Chapter 10

Opioid Analgesics

Pain is one of the most common of human experiences and one of the most common reasons people seek medical care. Nevertheless, as a sensory phenomenon, pain is very difficult to measure because it is such a subjective and personal experience. The International Association for the Study of Pain (IASP) defines pain as a “highly unpleasant sensory and emotional experience associated with actual or potential tissue damage” (Stone and Molliver, 2009, 237).

*Acute,* short-acting pain is biologically useful because it provides a warning system against real or potential damage to the body, and it resolves once the injury heals.

*Chronic* pain, generally defined as pain lasting more than 3 months and not caused by cancer, is typically not useful, causes suffering, restricts activities of daily living, and increases the costs of health care and disability. Common noncancerous or non-terminal chronic pain conditions include migraine, back pain, arthritis, neuropathic pain (defined as pain produced by damage to the nervous system, such as that which occurs in diabetes), AIDS, postherpetic neuralgia, multiple sclerosis, and fibromyalgia, among other disorders. Chronic nonmalignant pain is perhaps the single most common complaint brought by patients to physician offices. Chronic pain complaints are commonly treated with nonopioid analgesics, either alone or with nonprescription modalities, such as exercise, weight loss, physical therapy, psychological interventions, and so forth. Pain due to cancer and other terminal conditions, however, should be aggressively treated. A patient suffering the chronic pain of terminal illness should not be denied opioids, despite the inevitable development of tolerance and dependence as well as a potential for hastening the end of life.

**OPIOID MISUSE AND ABUSE**

In any given year, about 100 million people in the United States suffer from pain, with about 12 million reporting chronic pain (Califf et al., 2016). Over the past decade, physicians and patients alike have presumed that “no pain” should be the goal of therapy of chronic nonmalignant pain (Lee, 2016). Recently, it has been recognized that this “zero pain” goal has led to thousands of overdose deaths and millions of addicted persons (Ray et al., 2016). The prescribing of opioid pain relievers
has quadrupled since 1999, which is in parallel with the surge in opioid fatalities. The number of annual prescriptions written for chronic pain in the United States roughly equals the number of persons in our population. The number of drug overdose deaths in the United States has more than doubled since 1999—from 6.1 to 16 per 100,000 population. In the 6-year period between 2009 and 2015, admissions to intensive care units (ICU) for opioid overdoses increased by 46 percent, and opioid deaths saw an 86 percent increase (Stevens et al., 2016). Specifically, dramatic increases in opioid deaths have occurred from heroin and synthetic opioids such as fentanyl (both discussed later in this chapter), according to new data from the Centers for Disease Control and Prevention (CDC) (Figure 10.1). In 2015, the most recent data year available, people aged 45 to 54 had the highest rate of overdose death (30 per 100,000), but the greatest percentage increase occurred in those aged 55 to 64, with an annual increase of 11 percent, partly because persons often underestimate their risk for overdoses and death (Wilder et al., 2016). Brady and colleagues (2016) review the extent of the opioid epidemic, including the evaluation, treatment, and prevention of prescription opioid abuse and dependence.

In response to this epidemic, the U.S. Food and Drug Administration (FDA) in 2016 released sweeping changes to opioid prescribing policies (Califf et al., 2016), and Congress passed the Comprehensive Addiction and Recovery Act of 2016, with provisions addressing the total range of care from primary prevention to recovery support. The act includes important changes to increase access to addiction treatment and medications that reverse overdoses. It also includes provisions dealing with criminal justice and law enforcement. In March 2016, the CDC released its Guideline for Prescribing Opioids for Chronic Pain, which provides policies for a safer, more effective treatment regimen (Frieden and Houry, 2016). In spite of these efforts, the CDC reported that 64,000 people died from overdose deaths in 2016, the majority from opiate drugs.
Consequently, on October 26, 2017, the president directed the acting Secretary of Health and Human Services, Eric Hargan, to declare the opiate epidemic to be a public health emergency, as defined under the Public Health Services Act. This designation means that federal agencies can provide more grant money to address the epidemic. The order lasts 90 days and can be renewed indefinitely as long as it is considered necessary. The administration will need to work with Congress to find money for the Public Health Emergency fund.

**OPIOID TERMINOLOGY**

An opioid is any exogenous drug (natural, semisynthetic, or synthetic) that binds to an opiate receptor, produces analgesia, and is blocked by an opiate antagonist. An opioid drug may sometimes be referred to as a narcotic, a word derived from the Greek word *narke*, meaning “numbness,” “sleep,” or “stupor.” Originally referring to any drug that induced sleep, the term later also became associated with opioids such as morphine and heroin. Narcotic is an inaccurate term, however, because it is sometimes used in a legal context to refer to a wide variety of abused substances that includes nonopioids such as cocaine and marijuana. The term is not useful in a pharmacological context and its use in referring to opioids is discouraged.

Opioid drugs can be categorized in different ways. Four naturally occurring alkaloids (plant-derived amines) can be isolated from the poppy plant: *morphine*, *codeine*, *papaverine*, and *thebaine* (Pathan and Williams, 2012). Chemical modification of these opiate alkaloids produced many semisynthetic opiates; totally synthetic (man-made) opiates then followed.

In regard to their action at opiate receptors, opioids can also be classified as agonists, partial agonists, mixed agonists-antagonists, or antagonists:

- **Full agonists.** All clinically used opioids produce their effects at least partly by attaching to and activating the receptors upon which our own endogenous opioids bind. Morphine is the prototype opioid full agonist, but there are many others, as shown in Table 10.1.

- **Partial agonists.** A partial agonist is a drug that binds to opioid receptors, but has a lower intrinsic activity (lower efficacy) than a full agonist. Therefore, a partial agonist exerts an analgesic effect, but the effect has a ceiling at less than the maximal effect produced by morphine. (Here, a ceiling effect is defined as a phenomenon in which a drug action reaches a maximum, such that increasing the drug dosage does not increase its effectiveness.)

- **Buprenorphine** is the prototype partial opioid agonist. When administered to a person who is not opioid dependent, it produces analgesia. When administered to an opioid-dependent person, however, buprenorphine may compete with a full agonist, preventing its full effect, and withdrawal may be precipitated. Buprenorphine has become very important in opioid dependence treatment programs, which is discussed later in this chapter.

