJ, et al. QTc interval screening in methadone treatment. *Ann Intern Med.* 2009;150:387-395.
123. Kriegstein AR, et al. Leukoencephalopathy and raised brain lactate from heroin vapor inhalation (chasing the dragon). *Neurology.* 1999;53:1765-1773.
124. Lötsch J, et al. Genetic predictors of the clinical response to opioid analgesics: clinical utility and future perspectives. *Clin Pharmacokinet.* 2004;43:983-1013.
125. LaBarbera M, Wolfe T. Characteristics, attitudes and implications of fentanyl use based on reports from self-identified fentanyl users. *J Psychoactive Drugs.* 1983;15:293-301.
126. Lalley PM. Opioidergic and dopaminergic modulation of respiration. *Respir Physiol Neurobiol.* 2008;164:160-167.
127. Lee HK, Wang SC. Mechanism of morphine-induced miosis in the dog. *J Pharmacol Exp Ther.* 1975;192:415-431.
128. Leysen JE, et al. [3H]sufentanil, a superior ligand for mu-opiate receptors: binding properties and regional distribution in rat brain and spinal cord. *Eur J Pharmacol.* 1983;87:209-225.
129. Li L, et al. Fatal methadone poisoning in children: Maryland 1992-1996. *Subst Use Misuse.* 2000;35:1141-1148.
130. Litovitz T, et al. Surveillance of loperamide ingestions: an analysis of 216 poison center reports. *J Toxicol Clin Toxicol.* 1997;35:11-19.
131. Long H, et al. A fatal case of spongiform leukoencephalopathy linked to chasing the dragon. *J Toxicol Clin Toxicol.* 2003;41:887-891.
132. Magnani B, Kwong T. Urine drug testing for pain management. *Clin Lab Med.* 2012;32:379-390.
133. Marks CE, Goldring RM. Chronic hypercapnia during methadone maintenance. *Am Rev Respir Dis.* 1973;108:1088-1093.
134. Martell BA, et al. Impact of methadone treatment on cardiac repolarization and conduction in opioid users. *Am J Cardiol.* 2005;95:915-918.
135. Martin WR, et al. The effects of morphine- and nalorphine- like drugs in the nondependent and morphine-dependent chronic spinal dog. *J Pharmacol Exp Ther.* 1976;197:517-532.
136. Matthes HW, et al. Loss of morphine-induced analgesia, reward effect and withdrawal symptoms in mice lacking the mu-opioid-receptor gene. *Nature.* 1996;383:819-823.
137. McAuley A, et al. Exploring the life-saving potential of naloxone: a systematic review and descriptive meta-analysis of take home naloxone (THN) programmes for opioid users. *Int J Drug Policy.* 2015;26:1183-1188.
138. McCarron MM, et al. Diphenoxylate-atropine (Lomotil) overdose in children: an update (report of eight cases and review of the literature). *Pediatrics.* 1991;87:694-700.
139. McGregor C, et al. A comparison of antagonist-precipitated withdrawal under anesthesia to standard inpatient withdrawal as a precursor to maintenance naltrexone treatment in heroin users: outcomes at 6 and 12 months. *Drug Alcohol Depend.* 2002;68:5-14.
140. McGuire G, et al. Activation of electrocorticographic activity with remifentanil and alfentanil during neurosurgical excision of epileptogenic focus. *Br J Anaesth.* 2003;91:651-655.
141. McNicol E, et al. Efficacy and safety of mu-opioid antagonists in the treatment of opioid-induced bowel dysfunction: systematic review and meta-analysis of randomized controlled trials. *Pain Med.* 2008;9:634-659.
142. Meissner W, et al. Oral naloxone reverses opioid-associated constipation. *Pain.* 2000;84:105-109.
143. Millan MJ, et al. Kappa-opioid receptor-mediated antinociception in the rat. II. supraspinal in addition to spinal sites of action. *J Pharmacol Exp Ther.* 1989;251:342-350.
144. Mills CA, et al. Narcotic reversal in hypercapnic dogs: comparison of naloxone and nalbuphine. *Can J Anaesth.* 1990;37:238-244.
145. Mills CA, et al. Cardiovascular effects of fentanyl reversal by naloxone at varying arterial carbon dioxide tensions in dogs. *Anesth Analg.* 1988;67:730-736.
146. Minozzi S, et al. Development of dependence following treatment with opioid analgesics for pain relief: a systematic review. *Addiction.* 2013;108:688-698.
147. Moeller MR, et al. Poppy seed consumption and toxicological analysis of blood and urine samples. *Forensic Sci Int.* 2004;143:183-186.
148. Mohr AL, et al. Analysis of novel synthetic opioids U-47700, U-50488 and furanyl fentanyl by LC-MS/MS in postmortem casework. *J Anal Toxicol.* 2016;40:709-717.
149. Moresco A, et al. Use of naloxone to reverse carfentanil citrate-induced hypoxemia and cardiopulmonary depression in rocky mountain wapiti (cervus elaphus nelsoni). *J Zoo Wildl Med.* 2001;32:81-89.
150. Mulé S J, Casella GA. Rendering the poppy-seed defense defenseless: identification of 6-monoacetylmorphine in urine by gas chromatography/mass spectroscopy. *Clin Chem.* 1988;34:1427-1430.
151. Nelson AD, Camilleri M. Opioid-induced constipation: advances and clinical guidance. *Ther Adv Chronic Dis.* 2016;7:121-134.
152. Nelson LS. Toxicologic myocardial sensitization. *J Toxicol Clin Toxicol.* 2002;40:867-879.
153. Niesters M, et al. Opioid-induced respiratory depression in paediatrics: a review of case reports. *Br J Anaesth.* 2013;110:175-182.
154. Offiah C, Hall E. Heroin-induced leukoencephalopathy: characterization using MRI, diffusion-weighted imaging, and MR spectroscopy. *Clin Radiol.* 2008;63:146-152.
155. Oldendorf WH, et al. Blood-brain barrier: penetration of morphine, codeine, heroin, and methadone after carotid injection. *Science.* 1972;178:984-986.
156. Osler W. Oedema of the left lung-morphia poisoning. *Montreal Gen Hosp Rep.* 1880;1:291-293.
157. Papsun D, et al. Analysis of MT-45, a novel synthetic opioid, in human whole blood by LC-MS-MS and its identification in a drug-related death. *J Anal Toxicol.* 2016;40:313-317.
158. Perrone J, et al. Prescribing practices, knowledge, and use of prescription drug monitoring programs (PDMP) by a national sample of medical toxicologists, 2012. *J Med Toxicol.* 2012;8:341-352.
159. Pert CB, Snyder SH. Opiate receptor: demonstration in nervous tissue. *Science.* 1973;179:1011-1014.
160. Philbin DM, et al. The use of H1 and H2 histamine antagonists with morphine anesthesia: a double-blind study. *Anesthesiology.* 1981;55:292-296.
161. Pick CG, et al. Nalbuphine, a mixed kappa 1 and kappa 3 analgesic in mice. *J Pharmacol Exp Ther.* 1992;262:1044-1050.
162. Prasad V, Jena AB. The Peltzman effect and compensatory markers in medicine. *Healthc (Amst).* 2014;2:170-172.
163. Prough DS, et al. Acute pulmonary edema in healthy teenagers following conservative doses of intravenous naloxone. *Anesthesiology.* 1984;60:485-486.
164. Racoosin JA, et al. New evidence about an old drug—risk with codeine after adenotonsillectomy. *N Engl J Med.* 2013;368:2155-2157.
165. Raffa RB, et al. Mechanistic and functional differentiation of tapentadol and tramadol. *Expert Opin Pharmacother.* 2012;13:1437-1449.