- **Mixed agonist-antagonists.** A mixed agonist-antagonist drug produces an agonistic effect at one opioid receptor and an antagonistic effect at another. Like a partial
TABLE 10.1 Classification of Commonly Used Opiate Analgesic Agonist and Antagonist Medications

<table>
<thead>
<tr>
<th>Opioid (Trade Name)</th>
<th>Origin</th>
<th>Chemical Class</th>
<th>Opioid Receptor Mechanism(s)</th>
<th>Nonopioid Mechanisms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>Natural</td>
<td>Morphinan</td>
<td>Full Agonist $\mu$</td>
<td></td>
</tr>
<tr>
<td>Codeine</td>
<td>Natural</td>
<td>Morphinan</td>
<td>Full Agonist $\mu$</td>
<td></td>
</tr>
<tr>
<td><strong>Levorphanol</strong> (Levo Dromoran)</td>
<td>Synthetic</td>
<td>Morphinan</td>
<td>Full Agonist $\mu$, $\kappa$</td>
<td>NE Reuptake block; NMDA receptor antagonist</td>
</tr>
<tr>
<td><strong>Oxycodone</strong> (Oxycontin)</td>
<td>Semisynthetic</td>
<td>Morphinan</td>
<td>Full Agonist $\mu$</td>
<td></td>
</tr>
<tr>
<td><strong>Hydrocodone</strong> (Vicodin)</td>
<td>Semisynthetic</td>
<td>Morphinan</td>
<td>Full Agonist $\mu$</td>
<td></td>
</tr>
<tr>
<td><strong>Hydromorphone</strong> (Dilaudid)</td>
<td>Semisynthetic</td>
<td>Morphinan</td>
<td>Full Agonist $\mu$</td>
<td></td>
</tr>
<tr>
<td><strong>Oxymorphone</strong> (Opana)</td>
<td>Semisynthetic</td>
<td>Morphinan</td>
<td>Full Agonist $\mu$</td>
<td></td>
</tr>
<tr>
<td><strong>Fentanyl</strong> (Abstral, Actiq, et al.)</td>
<td>Synthetic</td>
<td>Phenylpiperidine</td>
<td>Full Agonist $\mu$</td>
<td></td>
</tr>
<tr>
<td><strong>Meperidine</strong> (Demerol)</td>
<td>Semisynthetic</td>
<td>Phenylpiperidine</td>
<td>Full Agonist $\mu$</td>
<td></td>
</tr>
<tr>
<td><strong>Methadone</strong> (Dolophine)</td>
<td>Synthetic</td>
<td>Diphenylheptane</td>
<td>Full Agonist $\mu$</td>
<td>NE Reuptake block; NMDA receptor antagonist</td>
</tr>
<tr>
<td><strong>Buprenorphine</strong> (Subutex)</td>
<td>Semisynthetic</td>
<td>Morphinan</td>
<td>Partial Agonist $\mu$</td>
<td></td>
</tr>
<tr>
<td><strong>Tapentadol</strong> (Nucynta)</td>
<td>Synthetic</td>
<td></td>
<td>Agonist $\mu$</td>
<td>NE Reuptake block</td>
</tr>
<tr>
<td><strong>Tramadol</strong> (Ultram)</td>
<td>Semisynthetic</td>
<td></td>
<td>Agonist $\mu$</td>
<td>NE Reuptake block; 5-HT Release</td>
</tr>
<tr>
<td><strong>Butorphanol</strong> (Stadol)</td>
<td>Synthetic</td>
<td>Morphinan</td>
<td>Mixed Ag $\kappa$/Antag $\mu$</td>
<td></td>
</tr>
<tr>
<td><strong>Pentazocine</strong> (Talwin)</td>
<td>Synthetic</td>
<td>Benzomorphan</td>
<td>Mixed Ag $\kappa$/Antag $\mu$</td>
<td></td>
</tr>
<tr>
<td><strong>Naloxone</strong> (Narcan)</td>
<td>Semisynthetic</td>
<td></td>
<td>Antagonist $\mu$</td>
<td></td>
</tr>
<tr>
<td><strong>Naltrexone</strong> (ReVia; Vivitrol)</td>
<td>Semisynthetic</td>
<td></td>
<td>Antagonist $\mu$</td>
<td></td>
</tr>
<tr>
<td><strong>Nalmefene</strong> (Revel)</td>
<td>Semisynthetic</td>
<td></td>
<td>Partial Ag $\kappa$/Antag $\mu$</td>
<td></td>
</tr>
</tbody>
</table>
agonist, a mixed agonist-antagonist usually displays a ceiling effect for analgesia; in other words, it has decreased efficacy compared to a full agonist, such as morphine, and usually is not as effective in treating severe pain. Also, when a mixed agonist-antagonist is administered to an opioid-dependent person, the antagonistic effect precipitates an acute withdrawal syndrome. *Pentazocine* (Talwin) is the prototype mixed agonist-antagonist. Today, mixed agonist-antagonist opioids are infrequently used clinically.

- **Antagonists.** Antagonists have affinity for an opioid receptor, but, after attaching, they elicit no change in cellular functioning (for example, they lack intrinsic activity). Antagonists compete with the agonist for the receptor, precipitating withdrawal in an opioid-dependent person and reversing any analgesia caused by the agonist. An example of this is the clinical use of the opioid antagonist *naltrexone* in treatment programs for heroin addicts, where heroin taken after naltrexone elicits no analgesic or euphoric effects. Naloxone is another example of an antagonist. Recently, the FDA approved a nasal spray containing naloxone as an easy-to-use product to treat opioid overdose (Krieter et al., 2016; Strang et al., 2016).

Finally, opiates can be classified according to the type of receptor through which they exert their effects. Some of the most commonly used opiate drugs discussed in this chapter are shown in Table 10.1.