166. Rhodin A, et al. Opioid endocrinopathy: a clinical problem in patients with chronic pain and long-term oral opioid treatment. *Clin J Pain*. 2010;26:374-380.
167. Richardson DE, Akil H. Pain reduction by electrical brain stimulation in man. Part 1: Acute administration in periaqueductal and periventricular sites. *J Neurosurg*. 1977;47:178-183.
168. Rigg JR, Rondi P. Changes in rib cage and diaphragm contribution to ventilation after morphine. *Anesthesiology*. 1981;55:507-514.
169. Risser D, et al. Quality of heroin and heroin-related deaths from 1987 to 1995 in Vienna, Austria. *Addiction*. 2000;95:375-382.
170. Rohrig TP, Moore C. The determination of morphine in urine and oral fluid following ingestion of poppy seeds. *J Anal Toxicol*. 2003;27:449-452.
171. Romberg R, et al. Comparison of morphine-6-glucuronide and morphine on respiratory depressant and antinociceptive responses in wild type and mu-opioid receptor deficient mice. *Br J Anaesth*. 2003;91:862-870.
172. Rook EJ, et al. Pharmacokinetics and pharmacokinetic variability of heroin and its metabolites: review of the literature. *Curr Clin Pharmacol*. 2006;1:109-118.
173. Rudd RA, et al. Increases in drug and opioid overdose deaths—United States, 2000-2014. *MMWR Morb Mortal Wkly Rep*. 2016;64:1378-1382.
174. Rudd RA, et al. Increases in drug and opioid-involved overdose deaths—United States, 2010-2015. *MMWR Morb Mortal Wkly Rep*. 2016;65:1445-1452.
175. Santiago TV, et al. Control of breathing during methadone addiction. *Am J Med*. 1977;62:347-354.
176. Sarton E, et al. Naloxone reversal of opioid-induced respiratory depression with special emphasis on the partial agonist/antagonist buprenorphine. *Adv Exp Med Biol*. 2008;605:486-491.
177. Schaeffer T. Abuse-deterrent formulations, an evolving technology against the abuse and misuse of opioid analgesics. *J Med Toxicol*. 2012;8:400-407.
178. Schier J. Avoid unfavorable consequences: dextromethorphan can bring about a false-positive phencyclidine urine drug screen. *J Emerg Med*. 2000;18:379-381.
179. Seal KH, et al. Attitudes about prescribing take-home naloxone to injection drug users for the management of heroin overdose: a survey of street-recruited injectors in the San Francisco Bay Area. *J Urban Health*. 2003;80:291-301.
180. Seaman SR, et al. Mortality from overdose among injecting drug users recently released from prison: database linkage study. *BMJ*. 1998;316:426-428.
181. Seftel AD. Re: opioid-induced androgen deficiency (OPIAD). *J Urol*. 2013;189:251.
182. Selley DE, et al. Mu opioid receptor-mediated G-protein activation by heroin metabolites: evidence for greater efficacy of 6-monoacetylmorphine compared with morphine. *Biochem Pharmacol*. 2001;62:447-455.
183. Sgherza AL, et al. Effect of naloxone on perceived exertion and exercise capacity during maximal cycle ergometry. *J Appl Physiol*. 2002;93:2023-2028.
184. Shah A, et al. Characteristics of initial prescription episodes and likelihood of long-term opioid use—United States, 2006-2015. *MMWR Morb Mortal Wkly Rep*. 2017;66:265-269.
185. Shaw KA, et al. Methadone, another cause of opioid-associated hearing loss: a case report. *J Emerg Med*. 2011;41:635-639.
186. Sheffler DJ, et al. The magic mint hallucinogen finds a molecular target in the kappa opioid receptor. *Trends Pharmacol Sci*. 2003;24:107-109.
187. Shook JE, et al. Differential roles of opioid receptors in respiration, respiratory disease, and opiate-induced respiratory depression. *Am Rev Respir Dis*. 1990;142:895-909.
188. Skarke C, et al. Analgesic effects of morphine and morphine-6-glucuronide in a transcutaneous electrical pain model in healthy volunteers. *Clin Pharmacol Ther*. 2003;73:107-121.
189. Skarke C, et al. Respiratory and miotic effects of morphine in healthy volunteers when P-glycoprotein is blocked by quinidine. *Clin Pharmacol Ther*. 2003;74:303-311.
190. Skipper GE, et al. Tramadol abuse and dependence among physicians. *JAMA*. 2004;292:1818-1819.
191. Smith GM, Beecher HK. Subjective effects of heroin and morphine in normal subjects. *J Pharmacol Exp Ther*. 1962;136:47-52.
192. Smith NT, et al. Seizures during opioid anesthetic induction—are they opioid-induced rigidity? *Anesthesiology*. 1989;71:852-862.
193. Sneader W. The discovery of heroin. *Lancet*. 1998;352:1697-1699.
194. Sovner R, Wolfe J. Interaction between dextromethorphan and monoamine oxidase inhibitor therapy with isocarboxazid. *N Engl J Med*. 1988;319:1671.
195. Spangler DC, et al. Dextromethorphan: a case study on addressing abuse of a safe and effective drug. *Subst Abuse Treat Prev Policy*. 2016;11:22.
196. Spiller HA, et al. Prospective multicenter evaluation of tramadol exposure. *J Toxicol Clin Toxicol*. 1997;35:361-364.
197. Stanciu CN, et al. Loperamide, the "poor man's methadone": brief review. *J Psychoactive Drugs*. 2017;49:18-21.
198. Stein C, et al. Analgesic effect of intraarticular morphine after arthroscopic knee surgery. *N Engl J Med*. 1991;325:1123-1126.
199. Stein C, et al. Attacking pain at its source: new perspectives on opioids. *Nat Med*. 2003;9:1003-1008.
200. Storrow AB, et al. The dextromethorphan defense: dextromethorphan and the opioid screen. *Acad Emerg Med*. 1995;2:791-794.
201. Strain EC, et al. Moderate- vs high-dose methadone in the treatment of opioid dependence: a randomized trial. *JAMA*. 1999;281:1000-1005.
202. Strang J, et al. Loss of tolerance and overdose mortality after inpatient opiate detoxification: follow up study. *BMJ*. 2003;326:959-960.
203. Streisand JB, et al. Fentanyl-induced rigidity and unconsciousness in human volunteers. incidence, duration, and plasma concentrations. *Anesthesiology*. 1993;78:629-634.
204. Szeto HH, et al. Accumulation of normeperidine, an active metabolite of meperidine, in patients with renal failure of cancer. *Ann Intern Med*. 1977;86:738-741.
205. Takahama K, Shirasaki T. Central and peripheral mechanisms of narcotic antitussives: codeine-sensitive and -resistant coughs. *Cough*. 2007;3:8.
206. Takahashi M, et al. Naloxone reversal of opioid anesthesia revisited: clinical evaluation and plasma concentration analysis of continuous naloxone infusion after anesthesia with high-dose fentanyl. *J Anesth*. 2004;18:1-8.
207. Tharp AM, et al. Fatal intravenous fentanyl abuse: four cases involving extraction of fentanyl from transdermal patches. *Am J Forensic Med Pathol*. 2004;25:178-181.
208. The US Department of Health and Human Services. HHS takes strong steps to address opioid-drug related overdose, death and dependence. http://www.hhs.gov/about/news/2015/03/26/hhs-takes-strong-steps-to-address-opioid-drug-related-overdose-death-and-dependence.html. Accessed May 11, 2017.
209. Thiblin I, et al. Fatal intoxication as a consequence of intranasal administration (snorting) or pulmonary inhalation (smoking) of heroin. *Forensic Sci Int*. 2004;139:241-247.
210. Tracqui A, et al. Buprenorphine-related deaths among drug addicts in France: a report on 20 fatalities. *J Anal Toxicol*. 1998;22:430-434.
211. Traub SJ, et al. Body packing—the internal concealment of illicit drugs. *N Engl J Med*. 2003;349:2519-2526.
212. United States Department of Justice, Diversion Control Division. *Scheduling Actions Controlled Substances Regulated Chemicals*. May 2017:80.
213. Upton RN. Cerebral uptake of drugs in humans. *Clin Exp Pharmacol Physiol*. 2007;34:695-701.
214. Vakkalanka JP, et al. Epidemiologic trends in loperamide abuse and misuse. *Ann Emerg Med*. 2017;69:73-78.
215. van Dorp E, et al. Naloxone reversal of buprenorphine-induced respiratory depression. *Anesthesiology*. 2006;105:51-57.
216. Van Zee A. The promotion and marketing of oxycontin: commercial triumph, public health tragedy. *Am J Public Health*. 2009;99:221-227.
217. Vandenbossche J, et al. Loperamide and P-glycoprotein inhibition: assessment of the clinical relevance. *J Pharm Pharmacol*. 2010;62:401-412.
218. Villiger JW, Ray et al. Characteristics of [3H]fentanyl binding to the opiate receptor. *Neuropharmacology*. 1983;22:447-452.
219. von Euler M, et al. Interpretation of the presence of 6-monoacetylmorphine in the absence of morphine-3-glucuronide in urine samples: evidence of heroin abuse. *Ther Drug Monit*. 2003;25:645-648.
220. Waldhoer M, et al. Opioid receptors. *Annu Rev Biochem*. 2004;73:953-990.
221. Walker JS. Anti-inflammatory effects of opioids. *Adv Exp Med Biol*. 2003;521:148-160.
222. Walsh SL, et al. The relative abuse liability of oral oxycodone, hydrocodone and hydromorphone assessed in prescription opioid abusers. *Drug Alcohol Depend*. 2008;98:191-202.
223. Wanger K, et al. Intravenous vs subcutaneous naloxone for out-of-hospital management of presumed opioid overdose. *Acad Emerg Med*. 1998;5:293-299.
224. Ward CF, et al. Drug abuse in anesthesia training programs. A survey: 1970 through 1980. *JAMA*. 1983;250:922-925.
225. Ward JM, et al. Effects of morphine on the peripheral vascular response to sympathetic stimulation. *Am J Cardiol*. 1972;29:659-666.
226. Wax PM, et al. Unexpected gas casualties in Moscow: a medical toxicology perspective. *Ann Emerg Med*. 2003;41:700-705.
227. Weil JV, et al. Diminished ventilatory response to hypoxia and hypercapnia after morphine in normal man. *N Engl J Med*. 1975;292:1103-1106.
228. Weinhold LL, Bigelow GE. Opioid miosis: effects of lighting intensity and monocular and binocular exposure. *Drug Alcohol Depend*. 1993;31:177-181.
229. Welsh C, et al. A case of heroin overdose reversed by sublingually administered buprenorphine/naloxone (suboxone). *Addiction*. 2008;103:1226-1228.
230. Wheeler E, et al; Centers for Disease Control and Prevention (CDC). Opioid overdose prevention programs providing naloxone to laypersons—United States, 2014. *MMWR Morb Mortal Wkly Rep*. 2015;64:631-635.
231. Whipple JK, et al. Difficulties in diagnosing narcotic overdoses in hospitalized patients. *Ann Pharmacother*. 1994;28:446-450.
232. Wightman RS, et al. Comparative analysis of opioid queries on erowid.org: an opportunity to advance harm reduction. *Subst Use Misuse*. 2017:1-5.
233. Wingert WE, et al. Detection of clenbuterol in heroin users in twelve postmortem cases at the Philadelphia medical examiner's office. *J Anal Toxicol*. 2008;32:522-528.
234. Yajima Y, et al. Effects of differential modulation of mu-, delta- and kappa-opioid systems on bicuculline-induced convulsions in the mouse. *Brain Res*. 2000;862:120-126.
235. Yealy DM, et al. The safety of prehospital naloxone administration by paramedics. *Ann Emerg Med*. 1990;19:902-905.
236. Zacny JP, Gutierrez S. Characterizing the subjective, psychomotor, and physiological effects of oral oxycodone in non-drug-abusing volunteers. *Psychopharmacology (Berl)*. 2003;170:242-254.
237. Zawertailo LA, et al. Psychotropic effects of dextromethorphan are altered by the CYP2D6 polymorphism: a pilot study. *J Clin Psychopharmacol*. 1998;18:332-337.

A4 OPIOID ANTAGONISTS

Lewis S. Nelson and Mary Ann Howland



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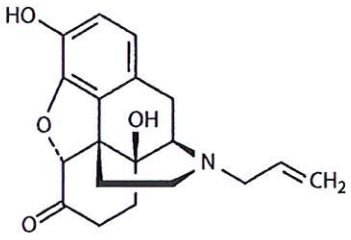
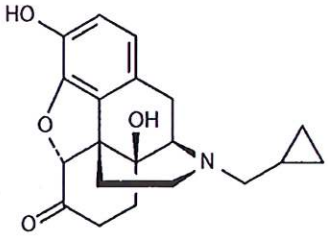
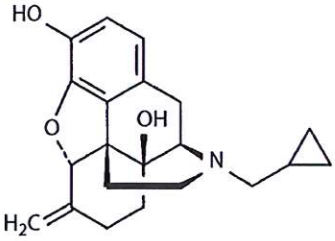


Naloxone



Naltrexone



Nalmefene

INTRODUCTION

Naloxone, naltrexone, and methylnaltrexone are pure competitive opioid antagonists at the mu (μ), kappa (κ), and delta (δ) receptors. Opioid antagonists prevent the actions of opioid agonists, reverse the effects of both endogenous and exogenous opioids, and cause opioid withdrawal in opioid-dependent patients. Naloxone is the primary opioid antagonist used to reverse respiratory depression in patients manifesting opioid toxicity. The parenteral dose should be titrated to maintain adequate airway reflexes and ventilation. By titrating the dose, in small increments based on clinical response, abrupt opioid withdrawal should be prevented. This titrated low dose method of administration limits withdrawal-induced adverse effects, such as vomiting and the potential for aspiration pneumonitis, and a surge in catecholamines with the potential for cardiac dysrhythmias and the acute respiratory distress syndrome (ARDS). Because of its poor oral bioavailability, oral naloxone was previously suggested as treatment for patients with opioid-induced constipation. Methylnaltrexone, a parenteral medication, and naloxegol, an oral formulation, are effective in reversing opioid-induced constipation without inducing opioid withdrawal. This is because their central nervous system (CNS) entry is restricted. Naltrexone is used both orally and intramuscularly in patients after opioid detoxification to maintain opioid abstinence and as an adjunct to achieve ethanol abstinence.

HISTORY

The understanding of structure–activity relationships led to the synthesis of many new molecules in the hope of producing potent opioid agonists free of abuse potential. Although this goal is not yet realized, opioid antagonists and partial agonists resulted from these investigations. *N*-Allylnorcodeine was the first opioid antagonist synthesized (in 1915), and *N*-allylnormorphine (nalorphine) was synthesized in the 1940s.[40,82] Nalorphine was recognized as having both agonist and antagonist effects in 1954. Naloxone was synthesized in 1960, and naltrexone in 1963. The synthesis of opioid antagonists that are unable to cross the blood–brain barrier (sometimes called peripherally restricted) allowed patients receiving long-term opioid analgesics to avoid opioid-induced constipation, one of the most uncomfortable side effects associated with opioid therapy. Since the mid-1990s and the reappearance of the opioid epidemic of the 21st century, there has been a steady increase in the use of naloxone that is prescribed or directly dispensed to users of any opioid who are at risk of overdose as well as for administration by bystanders.[14]

PHARMACOLOGY

Chemistry

Minor structural alterations are used to convert an agonist into an antagonist. The substitution of the *N*-methyl group on morphine by a larger functional group led to nalorphine and converted the agonist levorphanol to the antagonist levallorphan.[38] Naloxone and naltrexone are derivatives of oxymorphone with antagonist properties resulting from addition of organic or other functional groups.[38,42]

Mechanism of Action

The mu receptors are responsible for analgesia, sedation, miosis, euphoria, respiratory depression, and decreased gastrointestinal (GI) motility. Kappa receptors are responsible for spinal analgesia, miosis, dysphoria, anxiety, nightmares, and hallucinations. Delta receptors are responsible for analgesia and hunger. The currently available opioid receptor antagonists are most potent at the mu receptor, with higher doses required to affect the kappa and delta receptors. They all bind to the opioid receptor in a competitive fashion, preventing the binding of agonists, partial agonists, or mixed agonist–antagonists without producing any independent action.

Pharmacokinetics

Naloxone and naltrexone differ primarily in their pharmacokinetics. Naltrexone has a longer duration of action and sufficient oral bioavailability to produce systemic effects. At therapeutic doses, methylnaltrexone is relatively

effectively excluded from the CNS and only produces peripheral effects in overdose. Selective antagonists for mu, kappa, and delta are available experimentally and are undergoing investigation.

The oral bioavailability of naloxone is less than 2%,[30,76] rectal bioavailability is 15%,[76] and the sublingual bioavailability is only 10%.[8] The bioavailability of a concentrated intranasal naloxone formulation is approximately 44% that of naloxone administered by the intramuscular (IM) route.[1] In the same study, the apparent half-life of 4 mg of the 40 mg/mL formulation sprayed into one or both nostrils was approximately 2.1 hour compared with 1.24 hour for 0.4 mg administered IM into the thigh. In contrast, naloxone is well absorbed by all parenteral routes of administration. The approximate onset of action with the various routes of administration are as follows: intralingual, 30 seconds; intravenous (IV), 1 to 2 minutes; endotracheal, 60 seconds; intranasal, 3.4 minutes; inhalational (nebulized), 5 minutes; subcutaneous (SC), 5.5 minutes; and IM, 6 minutes.[26,44,62,91] The distribution half-life is rapid (~5 minutes) because of its high lipid solubility. Protein binding is low,[1] and the volume of distribution (V_d) is 0.8 to 2.64 L/kg.[34]

An IV naloxone dose of 13 mcg/kg (~1 mg in an 80-kg opioid-naïve adult) occupies approximately 50% of the available opioid receptors.[57] The duration of action of naloxone is approximately 20 to 90 minutes and depends on the dose and route of administration of naloxone and the rates of elimination of the agonist and naloxone.[8,28,85] Naloxone is hepatically metabolized to several compounds, including a glucuronide conjugate. The elimination half-life after IV administration is 60 to 90 minutes in adults and approximately two to three times longer in neonates.