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**HISTORY**

Opium, from which morphine is extracted, is an ancient drug, and there is evidence that the opium poppy, *Papaver somniferum*, was cultivated 10,000 years ago, although definite use as an analgesic is dated to about 3500 to 3000 years ago. Obtained from the sap of the seedpod of the poppy (Figure 10.2), opium has been used for thousands of years to produce euphoria, analgesia, sleep, and relief from diarrhea and cough. The English word *opium* is derived from the Greek word *opion*, which means

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1For thousands of years, the only way to obtain morphine has been by harvesting the milky exudate of the opium poppy. But soon not only drug companies, but drug traffickers as well, can synthesize it because of the development of genetically modified yeast (McNeil, 2015). In the last 8 years, the various steps in the process have been achieved. In 2015, the last biochemical procedure was made public, detailing an efficient method by which the morphine precursor, (S)-reticuline, could be grown in brewer’s yeast, *Saccharomyces cerevisiae*. Actually, the researchers were not trying to make morphine, but rather, they were trying to determine if they could make antibiotics or anticancer drugs from the 2500 other alkaloids for which reticuline is a precursor. The question is, who will find this discovery more useful, the pharmaceutical companies or drug cartels? Since the 1960s, India, Turkey and Australia, where licensed farmers can legally grow poppies, have provided an ample and inexpensive amount of opium for drug companies. These growers depend on the sales for their livelihood. Moreover, the drug companies are already able to synthesize many other opiates more powerful than morphine. In contrast, drug cartels would benefit immensely if they could brew their product near their customers and not risk the cost of illegal production and distribution. Scientists have suggested several possible steps that can be taken to prevent misuse of the technology so as to mitigate this concern.
“poppy juice” (Doweiko, 2012, 137). In ancient times, opium was used primarily for its constipating effect and later for its sleep-inducing properties (noted by writers such as Homer, Hippocrates, Dioscorides, Virgil, and Ovid). Although it was used recreationally, not much is known about this aspect before the eighteenth century (Doweiko, 2012). During the Middle Ages, opium was used for practically every known disease and its beneficial effects earned it the name “stone of immortality.” Opium, too, was often combined with alcohol, a mixture that the sixteenth-century Swiss physician Paracelsus called *laudanum*, meaning “something to be praised.”

Morphine, isolated from opium by the chemist Friedrich Sertürner in 1806, is considered the model opioid analgesic against which all others are compared. Its chemical formula was determined in 1847 and, after the invention of the hypodermic needle in 1853, its use in medicine increased, especially in the battlefield and military hospitals, where it was used liberally—and that often resulted in morphine addiction. (During and after the American Civil War, morphine addiction was referred to as “the soldier’s disease.”)

During the second half of the nineteenth century, both clinical and recreational use of morphine and opium saw further expansion. Being unregulated, morphine could easily be added to patent medicines and elixirs as an unidentified ingredient, which resulted in addiction among the civilian population. Opium smoking,
however, a practice introduced by Chinese immigrant workers in the United States, was more obviously recreational than therapeutic. By the year 1900, more than 4 percent of the entire U.S. population was addicted to opium or another opiate (Doweiko, 2012). In one survey of 35 Boston drugstores in 1888, 78 percent of the prescriptions that had been refilled three or more times contained opium (Levinthal, 2012).

By the turn of the century, physicians became increasingly aware of the opioid addiction, especially in regard to the overprescription of opioid drugs and the widespread use of opioids in patent medicine. That concern—and the increasingly epidemic-like abuse of opioids in the United States—led to the passage of the Pure Food and Drug Act of 1906, which required that manufacturers list the ingredients of their products on the labels. This allowed people to see that their medicines contained questionable compounds and the unregulated use of opioids began to decline.

The Harrison Narcotic Act of 1914 provided legislation that had more impact on the use of morphine and opium. The new law stated that only licensed physicians and dentists could prescribe opioids (and cocaine). The law also required medical professionals to register with the Internal Revenue Service (IRS) to write such prescriptions. Gradually, this law was interpreted by court decisions to mean that opioids could only be prescribed and taken for a medically approved purpose and not for nonmedical reasons; that is, it ultimately became illegal for opiate addicts to get the drug just to maintain a drug habit.

Since the early twentieth century, periodic cycles of opioid abuse have been followed by efforts to reduce the recreational use of opioids—but without much success. An important part of such efforts has been an ongoing search for drugs that would alleviate pain without the potential for addiction. This search has produced an expanding formulary of natural, semisynthetic, and synthetic opiate analgesics as described in this chapter. So far, however, the goal to separate the analgesic and euphoric–addictive properties of opiates has not been reached. Nevertheless, the ongoing epidemic abuse of prescription opiates, with the epicenter in the United States, is prompting further development of opioid formulations that are pharmacologically designed to prevent recreational misuse (Coplan et al., 2016).

Moreover, there is additional concern about the concomitant use of multiple medications that depress the central nervous system (CNS). On August 31, 2016, the FDA issued a warning about the combined use of opioid and benzodiazepine medications, as well as other drugs that inhibit the CNS. The agency added their strongest alert, the

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<sup>2</sup>The habit of smoking opium was acquired by the Chinese as a result of trade with the West, especially Britain, early in the nineteenth century. The British needed to balance their large purchases of tea from China. They did this by trading opium, grown in India, for tea. The Chinese government saw what the opium trade did to its people and had it outlawed throughout the Chinese Empire. The British, however, did not want to lose this valuable source of income and forced China to accept the opium trade. This led to the First Opium War of 1839–1842 and the Second Opium War of 1856–1860. Britain and its allies won the wars because of British naval superiority. Not only did the trade resume, China ceded the island of Hong Kong to Britain as a treaty port. (Hong Kong was ultimately returned to the People's Republic of China in 1999.)
“Boxed Warnings,” to the labeling of prescription opioid pain and prescription opioid cough medicines as well as benzodiazepines in an effort to reduce the use of these combinations. Subsequently, on September 20, 2017, after additional review, the FDA published a modification of the warning. This revision stated that “the opioid addiction medications buprenorphine and methadone should not be withheld from patients taking benzodiazepines or other drugs that depress the central nervous system” (U.S. Food and Drug Administration, 2017). While the FDA acknowledged that these drug combinations can result in serious adverse reactions, it also recognized that untreated opiate addiction is also a significant risk. Information to this effect will be added to the buprenorphine and methadone drug labels in addition to specific recommendations for reducing the combined use of these drugs.

**PAIN SIGNALING**

Normal pain transmission is triggered when a noxious (harmful or unpleasant) stimulus activates neurons that innervate a structure in the body, such as the skin, a joint, or an internal organ. These neurons are called primary afferent nociceptive sensory neurons (or just primary afferents); their cell bodies are located in ganglia, called dorsal root ganglia (DRG) (Figure 10.3), which are parallel to the spinal cord. Primary afferents send information about noxious stimulation from the body to the spinal cord, specifically to the dorsal horn.