Naltrexone is rapidly absorbed with an oral bioavailability of 5% to 60% because of extensive first pass effects, and peak serum concentrations occur at 1 hour.[37] Distribution is rapid, with a V_d of approximately 15 L/kg and low protein binding.[48] Naltrexone is metabolized in the liver to β-naltrexol (major metabolite with 2%–8% activity) and 2-hydroxy,3-methoxy-β-naltrexol and undergoes an enterohepatic cycle.[54,89] The plasma elimination half-lives are 4 hours for naltrexone and 13 hours for β-naltrexol, with a terminal phase of elimination of 96 hours and 18 hours, respectively.[87] The terminal elimination half-life corresponds most closely with the clinical effects of naltrexone.[51] Naltrexone for extended-release injectable suspension (Vivitrol, Alkermes) displays an initial peak concentration at approximately 2 hours after injection; a second peak 2 to 3 days later; and approximately 14 days after dosing, the concentration slowly declines over the subsequent month.[4]

Methylnaltrexone is a quaternary amine methylated derivative of naltrexone that is peripherally restricted because of its poor lipid solubility and limited ability to cross the blood–brain barrier.[99] After SC administration, peak serum concentrations occur in about 30 minutes. The drug has a V_d of 1.1 L/kg and is minimally protein bound (11%–15%). Although there are several metabolites, 85% of the drug is eliminated unchanged in the urine.[99]

Naloxegol is an orally bioavailable, pegylated derivative of naloxone. Pegylation reduces its ability to cross the blood–brain barrier and allows its removal by the P-glycoprotein efflux pump. Peak serum concentration occurs at about 2 hours. Elimination is primarily through CYP3A4 metabolism, and the half-life is 6 to 11 hours.

Pharmacodynamics

In the proper doses, pure opioid antagonists reverse all of the effects at the mu, kappa, and delta receptors of endogenous and exogenous opioid agonists. Buprenorphine, a partial agonist that behaves clinically like an antagonist in opioid dependent people, has a very high affinity for and slow rate of dissociation from the mu receptor.[65] Actions of opioid agonists that are not mediated by interaction with opioid receptors, such as direct mast cell liberation of histamine and the potassium channel blocking effects of methadone, are not reversed by these antagonists.[5] Chest wall rigidity from rapid fentanyl infusion is usually reversed with naloxone.[19] Opioid-induced seizures in animals, such as from propoxyphene, are antagonized by opioid antagonists, although seizures caused by meperidine (normeperidine) and tramadol are not.[33] The benefit of naloxone for opioid-induced seizures in humans is less clear. A report of two newborns who developed seizures associated with fentanyl and morphine infusion demonstrated abrupt clinical and electroencephalographic resolution after administration of naloxone.[22]

Opioids operate bimodally on opioid receptors.[20] At very low concentrations, mu opioid receptor agonism is excitatory and increases pain. This antianalgesic effect of opioids is modulated through a G_s protein and usually is less important clinically than the well-known inhibitory actions that result from coupling to a G_o protein at usual analgesic doses. For this reason, extremely low doses of opioid antagonists (ie, 0.25 mcg/kg/h of naloxone) enhance the analgesic potency of opioids, including morphine, methadone, and buprenorphine.[21,32] Naloxone also attenuates or prevents the development of tolerance and dependence.[32] Coadministration of these very low doses of antagonists with the opioid also limits opioid-induced adverse effects such as nausea, vomiting, constipation, and pruritus.[99]

Opioid antagonists reverse the effects of endogenous opioid peptides, including endorphins, dynorphins, and enkephalins with variable effectiveness. Endogenous opioids are found in tissues throughout the body and work in concert with other neurotransmitter systems to modulate many physiologic effects.[29,84] For instance, during shock, the release of circulating endorphins produces an inhibition of central sympathetic tone by stimulating kappa receptors within the locus coeruleus, resulting in vasodilation. Vagal tone is also enhanced through stimulation of opioid receptors in the nucleus ambiguus. Naloxone continues to be explored in resuscitation from cardiac arrest,[71] which appears to be related to its effects at the delta-opioid receptor. The data do not support its routine administration at this time.[55,64]

ROLE IN OPIOID TOXICITY

Naloxone use by medical personnel for the management of patients with opioid toxicity has evolved over the past 50 years. Initial studies found the use of naloxone to be relatively safe and highly effective in awakening opioid-toxic patients.[43,97] Although once recommended to be administered empirically to nearly every patient with a depressed level of consciousness and respiratory depression,[41] as complications of precipitated opioid withdrawal in opioid-dependent patients became more apparent, such aggressive use diminished dramatically.[9] Currently, the empiric parenteral dose that we recommend for all opioid-dependent patients is 0.04 mg,[18] although in nondependent patients, higher doses are administered without concern for precipitating withdrawal. The goal of reversal of opioid toxicity is to improve the patient's ventilation while avoiding withdrawal (see later discussion).

Take-home naloxone distribution and naloxone prescribing for bystander administration in addition to programs for nonmedical first responders continue to significantly expand around the world.[90] The majority of the naloxone available for community-based use is intended for administration by the intranasal route.[3,7] Increasing the availability of naloxone leads to an increased rate of reversal from opioid-induced unresponsiveness, although the absolute numbers and rates of preventing death are unknown.[91] However, debates exist on best approaches to this public health attempt at harm reduction (see Adverse Effects and Safety Issues). See further discussion in Special Considerations: SC6 on harm reduction.

ROLE IN MAINTENANCE OF OPIOID ABSTINENCE

Opioid dependence is managed either by substitution of the primary opioid, typically heroin or a prescription opioid, with methadone or buprenorphine or by detoxification and subsequent abstinence. Maintenance of abstinence is facilitated by the administration of daily or depot formulations of naltrexone.[74] This is of particular importance in patients whose opioid tolerance has waned because of abstinence, whether voluntary or forced, such as in the immediate period after incarceration.[50]

Before naltrexone is administered for abstinence maintenance, the patient must be weaned from opioid dependence and be a willing participant. Naloxone should be administered intravenously to confirm that the patient is no longer opioid dependent and is therefore safe for naltrexone administration. With naloxone, opioid withdrawal, if it occurs, will be short

lived instead of prolonged as it is after the administration of naltrexone. Prolonged treatment with naltrexone (and naloxone) results in upregulation and supersensitivity of opioid receptors.[75] Although the clinical implications are undefined, concern should be heightened for enhanced clinical response to an opioid after resumption of opioid use in patients who discontinue naltrexone therapy.

ROLE IN ETHANOL ABSTINENCE

Naltrexone, particularly the IM depot form, is used as adjunctive therapy in ethanol dependence based on the theory that the endogenous opioid system modulates ethanol intake.[13,81] Naltrexone reduces ethanol craving, the number of drinking days, and relapse rates.[52,68] Naltrexone induces moderate to severe nausea in 15% of patients, possibly as a result of alterations in endogenous opioid tone induced by prolonged ethanol ingestion.

OTHER USES

Poorly orally bioavailable opioid antagonists (eg, naloxone) and peripherally restricted opioid antagonists (eg, methylnaltrexone) are used to prevent or treat the constipation occurring as a side effect of opioid use, whether for pain management or addiction therapy.[11] Evacuation resulted from methylnaltrexone, within 4 hours, and naloxegol, within 6 hours, but the beneficial effect was small by absolute standards, and the drugs are expensive.[15,80]

Opioid antagonists are sometimes used in the management of overdoses with nonopioids such as ethanol,[25] clonidine,[73] captopril,[86] and valproic acid.[79] In none of these instances is the reported improvement as dramatic or consistent as in the reversal of an opioid. The mechanisms for each of these, although undefined, is suggested to relate to reversal of endogenous opioid peptides at opioid receptors.

Naloxone was used to reverse the effects of endogenous opioid peptides in patients with septic shock, although the results were variable.[24] Treatment is often ineffective and will result in adverse effects in patients who are opioid tolerant.

Opioid antagonists at low doses are used for treatment of morphine-induced pruritus resulting from systemic or epidural exposure and for treat of pruritus associated with cholestasis.[61,66]

ADVERSE EFFECTS AND SAFETY ISSUES

Pure opioid antagonists produce no clinical effects in opioid-naïve or nondependent patients even when administered in massive doses (grams) in a spinal cord injury study.[10] Although in another study when naloxone was administered to opioid-naïve patients in large doses (2 mg/kg), a variety of symptoms, including anxiety, difficulty concentrating, sadness, irritability, sweating, and GI manifestations were reported.[2] Some of these findings lasted for a few days.