The terminals of the primary afferent neurons synapse onto neurons in the dorsal horn of the spinal cord. Those spinal neurons then send the message up to the thalamus, which in turn projects to (makes contact with) the cortex in the forebrain. Here is where the subjective experience of pain occurs. As the dorsal horn neurons ascend to the cortex (Figure 10.3), their axonal fibers also send out branches that synapse with other neurons in the hindbrain—called the rostral ventral medulla (RVM)—and neurons in the midbrain—called the periaqueductal gray (PAG). In addition, neurons in the cortex and other structures in the brain, such as the limbic structures, send descending fibers (axons) back down to the same midbrain, hindbrain, and spinal centers that transmitted the pain message. In this way, various brain structures can either inhibit or facilitate the experience of pain.

All of these sites may provide a target for analgesic medications. For example, drugs may provide pain relief by reducing the firing of the primary afferent neurons at the periphery; that is, at the site of the injury. This might be accomplished by antagonizing the neurochemical substances that are triggered by pain (the inflammatory reactions), which stimulate the primary afferents. This is essentially how nonsteroidal anti-inflammatory drugs (NSAIDs) such as aspirin work. Alternatively, drugs such as the anticonvulsants gabapentin and pregabalin act to reduce the excitation of the primary afferent axons and thereby decrease the signal that is transmitted to the spinal cord. Other drugs may reduce the transmission of the pain signal from within the spinal cord to the brain. Another approach is to activate the descending pathways from the brain to the spinal cord that inhibit ascending pain signals. Some of these descending pathways release the neurotransmitters serotonin and norepinephrine. The reason why some antidepressants can reduce pain (see Chapter 12) is because they increase the
Finally, by acting on higher brain structures, analgesic drugs also alter the emotional reaction to pain and reduce the suffering it causes, independently of influencing the sensory phenomenon itself. This is what opioids do.
Unfortunately, in spite of an expanding knowledge of the underlying pathology and a growing range of therapeutic options, current treatment of chronic pain remains inadequate. One review found that across all treatments, only about half of the patients responded to therapy and the reduction in pain was only about 30 percent (Turk et al., 2011). Efforts are currently directed toward nonopioid medications as well as non-pharmacological modalities that act in conjunction to alleviate the suffering in chronic pain patients (Volkow and McLellan, 2016).

**OPIOID RECEPTORS**

There is general agreement on the existence of at least three types of opioid receptors, all of them G-protein coupled receptors (GPCRs) (see Chapter 3). They are mu (after morphine), kappa (after the first agent known to act at this receptor, ketocyclazocine), and delta (after vas deferens, the tissue in which it was first isolated) (Pathan and Williams, 2012). In 2000, the nomenclature was changed and the respective receptor types are now also identified as MOP, KOP, and DOP. The genes encoding these three families of opioid receptors, as well as the receptors themselves, have been cloned and sequenced.
Each receptor type—mu, kappa, and delta—arises from its own gene and is expressed through a specific messenger RNA (mRNA). Each receptor is a chain of approximately 400 amino acids, and the amino acid sequences are about 60 percent identical to one another and 40 percent different. Some authorities support the existence of subtypes for the receptors, but this is not universally accepted.

The three classical opioid receptors are distributed widely throughout the central nervous system and, to a lesser extent, in the periphery (including the vas deferens, knee joint, gastrointestinal tract, and other sites). The existence of receptors on which the natural substance opium could exert such significant effects implied that there must be some inherent, endogenous substance or substances within our body that normally acted on these receptors. Presumably the receptors did not evolve just to respond to an extract of the poppy plant! Soon after the opioid receptors were discovered, these endogenous substances were also determined. Each comes from a precursor compound shown in Table 10.2. As indicated in this table, the prohormone proenkephalin is cleaved to form met-enkephalin and leu-enkephalin, which have the greatest affinity for the DOP receptor. Dynorphin A and B are agonists at the KOP receptor and are derived from the prohormone prodynorphin. The parent compound of the endogenous agonist for the MOP receptor, β-endorphin, is pro-opiomelanocortin (POMC). There are two other MOP agonists, endomorphin 1 and 2, but their precursor has not yet been identified.

As seen in Table 10.2, a fourth type of opiate receptor has also been identified, for which an endogenous ligand and a precursor substance has been determined. However, because this receptor, the nociceptin (NOP) receptor, does not respond to the classical opiate antagonist, naloxone, its categorization has been questioned. It is considered to be a nonopioid “branch” of the opioid receptor family (Pathan and Williams, 2012).

What is the consequence of the binding of an opioid agonist to a mu (MOP) receptor? Figure 10.4 summarizes this process. As is generally the case with GPCRs,

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Precursor</th>
<th>Peptide</th>
</tr>
</thead>
<tbody>
<tr>
<td>The mu receptor (MOP)</td>
<td>Proopiomelanocortin (POMC)</td>
<td>β-endorphin</td>
</tr>
<tr>
<td></td>
<td>Unknown</td>
<td>Endomorphin-1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Endomorphin-2</td>
</tr>
<tr>
<td>The kappa receptor (KOP)</td>
<td>Prodynorphin</td>
<td>Dynorphin-A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dynorphin-B</td>
</tr>
<tr>
<td>The delta receptor (DOP)</td>
<td>Proenkephalin</td>
<td>[Met]-enkephalin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>[Leu]-enkephalin</td>
</tr>
<tr>
<td>The nociceptin receptor (NOP)</td>
<td>Prepronociceptin</td>
<td>Nociceptin/orphanin FQ</td>
</tr>
</tbody>
</table>

SOURCE: Pathan and Williams (2012)

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3 The hallucinogenic agent salvinorin A, from the psychedelic mint plant *Salvia divinorum*, is a potent agonist of the kappa opioid receptor (discussed in Chapter 8).
the G-protein consisting of the $\alpha$, $\beta$, and $\gamma$ subunits breaks off from the rest of the receptor—that is, dissociates—and separates into two parts, the $\alpha$ component and the $\beta\gamma$ components. These components interact with other parts of the neuron: they activate potassium channels, inhibit calcium channels, and reduce the amount of the substance cyclicAMP inside the neuron (by inhibiting the enzyme adenylyl cyclase), as indicated in Figure 10.4. These actions hyperpolarize the neuron; that is, the neuron is inhibited. Activating potassium channels will allow more of the positively charged potassium ions to leave the neuron; blocking calcium channels will prevent more of the positively charged calcium ions from entering the neuron. Both of these

![Figure 10.4](image.png)

**FIGURE 10.4** Schematic of the opiate receptor. The opiate receptor is a G-protein coupled receptor (GPCR). When a molecule of an opiate (ligand), such as morphine, attaches to its binding site on the receptor, it activates the G-protein, causing it to dissociate into its $\alpha$ component and the dual $\beta\gamma$ component. The $\alpha$ component inhibits the activity of the enzyme, adenylyl cyclase. The $\beta\gamma$ component does two things. First, it opens a channel in the membrane through which potassium ions ($K^+$) flow out. The movement of positively charged potassium ions *out of the neuron* makes the inside more negative, which means the neuron is inhibited and is less likely to fire. Second, the $\beta\gamma$ component inhibits channels through which positively charged calcium ions flow *into the neuron*. This reduces neurotransmitter release. All of these processes contribute to reduce the transmission of pain.
actions will make the inside of the neuron more negative, relative to the outside. This means the neuron is less likely to fire when stimulated or, if active, it will release less transmitter.