When patients dependent on opioid agonists are exposed to opioid antagonists, agonist–antagonists, or partial agonists, they exhibit opioid withdrawal, including yawning, lacrimation, diaphoresis, rhinorrhea, piloerection, mydriasis, vomiting, diarrhea, myalgias, mild elevations in heart rate and blood pressure, and insomnia. Antagonist-precipitated withdrawal also sometimes results in an "overshoot" phenomenon, from a transient increase in circulating catecholamines, resulting in hyperventilation, tachycardia, and hypertension.[47]

Under these circumstances, there is a potential for related withdrawal-related complications. In the cardiovascular system, myocardial ischemia and infarction, myocardial stunning (takotsubo, stress cardiomyopathy), heart failure, hypertension, and dysrhythmia are rarely reported.[46] In the CNS, agitation should be expected and is occasionally profound, and seizures, although rare, may occur. Delirium, although rarely reported in patients withdrawing because of opioid abstinence, occur during precipitated opioid withdrawal.[35]

In the lungs, case reports describe acute respiratory distress syndrome (ARDS) in association with naloxone administration, almost uniformly in opioid-dependent patients.[67,72] The clinical complexities of the setting make it difficult to analyze and attribute these adverse effects solely to naloxone.[12] Adult respiratory distress syndrome occurs after heroin overdose in the absence of naloxone,[27] making the exact contribution of naloxone unclear. Rather, in certain patients, naloxone likely unmasks ARDS previously induced by the opioid but unrecognized because of the patient's concomitant opioid-induced respiratory depression.

If the patient's airway is unprotected during withdrawal and vomiting occurs, aspiration pneumonitis may complicate the recovery.[17] Given the frequency of polysubstance abuse and overdose associated with altered consciousness, the risk of precipitating withdrawal-associated vomiting should always be a concern.

These severe manifestations of precipitated opioid withdrawal also occur with ultra-rapid opioid detoxification and are associated with fatalities occurring in the postdetoxification period.[39] This rapid form of deliberate detoxification differs significantly from the opioid withdrawal associated with volitional opioid abstinence (Chap. 14).

Many of the adverse effects observed in patients with precipitated opioid withdrawal are the result of excessive circulating catecholamines. The catecholamine response to naloxone is significantly greater in dogs with hypercapnia compared with those that are normocapnic or hypocapnic.[59] Although not studied in humans, this highlights the potential ability of manual ventilation before the administration of naloxone to ameliorate the aforementioned complications.

Resedation is a function of the relatively short duration of action of the opioid antagonist compared with the opioid agonist. Most opioid agonists have durations of action longer than that of naloxone and shorter than that of naltrexone (with the exception of methadone). A long duration of action is advantageous when the antagonist is used to promote abstinence (naltrexone) but is undesired when inappropriately administered to an opioid-dependent patient (see Observation Period After Antagonist Administration).

Unmasking underlying cocaine or other stimulant toxicity may explain some of the cardiac dysrhythmias that develop after naloxone-induced opioid reversal in a patient simultaneously using both opioids and stimulants (Chaps. 73 and 75).[58]

Antagonists stimulate the release of hormones from the pituitary, resulting in increased concentrations of luteinizing hormone, follicle-stimulating hormone, and adrenocorticotropic hormone and stimulate the release of prolactin in women.[69]

Observation Period After Antagonist Administration

What constitutes an appropriate observation period after antagonist administration depends on many factors. After IV bolus naloxone at doses less than 2 mg, observation for 2 hours is typically adequate to determine whether sedation and respiratory depression will return as the naloxone effect diminishes and the initial opioid effects return. Therefore, although the matched pharmacokinetics of heroin and naloxone suggest potential utility for this practice, the high frequency of methadone, extended-release prescription opioids, transdermal fentanyl, and novel opioids such as the fentanyl derivatives in many communities raises concern for this practice.[49] That is, the pharmacokinetic mismatch between naloxone and these other opioids would expectedly result in recurrent opioid toxicity from long acting and extended release opioids.[88]

Although no fatalities were identified in death certificate searches after the rapid prehospital release of patients who were administered naloxone after presumably overdosing with heroin, these studies are limited by the use of heroin primarily, and not methadone, the potential for incomplete follow-up, the low death rate following heroin overdose and the minimization of the nonfatal consequences of resedation.[16,88,95] In clinical practice, it is common for patients with opioid overdose to receive repetitive doses of naloxone, raising questions about the safety of releasing patients before transport.[16,95] Additionally, the benefit of the observation period in the emergency department permits harm reduction education, recognition of suicidal ideation, evaluation and referral for long-term addiction treatment, and initiation of preventive intervention (Chap. 36 and Special Considerations: SC6).

Similarly, patients discontinued from a continuous naloxone infusion or those who received large total initial doses of naloxone by any route, including intranasal, typically necessitate subsequent observation for at least 4 hours, and perhaps 6 hours, to ensure that respiratory depression or sedation does not recur. Observation should be meticulous and include periodic direct assessment of arousability and ventilatory rate and effort, as well as continuous pulse oximetry off supplemental oxygen. Optimally, continuous capnometry should be used.

Management of Iatrogenic Withdrawal

Excessive administration of an opioid antagonist to an opioid-dependent patient will predictably result in opioid withdrawal. When induced by naloxone, all that is generally required is protecting the patient from harm and reassuring the patient that the effects will be short lived. Supportive care is valuable during the transient withdrawal. After inadvertent administration of naltrexone, the expected duration of the withdrawal syndrome generally mandates the use of pharmacologic intervention.[31,53] Overcoming the opioid receptor antagonism is difficult, but if used in titrated doses, fentanyl or morphine is often successful. Fentanyl has the advantage over morphine of causing less histamine release. Although the use of buprenorphine was only indirectly studied in this role,[83] it has several potential advantages, including high receptor affinity, long duration of action, low risk of oversedation and the possibility of converting to long term buprenophine treatment. If only moderate withdrawal is present, the administration of metoclopramide, clonidine, or a benzodiazepine is usually adequate.[46]

PREGNANCY AND LACTATION

Naloxone and naltrexone are pregnancy Category C medications. A risk-to-benefit analysis must be performed for pregnant women, particularly those who are opioid tolerant, and their newborns. Inducing opioid withdrawal in the mother probably will induce withdrawal in the fetus and should be avoided. Similarly, administering naloxone (or naltrexone) to newborns of opioid-tolerant mothers may induce neonatal withdrawal and should be used cautiously (Chaps. 30, 31, and 36).[60]

DOSING AND ADMINISTRATION

Before administration of naloxone, the patient should receive adequate ventilation to ensure that the patient is not hypercapnic (see Adverse Effects and Safety Issues). The initial dose of antagonist is dependent on the dose of agonist, the amount that reaches the brain, and the relative binding affinity of the agonist and antagonist at the opioid receptors. The presently available antagonists have a greater affinity for the mu receptor than for the kappa or delta receptors. Some opioids, such as buprenorphine, require greater than expected doses of antagonist to reverse the effects at the mu receptor and exhibit a bell-shaped response to naloxone (see later).[83,96] The duration of action of the antagonist depends on many drug and patient variables, such as the dose and the clearance of both antagonist and agonist.[63]

A dose of naloxone 0.4 mg IV will reverse the respiratory depressant effects of most opioids and is an appropriate starting dose in non–opioid-dependent patients. However, this dose in an opioid-dependent patient usually produces withdrawal, which should be avoided if possible. The goal is to produce a spontaneously and adequately ventilating patient without precipitating significant or abrupt opioid withdrawal. Therefore, 0.04 mg IV is a reasonable starting dose in most patients, with incremental increases by 0.04 mg, while supporting the patient's ventilation and oxygenation, up to a dose of 0.12 mg. The readily available 0.4 mg/mL formulation of parenteral naloxone can be diluted with 9 mL of 0.9% sodium chloride for a total volume of 10 mL, yielding a concentration of 0.04 mg/mL. In those without response, increasing by 0.2 or 0.4 mg up to a dose of 2 mg is a reasonable approach.[9] Dosing beyond 2 mg for those who have an opioid toxidrome is often suggested by 2 mg additional doses, even up to 10 mg,[9] but this is not prospectively validated and rarely required. In situations in which an ultrapotent opioid, often a fentanyl derivative, has been administered, there are reports of response after very large naloxone doses of 10 mg. Whether this is due to the relatively large dose or unique receptor kinetics of these opioids is unknown, but this practice seems reasonable. Failure of the patient to respond to 8 to 10 mg of naloxone suggests that a conventional opioid is not responsible for the respiratory depression and sedation, an additional respiratory depressant is present, or the patient has hypoxic encephalopathy. In this latter situation, pupillary dilation may help in the assessment.