Exogenous and endogenous opiates exert their effects throughout the body, including the periphery (outside of the central nervous system), on neurons in the dorsal horn of the spinal cord, and within various brain sites. In the spinal cord, opioid receptors are located on the presynaptic terminals of the nociceptive primary afferents. When activated by an opioid agonist, the result will be to block the release of pain-producing substances such as glutamate, substance P, and calcitonin gene-related peptide (CGRP). By blocking the release of pain-producing substances, opiates reduce ascending pain signals to higher brain centers.

In the brain, opioid analgesia is believed to be mediated by the activation of mu receptors in the midbrain and hindbrain. High densities of opiate receptors are found in midbrain periaqueductal gray (PAG) neurons, and in hindbrain nuclei located in the rostral ventral medulla (RVM). Opiate agonists indirectly activate the descending inhibitory input from these sites onto the pain processing neurons of the spinal cord. As noted, these pathways release serotonin, norepinephrine, and enkephalin, which further suppress the transmission of pain signals (Figure 10.3).

MAJOR PHARMACOLOGICAL EFFECTS OF OPIATES

Analgesia

Opiates produce analgesia and indifference to pain, reducing the intensity of pain and thus reducing the associated distress by altering the central processing of pain. Analgesia occurs without loss of consciousness and without affecting other sensory modalities. The pain may actually persist as a sensation, but patients feel more comfortable and are able to tolerate it. In other words, the perception of the pain is significantly altered.

Euphoria

Opiates produce a euphoric state, which includes a strong feeling of contentment, well-being, and lack of concern. Regular users of morphine describe the effects of intravenous injection in ecstatic and often sexual terms, but the euphoric effect becomes progressively less intense after repeated use. As with other drugs of abuse, opiates produce their rewarding effects by increasing dopamine release in the limbic reward pathway. It is postulated that opiates act indirectly in the ventral tegmental area by inhibiting GABA neurons via mu opioid receptors. The GABA neurons exert an inhibitory effect on dopamine neurons. Thus, opiates are believed to be rewarding at least partly because they disinhibit dopaminergic neurons and increase dopamine input in the nucleus accumbens and other areas (see Chapter 4).
Depression of Respiration

Opiates cause a profound depression of respiration by decreasing the brain stem respiratory center’s sensitivity to higher levels of carbon dioxide in the blood. Respiratory rate is reduced even at therapeutic doses. At higher doses, the rate slows even further, respiratory volume decreases, breathing patterns become shallow and irregular and, at sufficiently high levels, breathing ceases and death follows (Figure 10.5).

Respiratory depression is the single most important acute side effect of morphine and is the cause of death from acute opioid overdosage. A respiratory rate of eight breaths per minute or less in a patient who is not actually sleeping strongly suggests acute opioid intoxication, particularly if miosis (pinpoint pupils) and/or stupor are also present. Treatment, in adults, consists of 0.4 to 2.0 milligrams of the antagonist naloxone, which can be increased up to a maximum of 10 milligrams. If respiratory depression persists after 10 milligrams of naloxone, it is unlikely that it is due to opioid overdose. Because naloxone is short-acting, reversal of opioid analgesic toxicity might require continuous infusion (Boyer, 2012). As discussed later in this chapter, this is an important consideration in regard to the current opioid epidemic. Until recently, naloxone had to be injected, which was a drawback. However, as mentioned, a nebulized (nasal spray) formulation was approved and marketed in 2016. Of course, naloxone, as an opioid antagonist, precipitates withdrawal symptoms.

Tolerance of respiratory depression appears to develop at a slower rate than analgesic tolerance. Because of this delay, patients with a long history of opioid use are, paradoxically, at increased risk for respiratory depression. Methadone may confer greater risk of overdose toxicity than other opiates because respiratory depression may occur later than the analgesic effect. A patient may believe that an analgesic dose is too low and then take more of the drug before it has time to take effect. Moreover, patients

![Brain structures where morphine acts to produce analgesia, respiratory depression, or euphoria.](image-url)
tolerant to high doses of other opiates may not be tolerant to methadone (Stachnik, 2011). This may be relevant to recent efforts to understand the current dramatic increase in opiate overdose deaths. Reviews have found that overdose deaths are more likely to occur when patients are “rotated” from one opioid to another, when higher dosages are prescribed, or when drug addicts either begin or terminate opiate use. That is, loss of tolerance (after abstinence), overconfidence about dosage, or ignorance of the ingested formulation often kill relapsing opioid addicts (Courtwright, 2015).

Suppression of Cough

Opiates suppress the cough center in the hindbrain and have historically been used as cough suppressants. This is termed an antitussive action. Codeine is particularly popular for this purpose. Today, however, less-addicting drugs are used as cough suppressants and opioids have become inappropriate choices for treating persistent cough.

Sedation and Anxiolysis

Opiates reduce anxiety and produce sedation and drowsiness, but the level of sedation is not so deep as that produced by other CNS depressants. Although people who take morphine will doze, they can usually be awakened readily. During this state, cognitive slowing is prominent, accompanied by a lack of concentration, apathy, complacency, lethargy, and a sense of tranquility. This effect becomes tolerant with repeated use. Nevertheless, this action may be therapeutically useful, as it has been reported that morphine has helped to reduce the development of posttraumatic stress disorder (PTSD) in soldiers who were injured in combat during the Iraq war (Holbrook et al., 2010). That said, concern has been raised about the relatively high use of opiates in returning members of the military (Toblin et al., 2014).

Nausea and Vomiting

Opioids stimulate receptors in an area of the medulla called the chemoreceptor trigger zone. Stimulation of this area produces nausea and vomiting, which are characteristic and unpleasant side effects of morphine and other opioids, but they are not life-threatening. Like drowsiness, this effect becomes tolerant with chronic use.

Gastrointestinal Symptoms

As a result of their direct actions on the intestine, opiates relieve diarrhea, the most important action of opioids outside the central nervous system (CNS). These drugs cause intestinal tone to increase, motility to decrease, feces to dehydrate, and intestinal spasm (and cramping). The combination of decreased propulsion, increased intestinal tone, decreased rate of movement of food, and dehydration hardens the stool and further retards the advance of fecal material. Nothing more effective than opioids has yet been discovered for treating severe diarrhea. Two opioids have been developed that
only very minimally cross the blood–brain barrier into the CNS. One is *diphenoxylate* (the primary active ingredient in Lomotil) and the other is *loperamide* (Imodium). These two drugs are exceedingly effective opioid antidiarrheals. The reason that loperamide (and other substances) cannot get into the systemic circulation or the brain is that P-glycoprotein (P-gp) blocks entry. However, opioid abusers have discovered that when taken in amounts of 10 times or more the therapeutic dose, loperamide can overcome the protective effects of P-gp and reach the brain. Use of huge-dose loperamide to relieve opioid withdrawal systems or to get high is increasing. Unfortunately, loperamide can cause cardiotoxic effects, and several deaths have been reported, possibly from this cause. In June 2016, the FDA issued a “Drug Safety Communication,” warning about high-dose loperamide (Lasoff et al., 2016; Vakkalanka et al., 2016).

Opioid-induced constipation is a common and undesirable adverse consequence of chronic use, estimated to occur in 40 to 90 percent of patients (Peppin, 2012). Moreover, there appears to be little tolerance to this side effect. Treatment generally consists of administering an anticonstipatory agent together with the opiate. Although there are numerous options, in the context of this chapter, the opioid antagonists are most relevant. Naloxone, while not officially approved for this indication, is still commonly used. However, because it crosses the blood–brain barrier, naloxone can also reverse the analgesic effect of opiates and precipitate withdrawal symptoms. Therefore, newer agents have been developed that have a methyl group added to the opioid antagonist naltrexone. This prevents the antagonist from entering the brain and limits the effects to the periphery. *Methylnatrexone* (Relistor) was the first such drug and is intended to restore bowel function in adults with advanced illnesses who are receiving opioids on a continuous basis and suffer from their constipating effects (Siemens and Becker, 2016). Another injectable opiate antagonist, *alvimopan* (Entereg) is intended to restore normal bowel function in hospitalized patients who have undergone bowel surgery. *Naloxegol* (Movantik) is a third peripherally acting opioid antagonist approved by the FDA and indicated for the treatment of opioid-induced constipation in adult patients with chronic noncancer pain.

A nonopioid laxative agent, *lubiprostone* (Amitiza), already approved in 2013 for chronic idiopathic constipation in adults and in adult women with irritable bowel syndrome, was also approved for opioid-induced constipation in chronic pain patients. Although not an opioid antagonist, lubiprostone increases fluid in the gastrointestinal (GI) tract and helps one pass stool (Holder and Rhee, 2016).

**Pupillary Constriction**

Opiates cause pupillary constriction (miosis). Indeed, pupillary constriction in the presence of analgesia is characteristic of opioid ingestion. As noted later in this chapter, one opiate drug that does not elicit this effect is meperidine.

**Endocrine Effects**

Opiates exert subtle but important effects on the functioning of the endocrine system. Effects include reduced libido in men and menstrual irregularities and infertility in women. These actions occur secondary to drug-induced reductions in sex hormone-releasing agents from the hypothalamus. As a result, testosterone levels in males fall, as
do the levels of luteinizing and follicle-stimulating hormones in females. If a person is
taking an opioid for chronic pain, both the reduction in sex hormones and the chronic
pain may result in loss of sexual desire and impaired performance, alterations in gen-
der role, fatigue, mood alterations, loss of muscle mass and strength, abnormal menses,
infertility, and osteoporosis and fractures. However, it is not always clear whether
the opioid-induced hypogonadism or the chronic pain is responsible (Brennan, 2013).
In addition to changes in sex hormones, patients maintained on opiates for many years
may have a variety of hormonal abnormalities (Tennant, 2012).

Other Effects
Opiates can release histamine from its storage sites in mast cells in the blood, which
may elicit localized itching or more severe allergic reactions, including bronchocon-
striction. Opioids also affect white blood cell function, producing complex alterations
in the immune system. It is advisable, perhaps, to avoid the use of morphine in patients
with compromised immune function.

GENETIC OPIOID METABOLIC DEFECTS
With the current dramatic increase in opioid prescription abuse and concern about
the accidental overdose of these medications, the phenomenon of genetic anomalies
in opiate metabolism is receiving increasing attention (Kapur et al., 2014; Tennant,
2010, 2011, 2016; Trescott and Faynboym, 2014; Tverdohleb et al., 2016). The primary
pathways for opioid metabolism involve the cytochrome P450 (CYP) 2D6 and 3A4 iso-
enzymes. These two isoenzymes account for over 90 percent of opiate metabolism;
CYP-3A4 alone accounts for 40 to 60 percent. Although the evidence is somewhat indi-
rect, estimates are that 20 to 30 percent of pain patients have a genetic opioid meta-
bolic defect (GOMD) in one of these enzymes.

In some cases, the enzyme is too active. Such patients are termed “rapid” or
“ultrarapid” metabolizers in whom the opioid is rapidly metabolized and pain returns
much quicker than usual. These patients require a higher than normal dosage of
opiate, which may cause them to be mislabeled as addicts and undertreated. Singa
(2016) recently described a case history of such a patient. In other cases, the metabolic
enzyme is either inactive or absent, which results in slower than normal rates of drug
metabolism, causing the opioid to accumulate in the blood and increasing its toxicity
from drug-induced respiratory depression.

According to Tennant (2010), it is possible that many of the numerous overdose
deaths that have occurred since opioid pain prescriptions became popular in the last
decade were due to this phenomenon. Tennant also discusses simple ways to diagnose
and treat these conditions. One very helpful approach is to use opiates that bypass the
CYP450 system and are metabolized by glucuronidation. These include oxymorphone,
hydromorphone, and tapentadol (Tennant, 2016).

Even without a genetic metabolic defect, interactions between opioids and other
psychotropic drugs are prevalent and can be dangerous as well as fatal. Many of the
metabolic enzymes involved in opiate metabolism are either inhibited or induced by
other medications, especially antidepressants and benzodiazepines, and these effects have important implications for pain prescriptions. Pierce and Brahm (2011) provide a useful discussion of these relationships and some of the most relevant specific interactions.