The dose in children without opioid dependence is essentially the same as for adults (ie, 0.1 mg/kg to the adult dose of 2 mg). However, for those with opioid dependence and the possibility of precipitated withdrawal or recrudescence of severe underlying pain, a more gentle reversal with 0.04 mg, with concomitant supportive care, is warranted. Although both the adult and pediatric doses recommended here are lower than those conventionally suggested in other references, the availability of safe and effective interim ventilatory therapy permits these lower doses and lowers the acceptable risk of precipitating withdrawal (Chaps. 4 and 36).

When 1 mg of naloxone is administered IV, it prevents the action of 25 mg of IV heroin for 1 hour; 50 mg of oral naltrexone antagonizes this dose of heroin for 24 hours, 100 mg of oral naltrexone has a blocking effect for 48 hours, and 150 mg of oral naltrexone is effective for 72 hours.[54]

The use of low doses of IV naloxone to reverse opioid overdose prolongs the time to improvement of ventilation, and during this period, assisted ventilation is appropriate. The same limitation exists with SC naloxone administration, and the absorbed dose is more difficult to titrate than when administered IV.[91] Naloxone is also administered intranasally, although this route results in the delivery of unpredictable doses. In the prehospital setting, the time to onset of clinical effect of intranasal naloxone is comparable to that of IV or IM naloxone, largely because of the delay in obtaining IV access and slow absorption, respectively.[6,41] Intranasal naloxone is not recommended as first-line treatment by health care providers in hospitals but is reasonable for prehospital providers when other routes of administration are unavailable or undesirable.[45] Nebulized naloxone (2 mg is mixed with 3 mL of 0.9% sodium chloride solution) has similar limitations in dose accuracy and is further limited in patients with severe ventilatory depression, the group most in need of naloxone. Although reports suggest successful use of nebulized naloxone, patients with opioid overdose are not optimal candidates for inhalation therapy because of both the poor respiratory effort and to the likelihood of over- or underdosing of naloxone.[92] Although needleless delivery is a clear prehospital advantage,[56] the lack of the ability to titrate substantially reduces the usefulness of intranasal or nebulized naloxone in the hospital.

Evaluation for the redevelopment of respiratory depression after naloxone administration requires nearly continuous monitoring. This is significantly more likely to occur after an extended-release or long-acting opioid and is increasingly a concern with the unique fentanyl derivatives that currently appear as adulterants in the illicit opioid supply.[78] Resedation should be treated with either repeated dosing of the antagonist or, in some cases, such as after a long-acting opioid agonist, with another bolus followed by a continuous infusion of naloxone.[78] Two-thirds of the total bolus dose of naloxone that resulted in reversal, when given hourly, usually maintains the desired effect.[36] Titration upward or downward is easily accomplished as necessary to both maintain adequate ventilation and avoid withdrawal. A continuous infusion of naloxone is not a substitute for continued vigilance. A period of 12 to 24 hours often is chosen for observation based on the presumed opioid, the route of administration, and the dosage form (sustained release). Body packers are a unique subset of patients who, because of the reservoir of drug in the GI tract, require individualized antagonist management strategies (Special Considerations: SC5).

Use of longer acting opioid antagonists, such as naltrexone, places the patient at substantial risk for protracted withdrawal syndromes. The use of a long-acting opioid antagonist in acute care situations should be reserved for carefully considered special indications, such as unintentional exposures to short acting opioids in nondependent patients, together with extended periods of observation or careful follow-up. An oral dose of 150 mg of naltrexone generally lasts 48 to 72 hours and should be adequate as an antidote for the majority of patients with opioid toxicity.[51] As noted, this drug should not

be administered to a patient with opioid dependence. Discharge of patients with opioid toxicity after successful administration of a long-acting opioid antagonist, although theoretically attractive, is not well studied. There are concerns about attempts by patients to overcome the opioid antagonism by administering high doses of opioid agonist,[39] with subsequent respiratory depression as the effect of the antagonist wanes.

Naltrexone is administered orally in a variety of dosage schedules for treatment of opioid dependence. A common dosing regimen is 50 mg/day Monday through Friday and 100 mg on Saturdays. Alternatively, 100 mg every other day or 150 mg every third day can be administered. The IM extended-release suspension is injected monthly at a recommended dose of 380 mg.

Methylnaltrexone SC dosing for opioid-induced constipation is weight based.[98] The dose is 0.15 mg/kg for patients who weigh less than 38 kg and more than 114 kg. For patients who weigh between 38 and less than 62 kg, 8 mg is administered, and for those between 62 and 114 kg, 12 mg is provided. Dosing for patients with stage 4 or 5 chronic kidney disease is established at half the standard recommended dose.

Naloxegol tablets should be swallowed whole and not be crushed or chewed. The daily dose is 25 mg once in the morning at least 1 hour before or 2 hours after a meal, and the dose halved in patients who develop signs and symptoms of opioid withdrawal with the higher dose. The starting dosage for patients with a stage 4 or 5 kidney disease is 12.5 mg once daily.

Alvimopan is approved by the US Food and Drug Administration for the management of postoperative ileus in the hospital setting and is not indicated for outpatient or long-term use. It is contraindicated in patients who have taken opioids for more than 7 days. The dose is 12 mg orally 0.5 to 5 hours preoperatively. The day after surgery, the maintenance dose is 12 mg twice a day. The total maximum number of doses is 15 during hospitalization.

Buprenorphine

Naloxone reverses the respiratory depressant effects of buprenorphine in a unique dose–response curve.[23,70,85,96] Bolus doses of naloxone of 2 to 3 mg followed by a continuous infusion of 4 mg/h in adults were able to fully reverse the respiratory depression associated with IV buprenorphine administered in a total dose of 0.2 and 0.4 mg over 1 hour.[85] Reversal was not apparent until about 45 to 60 minutes after the infusion. A reappearance of respiratory depression occurred when the naloxone infusion was stopped because the distribution of naloxone out of the brain and its subsequent elimination from the body are much faster than those of buprenorphine. Consistent with the unique response curve, doses of naloxone greater than 4 mg/h actually led to the redevelopment of respiratory depression. It is postulated that buprenorphine has differential effects on the mu opioid receptor subtypes (Chap. 36), with agonist activity at low doses and antagonist action at high doses. Therefore, excess naloxone antagonizes the opioid antagonistic effects of high dose buprenorphine and worsens the respiratory depression.

Interestingly, there is support for the use of buprenorphine to manage patients with opioid overdose.[93,100] Perhaps not surprisingly, the antagonistic effects of buprenorphine are not dose related, and the maximal effects occurring at 1 mg IM (which equates to about 0.4 mg sublingually).[77] Given the partial agonist effects of buprenorphine, the resulting withdrawal syndrome is less severe than that after a pure opioid antagonist.[77] This practice requires additional study before recommending its use.

FORMULATION AND ACQUISITION

Naloxone (Narcan) for IV, IM, or SC administration is available in concentrations of 0.4 and 1 mg/mL, with and without parabens in 1- and 2-mL ampoules, vials, and syringes and in 10-mL multidose vials with parabens. Naloxone is frequently diluted in 0.9% sodium chloride solution or 5% dextrose to facilitate continuous IV infusion. Naloxone is stable in 0.9% sodium chloride solution at a variety of concentrations for up to 24 hours. An autoinjector containing 2 mg of naloxone is available. Intranasal formulations vary and include the use of the 1-mg/mL solution with a mucosal atomizer device (MAD) and a 2-mg/0.1 mL (20 mg/mL concentration) and 4-mg/0.1 mL (40 mg/mL concentration) naloxone administration device.

Naltrexone is available as a 50-mg capsule-shaped tablet. It is also available as a 380-mg vial for reconstitution with a carboxymethylcellulose and polysorbate diluent to form an injectable suspension intended for monthly IM administration.[4]

Methylnaltrexone is available as a 12-mg/0.6-mL solution for SC injection.[67]

Naloxegol is available as an oral tablet, in 12.5 mg and 25 mg strengths.

SUMMARY

- Naloxone and naltrexone are pure competitive opioid antagonists at the mu (μ), kappa (κ), and delta (δ) receptors.
- Methylnaltrexone (parenteral) and naloxegol (oral) are peripherally acting opioid antagonists used to counteract opioid induced constipation and do not have CNS effects except in overdose.
- Naloxone is the primary opioid antagonist used to reverse respiratory depression in patients manifesting opioid toxicity.
- A titrated low-dose method of IV administration, starting at 0.04 mg in an adult, limits withdrawal-induced adverse effects, such as vomiting and the potential for aspiration pneumonitis, and a surge in catecholamines with the potential for cardiac dysrhythmias and ARDS.
- Naltrexone is used orally for patients after opioid detoxification to maintain opioid abstinence and as an adjunct to achieve ethanol abstinence. It is used in specific circumstances to prevent recurrent opioid toxicity in nondependent patients with otherwise uncomplicated opioid overdoses.
- Intranasal naloxone is increasingly used by bystanders for the emergency reversal of patients with opioid-induced CNS and respiratory depression.