**TOLERANCE AND DEPENDENCE**

The development of tolerance and dependence with repeated use is a characteristic feature of all opioid drugs. This reflects a progressive failure of the receptors to initiate a signal after long-term opioid binding, a phenomenon termed *receptor desensitization*. The process is thought to involve the uncoupling of the receptors from the G-protein, after which the receptors are taken inside the neuron until they are eventually returned to the membrane and resensitized to opioid binding. It is believed that this cycle limits the degree of tolerance of the mu opioid receptors to their own endogenous opioid ligands. Endogenous opiates are released intermittently and they are metabolized very quickly after being released. As a result, binding of endogenous opiates is short lived. In contrast, when opioid analgesics are administered for long periods of time, they facilitate tolerance because they are constantly attached to the receptors and interfere with receptor recycling and resensitization (Boyer, 2012).

In other words, when morphine or other opioids are used only intermittently, little if any tolerance develops and the opioids retain their initial efficacy. When administration is repeated, tolerance becomes so marked that massive doses have to be administered to either maintain a degree of euphoria or prevent withdrawal discomfort. The degree of tolerance is illustrated by the fact that the dose of morphine can be increased from clinical doses (50 to 60 milligrams per day) to 500 milligrams per day over as short a period as 10 days.

Tolerance to one opioid leads to cross-tolerance for all other natural and synthetic opioids, even if they are chemically dissimilar. Cross-tolerance, however, does not develop between the opioids and the sedative hypnotics. In other words, a person who has developed a tolerance for morphine will also have a tolerance for other opiate agonists (Table 10.1) but not for alcohol or benzodiazepines.

Physical dependence is an altered physiological state induced by a drug, whereby withdrawal of a drug elicits biological reactions typical for that class of drugs. Generally, symptoms of withdrawal are the opposite of pharmacological effects. (For opiate withdrawal, see Table 10.3.) The magnitude of these acute withdrawal symptoms depends on the dose of opioid that had been used, the frequency of previous drug administration, and the duration of drug dependence. Acute opioid withdrawal is not considered life-threatening.

To help alleviate the symptoms of acute withdrawal, several approaches have been tried. These approaches include clonidine-assisted detoxification, buprenorphine-assisted detoxification, and rapid anesthesia-aided detoxification. Clonidine is a drug that acts on the sympathetic nervous system to reduce some of the physical manifestations of withdrawal. Buprenorphine will be discussed later in this chapter.
In rapid anesthesia-aided detoxification (RAAD), a pure opioid antagonist, such as naloxone or naltrexone, and the sympathetic blocker clonidine are administered intravenously to the opioid-dependent person while he or she is asleep under general anesthesia. The procedure continues for about 72 hours, during which time the withdrawal signs are blunted. The objective is to enable the patient to tolerate high doses of an opioid antagonist and thus undergo complete detoxification while unconscious. After awakening, the patient is maintained on naltrexone and undergoes supportive psychotherapy and group therapies for relapse prevention and to address the underlying causes of addiction. The RAAD technique is controversial, in part because it is expensive, involves the risks of anesthesia, and focuses only on short-term dependence rather than on long-term cravings and social adjustments. Thus, this technique for treating opioid addiction is infrequently used now.

Regardless of the method, there is a protracted opiate abstinence syndrome following acute withdrawal that can persist as long as 6 months. Symptoms include depression, abnormal responses to stressful situations, drug hunger, anxiety and other psychological disturbances, as well as other psychiatric disorders. Risk of relapse and overdosing is high, even following release from prison or from a detoxification program (Volkow and McLellan, 2016).

**FULL OPIOID AGONISTS**

**Morphine: The Prototype Full Opioid Agonist**

Among the analgesics found in the opium poppy, morphine is the most potent and represents about 10 percent of the crude exudate (in other words, the juice or sap that is harvested from the mature poppy flower). Codeine is much less potent and constitutes...
only 0.5 percent of the crude exudate. Despite decades of research, no other drug has been found that exceeds morphine's effectiveness as an analgesic, and no other drug is clinically superior for treating severe pain.

Morphine can be administered by injection, inhalation, or taken orally or rectally. Rylomine, an intranasal delivery system, remains under development. This product is intended to have a rapid onset of action in situations where oral use is not desired.

Orally, morphine is available in immediate-release formulation and as a long-acting, time-release product (MS-Contin). In January 2017, the FDA approved Arymo ER, the first product developed using an abuse-deterrent technology—a physical and chemical barrier approach—creating tablets that are difficult to crush, cut, grind, or break for the purpose of misuse and abuse.

In general, absorption of morphine from the gastrointestinal tract is slow and incomplete compared to absorption following injection or inhalation. Only about 20 percent of orally administered morphine reaches the CNS. Absorption through the rectum is adequate, and several opioids (morphine, hydromorphone, and oxymorphone) are available in suppository form.

The risk of an overdose increases in a dose–response manner. It will nearly double at 50 to 99 morphine milligram equivalents (MME) per day and increase by a factor of up to 9 at 100 MME or more per day compared with doses of less than 20 MME per day (Frieden and Houry, 2016).

The presence of opioid receptors in the spinal cord means administration of morphine directly onto the spinal cord, an intrathecal route through small surgically implanted catheters, is effective. This route places the drug right at its site of action and may avoid its effects both on higher CNS centers (maintaining wakefulness and avoiding respiratory depression) and in the periphery (avoiding drug-induced constipation). A variation of this approach is the epidural route, in which the drug is introduced above the dura mater of the spinal cord, and diffuses across the dural membrane to bind with spinal opiate receptors. In medicine, the epidural and intrathecal techniques are used to control the pain of obstetric labor and delivery, to treat postoperative pain, and (for long-term use) to relieve terminal cancer and other forms of intractable pain. In these situations, an implantable programmed pump for intraspinal infusion is available.

Morphine crosses the blood–brain barrier fairly slowly, as it is more water-soluble than lipid soluble. Other opioids cross the blood–brain barrier much more rapidly.

Opioids reach all body tissues, including the fetus. Infants born to addicted mothers are physically dependent on opioids and exhibit withdrawal symptoms. The habitual use of morphine or other opioids during pregnancy does not seem to increase the risk of congenital anomalies; thus, these drugs are not considered to be teratogenic. However, there are increased risks of birth-related problems and fetal growth retardation.