REFERENCES

1. Adapt Pharma, Inc. Narcan (Naloxone Hydrochloride) Nasal Spray Prescribing Information. 2017:1-17. http://www.narcannasalspray.com/pdf/NARCAN-Prescribing-Information.pdf.
2. Akorn, Inc. Naloxone Hydrochloride Injection, USP. 2017:1-11. https://dailymed.nlm.nih.gov/dailymed/getFile.cfm?setid=747e602c-93f9-4723-a899-4c1c55c35ef8&type=pdf.
3. Albert S, et al. Project Lazarus: community-based overdose prevention in rural North Carolina. *Pain Med.* 2011;12(suppl 2):S77-S85.
4. Alkermes, Inc. Vivitrol (Naltrexone for Extended Release Injectable Suspension). 2015:1-11.
5. Barke KE, Hough LB. Opiates, mast cells and histamine release. *Life Sci.* 1993;53:1391-1399.
6. Barton ED, et al. Efficacy of intranasal naloxone as a needleless alternative for treatment of opioid overdose in the prehospital setting. *J Emerg Med.* 2005;29:265-271.
7. Beletsky L, et al. Prevention of fatal opioid overdose. *JAMA.* 2012;308:1863-1864.
8. Berkowitz BA. The relationship of pharmacokinetics to pharmacological activity: morphine, methadone and naloxone. *Clin Pharmacokinet.* 1976;1:219-230.
9. Boyer EW. Management of opioid analgesic overdose. *N Engl J Med.* 2012;367:146-155.
10. Bracken MB, et al. A randomized, controlled trial of methylprednisolone or naloxone in the treatment of acute spinal-cord injury. Results of the Second National Acute Spinal Cord Injury Study. *N Engl J Med.* 1990;322:1405-1411.
11. Brock C, et al. Opioid-induced bowel dysfunction: pathophysiology and management. *Drugs.* 2012;72:1847-1865.
12. Buajordet I, et al. Adverse events after naloxone treatment of episodes of suspected acute opioid overdose. *Eur J Emerg Med.* 2004;11:19-23.
13. Canidate SS, et al. A systematic review of naltrexone for attenuating alcohol consumption in women with alcohol use disorders. *Alcohol Clin Exp Res.* 2017;41:466-472.
14. Centers for Disease Control and Prevention (CDC). Community-based opioid overdose prevention programs providing naloxone—United States, 2010. *MMWR Morbidity and Mortality Weekly Report.* 2012;61:101-105.
15. Chey WD, et al. Naloxegol for opioid-induced constipation in patients with noncancer pain. *N Engl J Med.* 2014;370:2387-2396.
16. Christenson J, et al. Early discharge of patients with presumed opioid overdose: development of a clinical prediction rule. *Acad Emerg Med.* 2000;7:1110-1118.
17. Clarke SFJ, et al. Naloxone in opioid poisoning: walking the tightrope. *Emerg Med J.* 2005;22:612-616.
18. Connors NJ, Nelson LS. The evolution of recommended naloxone dosing for opioid overdose by medical specialty. *J Med Toxicol.* 2016;12:414-415.
19. Coruh B, et al. Fentanyl-induced chest wall rigidity. *Chest.* 2013;143:1145-1146.

20. Crain SM, Shen KF. Antagonists of excitatory opioid receptor functions enhance morphine's analgesic potency and attenuate opioid tolerance/dependence liability. *Pain.* 2000;84:121-131.
21. Cruciani RA, et al. Ultra-low dose oral naltrexone decreases side effects and potentiates the effect of methadone. *J Pain Symptom Manage.* 2003;25:491-494.
22. da Silva O, et al. Seizure and electroencephalographic changes in the newborn period induced by opiates and corrected by naloxone infusion. *J Perinatol.* 1999;19:120-123.
23. Dahan A. Opioid-induced respiratory effects: new data on buprenorphine. *Palliat Med.* 2006;20(8 suppl):3-8.
24. DeMaria A, et al. Naloxone versus placebo in treatment of septic shock. *Lancet.* 1985;1:1363-1365.
25. Dole VP, et al. Arousal of ethanol-intoxicated comatose patients with naloxone. *Alcohol Clin Exp Res.* 1982;6:275-279.
26. Dowling J, et al. Population pharmacokinetics of intravenous, intramuscular, and intranasal naloxone in human volunteers. *Ther Drug Monit.* 2008;30:490-496.
27. Duberstein JL, Kaufman DM. A clinical study of an epidemic of heroin intoxication and heroin-induced pulmonary edema. *Am J Med.* 1971;51:704-714.
28. Evans JM, et al. Degree and duration of reversal by naloxone of effects of morphine in conscious subjects. *Br Med J.* 1974;2:589-591.
29. Faden AI, et al. Endorphins in experimental spinal injury: therapeutic effect of naloxone. *Ann Neurol.* 1981;10:326-332.
30. Fishman J, et al. Disposition of naloxone-7,8,3H in normal and narcotic-dependent men. *J Pharmacol Exp Ther.* 1973;187:575-580.
31. Fishman M. Precipitated withdrawal during maintenance opioid blockade with extended release naltrexone. *Addiction.* 2008;103:1399-1401.
32. Gan TJ, et al. Opioid-sparing effects of a low-dose infusion of naloxone in patient-administered morphine sulfate. *Anesthesiology.* 1997;87:1075-1081.
33. Gilbert PE, Martin WR. Antagonism of the convulsant effects of heroin, d-propoxyphene, meperidine, normeperidine and thebaine by naloxone in mice. *J Pharmacol Exp Ther.* 1975;192:538-541.
34. Glass PS, et al. Comparison of potency and duration of action of nalmefene and naloxone. *Anesth Analg.* 1994;78:536-541.
35. Golden SA, Sakhrani DL. Unexpected delirium during rapid opioid detoxification (ROD). *J Addict Dis.* 2004;23:65-75.
36. Goldfrank L, et al. A dosing nomogram for continuous infusion intravenous naloxone. *Ann Emerg Med.* 1986;15:566-570.
37. Gonzalez JP, Brogden RN. Naltrexone. A review of its pharmacodynamic and pharmacokinetic properties and therapeutic efficacy in the management of opioid dependence. *Drugs.* 1988;35:192-213.
38. Goodman AJ, et al. Mu opioid receptor antagonists: recent developments. *ChemMedChem.* 2007;2:1552-1570.
39. Hamilton RJ, et al. Complications of ultrarapid opioid detoxification with subcutaneous naltrexone pellets. *Acad Emerg Med.* 2002;9:63-68.
40. Hart ER, McCawley EL. The pharmacology of *N*-allylnormorphine as compared with morphine. *J Pharmacol Exp Ther.* 1944;82:339-348.
41. Hoffman JR, et al. The empiric use of naloxone in patients with altered mental status: a reappraisal. *Ann Emerg Med.* 1991;20:246-252.
42. Kane BE, et al. Molecular recognition of opioid receptor ligands. *Drug Addiction.* 2008:585-608.
43. Kaplan JL, et al. Double-blind, randomized study of nalmefene and naloxone in emergency department patients with suspected narcotic overdose. *Ann Emerg Med.* 1999;34:42-50.
44. Kelly A-M, et al. Randomised trial of intranasal versus intramuscular naloxone in prehospital treatment for suspected opioid overdose. *Med J Aust.* 2005;182:24-27.
45. Kerr D, et al. Intranasal naloxone for the treatment of suspected heroin overdose. *Addiction.* 2008;103:379-386.
46. Kienbaum P, et al. Sympathetic neural activation evoked by mu-receptor blockade in patients addicted to opioids is abolished by intravenous clonidine. *Anesthesiology.* 2002;96:346-351.
47. Kienbaum P, et al. Profound increase in epinephrine concentration in plasma and cardiovascular stimulation after mu-opioid receptor blockade in opioid-addicted patients during barbiturate-induced anesthesia for acute detoxification. *Anesthesiology.* 1998;88:1154-1161.
48. Kogan MJ, et al. Estimation of the systemic availability and other pharmacokinetic parameters of naltrexone in man after acute and chronic oral administration. *Res Commun Chem Pathol Pharmacol.* 1977;18:29-34.
49. Kolinsky D, et al. Is a prehospital treat and release protocol for opioid overdose safe? *J Emerg Med.* 2017;52:52-58.
50. Lee JD, et al. Extended-release naltrexone to prevent opioid relapse in criminal justice offenders. *N Engl J Med.* 2016;374:1232-1242.
51. Lee MC, et al. Duration of occupancy of opiate receptors by naltrexone. *J Nucl Med.* 1988;29:1207-1211.
52. Lin S-K. Pharmacological means of reducing human drug dependence: a selective and narrative review of the clinical literature. *Br J Clin Pharmacol.* 2014;77:242-252.
53. Lubman D, et al. Emergency management of inadvertent accelerated opiate withdrawal in dependent opiate users. *Drug Alcohol Rev.* 2003;22:433-436.
54. Mallinckrodt, Inc. Naltrexone Hydrochloride Prescribing Information. 2015:1-17. http://www2.mallinckrodt.com/WorkArea/DownloadAsset.aspx?id=1943.
55. Martins HS, et al. Effects of terlipressin and naloxone compared with epinephrine in a rat model of asphyxia-induced cardiac arrest. *Clinics (Sao Paulo).* 2013;68:1146-1151.
56. McDermott C, Collins NC. Prehospital medication administration: a randomised study comparing intranasal and intravenous routes. *Emerg Med Int.* 2012;2012:1-6.
57. Melichar JK, et al. Naloxone displacement at opioid receptor sites measured in vivo in the human brain. *Eur J Pharmacol.* 2003;459:217-219.
58. Merigian KS. Cocaine-induced ventricular arrhythmias and rapid atrial fibrillation temporally related to naloxone administration. *Am J Emerg Med.* 1993;11:96-97.
59. Mills CA, et al. Cardiovascular effects of fentanyl reversal by naloxone at varying arterial carbon dioxide tensions in dogs. *Anesth Analg.* 1988;67:730-736.
60. Moe-Byrne T, et al. Naloxone for opiate-exposed newborn infants. *Cochrane Database Syst Rev.* 2012;2:CD003483.
61. Murphy JD, et al. Analgesic efficacy of intravenous naloxone for the treatment of postoperative pruritus: a meta-analysis. *J Opioid Manag.* 2011;7:321-327.
62. Mycyk M. Nebulized naloxone gently and effectively reverses methadone intoxication. *J Emerg Med.* 2003;24:185-187.
63. Olofsen E, et al. Naloxone reversal of morphine- and morphine-6-glucuronide-induced respiratory depression in healthy volunteers: a mechanism-based pharmacokinetic-pharmacodynamic modeling study. *Anesthesiology.* 2010;112:1417-1427.
64. Partownavid P, et al. Involvement of opioid receptors in the lipid rescue of bupivacaine-induced cardiotoxicity. *Anesth Analg.* 2015;121:340-347.
65. Pasternak GW. Multiple opiate receptors: déjà vu all over again. *Neuropharmacology.* 2004;47(suppl 1):312-323.
66. Phan NQ, et al. Antipruritic treatment with systemic μ-opioid receptor antagonists: a review. *J Am Acad Dermatol.* 2010;63:680-688.
67. Prough DS, et al. Acute pulmonary edema in healthy teenagers following conservative doses of intravenous naloxone. *Anesthesiology.* 1984;60:485-486.
68. Rösner S, et al. Opioid antagonists for alcohol dependence. *Cochrane Database Syst Rev.* 2010:CD001867.
69. Russell JA, et al. Reduced hypothalamo-pituitary-adrenal axis stress responses in late pregnancy: central opioid inhibition and noradrenergic mechanisms. *Ann NY Acad Sci.* 2008;1148:428-438.
70. Sarton E, et al. Naloxone reversal of opioid-induced respiratory depression with special emphasis on the partial agonist/antagonist buprenorphine. *Adv Exp Med Bio.* 2008;605:486-491.
71. Saybolt MD, et al. Naloxone in cardiac arrest with suspected opioid overdoses. *Resuscitation.* 2010;81:42-46.
72. Schwartz JA, Koenigsberg MD. Naloxone-induced pulmonary edema. *Ann Emerg Med.* 1987;16:1294-1296.
73. Seger DL. Clonidine toxicity revisited. *J Toxicol Clin Toxicol.* 2002;40:145-155.
74. Sigmon SC, et al. Opioid detoxification and naltrexone induction strategies: recommendations for clinical practice. *Am J Drug Alcohol Abuse.* 2012;38:187-199.
75. Sirohi S, et al. Mu-opioid receptor up-regulation and functional supersensitivity are independent of antagonist efficacy. *J Pharmacol Exp Ther.* 2007;323:701-707.
76. Smith K, et al. Low absolute bioavailability of oral naloxone in healthy subjects. *Int J Clin Pharmacol Ther.* 2012;50:360-367.
77. Strain EC, et al. Buprenorphine effects in methadone-maintained volunteers: effects at two hours after methadone. *J Pharmacol Exp Ther.* 1995;272:628-638.
78. Sutter ME, et al. Fatal fentanyl: one pill can kill. *Acad Emerg Med.* 2017;24:106-113.
79. Thanacoody HKR. Chronic valproic acid intoxication: reversal by naloxone. *Emerg Med J.* 2007;24:677-678.
80. Thomas J, et al. Methylnaltrexone for opioid-induced constipation in advanced illness. *N Engl J Med.* 2008;358:2332-2343.
81. Thorsell A. The μ-opioid receptor and treatment response to naltrexone. *Alcohol Alcohol.* 2013;48:402-408.
82. Unna K. Antagonistic effect of *N*-allyl-normorphine upon morphine. *J Pharmacol Exp Ther.* 1943;79:28-31.
83. Urban V, Sullivan R. Buprenorphine rescue from naltrexone-induced opioid withdrawal during relatively rapid detoxification from high-dose methadone: a novel approach. *Psychiatry (Edgmont).* 2008;5:56-58.
84. van den Berg MH, et al. Endogenous opioid peptides and blood pressure regulation during controlled, stepwise hemorrhagic hypotension. *Circ Shock.* 1991;35:102-108.
85. van Dorp E, et al. Naloxone reversal of buprenorphine-induced respiratory depression. *Anesthesiology.* 2006;105:51-57.
86. Varon J, Duncan SR. Naloxone reversal of hypotension due to captopril overdose. *Ann Emerg Med.* 1991;20:1125-1127.
87. Verebey K, et al. Naltrexone: disposition, metabolism, and effects after acute and chronic dosing. *Clin Pharmacol Ther.* 1976;20:315-328.
88. Vilke GM, et al. Assessment for deaths in out-of-hospital heroin overdose patients treated with naloxone who refuse transport. *Acad Emerg Med.* 2003;10:893-896.
89. Wall ME, et al. Metabolism and disposition of naltrexone in man after oral and intravenous administration. *Drug Metabolism and Disposition.* 1981;9:369-375.
90. Walley AY. Opioid overdose prevention and naloxone rescue kits: what we know and what we don't know. *Addict Sci Clin Pract.* 2017;12:4.

91. Wanger K, et al. Intravenous vs subcutaneous naloxone for out-of-hospital management of presumed opioid overdose. *Acad Emerg Med.* 1998;5:293-299.
92. Weber JM, et al. Can nebulized naloxone be used safely and effectively by emergency medical services for suspected opioid overdose? *Prehosp Emerg Care.* 2012;16:289-292.
93. Welsh C, et al. A case of heroin overdose reversed by sublingually administered buprenorphine/naloxone (Suboxone). *Addiction.* 2008;103:1226-1228.
94. Wheeler E, et al. Opioid overdose prevention programs providing naloxone to laypersons—United States, 2014. *MMWR Morbidity and Mortality Weekly Report.* 2015;64:631-635.
95. Willman MW, et al. Do heroin overdose patients require observation after receiving naloxone? *Clin Toxicol (Phila).* 2016;55:308.
96. Yassen A, et al. Mechanism-based pharmacokinetic-pharmacodynamic modelling of the reversal of buprenorphine-induced respiratory depression by naloxone: a study in healthy volunteers. *Clin Pharmacokinet.* 2007;46:965-980.
97. Yealy DM, et al. The safety of prehospital naloxone administration by paramedics. *Ann Emerg Med.* 1990;19:902-905.
98. Yuan CS, et al. Methylnaltrexone for reversal of constipation due to chronic methadone use: a randomized controlled trial. *JAMA.* 2000;283:367-372.
99. Yuan CS. Tolerability, Gut effects, and pharmacokinetics of methylnaltrexone following repeated intravenous administration in humans. *J Clin Pharmacol.* 2005;45:538-546.
100. Zamani N, Hassanian-Moghaddam H. Intravenous buprenorphine: a substitute for naloxone in methadone-overdosed patients? *Ann Emerg Med.* 2017;69:737-739.