The liver metabolizes morphine and as much as 40 to 60 percent of the drug may not reach the systemic circulation because of first-pass metabolism. One of morphine's metabolites (morphine-6-glucuronide) is actually 10 to 20 times more potent as an analgesic than morphine itself, and much of morphine's analgesic action is mediated

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This kind of preparation might be indicated for patients suffering from muscle-wasting diseases who cannot tolerate other routes of administration.
by this active metabolite. The half-lives of morphine and morphine-6-glucuronide are both 3 to 5 hours. Patients with impaired kidney function tend to accumulate the metabolite and thus may be more sensitive to morphine administration.

Urine screening tests can be used to detect codeine (discussed in the next section) and morphine as well as their metabolites. Because heroin (discussed later in the chapter) is metabolized to monoacetylmorphine and then to morphine, heroin use is suspected when monoacetylmorphine, morphine, and codeine are present in either blood or urine. Frequently, urinalysis cannot accurately determine which specific drug (heroin, codeine, or morphine) has been used. However, a specific metabolite of heroin, 6-monoacetylmorphine, is also at times detected and would definitely confirm illicit drug (such as heroin) use. Even poppy seeds contain small amounts of morphine. Depending on the drug that was taken, morphine and codeine metabolites may be detected in a patient’s urine for two to four days.

**Codeine**

Codeine is a prodrug, which must be metabolized by the enzyme CYP 2D6 in the body to morphine, the pharmacologically active drug. Hence, the efficacy and safety of codeine is governed by CYP 2D6 activity (Crews et al., 2012). Codeine used to be widely prescribed as a low-potency opioid, but in recent years has fallen out of favor because of more reliable and stronger opioids such as hydrocodone and oxycodone. Codeine was usually combined with aspirin or acetaminophen for the relief of mild to moderate pain. These combination products were frequently sought drugs of abuse. Because it has been used for so long, codeine never underwent the safety studies required for new drugs. The plasma half-life and duration of action is about 3 to 4 hours, but codeine's pharmacokinetics are unpredictable. Moreover, almost 1 in 10 Americans have a genetic variation that causes very rapid metabolism of codeine. As a result, abnormally high levels of morphine may accumulate, leading to drowsiness and respiratory depression. Furthermore, morphine may also be passed to infants through breast milk. In 2013, the FDA warned that products containing codeine should not be used for pain relief in children after tonsillectomy or adenoidectomy because of the risk for adverse effects or death. This was based on medical reports of three deaths and one life-threatening case of respiratory depression in children with sleep apnea given codeine after one of the aforementioned surgeries. All the children were ultrarapid metabolizers.

In addition to its inherent pharmacokinetic disadvantages, four of the six selective serotonin reuptake inhibitor (SSRI) antidepressants (fluoxetine, fluvoxamine, sertraline, and paroxetine; see Chapter 12) can block the pain relief of codeine because they block the conversion of codeine to morphine. For patients taking one of these drugs, an analgesic drug other than codeine may be necessary.

**Heroin**

*Heroin* (diacetylmorphine) is three times more potent than morphine and is produced from morphine by a slight modification of its chemical structure. The increased lipid solubility of heroin leads to faster penetration of the blood–brain barrier, producing
an intense rush when the drug is either smoked or injected intravenously. Heroin is metabolized to monoacetylmorphine and morphine; morphine is eventually metabolized and excreted.

Although initially developed as an analgesic in the late nineteenth century in Germany—as a more heroisch (heroic or valiant) intervention to pain than aspirin—heroin is rarely used medicinally or clinically except, as in the case of the United Kingdom, under restricted clinical guidelines. In the United States, heroin is illegal and anyone who manufactures, sells, distributes, and uses heroin does so illicitly.

When heroin is smoked together with crack cocaine, euphoria is intensified, the anxiety and paranoia associated with cocaine are tempered, and the depression that follows, after the effects of cocaine wear off, seems to be reduced. Unfortunately, this combination creates a multidrug addiction that is extremely difficult to treat.

According to the National Center for Health Statistics (2017), between 2010 and 2015, the increased potency of heroin and the drop in the price of the drug resulted in the dramatic fourfold rise in the annual number of lethal heroin overdoses in the United States from 3036 to 12,989. This increase occurred in all age groups, but the largest percentage was seen in those aged 55 to 64.

Studies have shown a positive relationship between high rates of prescription opioid analgesic use and heroin abuse. The concurrent use of prescription opiates and heroin is increasing, and more people are alternating between these two drugs, depending on which one is available (Cicero et al., 2015). This progression of heroin use from prescription opioid abuse appears to be a new phenomenon. In the 1960s, more than 80 percent of opioid abusers noted that they started with heroin; this was nearly reversed by the 2000s, when 75 percent started using prescription opioids before initiating heroin use (Compton et al., 2016). Most of the few studies that have been done, show that heroin use increased before policies were in place that made opioid prescriptions more difficult to obtain. The fact that heroin increased in purity and accessibility, and became cheaper, has been considered important reasons for the increased use, especially in a subgroup of people with opiate dependence who frequently misuse prescribed opiates.

Compton and colleagues (2016) describe several approaches being developed to stem prescription opioid abuse. These initiatives involve educational efforts, monitoring programs for prescription drugs, increased enforcement to deal with illegal prescribers, and development of new abuse-deterrent drug formulations, which are discussed later in this chapter.

**Hydrocodone**

Hydrocodone is one of the most commonly prescribed and abused opioid medications. Like codeine, hydrocodone (dihydrocodeinone) is a relatively weak analgesic. CYP 2D6 converts much of the hydrocodone to the more active compound hydro- morphone (Dilaudid). Short-acting hydrocodone is commonly found in combination with acetaminophen in formulations such as Vicodin, Norco, and Lortab. In October 2014, these compounds, because of their high abuse risk, were rescheduled from Schedule III to Schedule II, which is a more restricted category. In addition to some
other restrictions, this means that doctors cannot call in a prescription to a pharmacy. Instead, they must write a prescription that the patient must, in most cases, present in person to a pharmacist in order to receive these drugs. In the first year following the rescheduling, there were 26.3 million fewer prescriptions (a 22 percent decline) and 1.1 billion fewer tablets sold (a 16 percent decline). The decrease was mostly due to the fact that patients were not able to get refills over the phone. Further analysis also revealed there was no increase in prescriptions for the synthetic opioid tramadol (see below) after hydrocodone rescheduling (Jones et al., 2016), indicating that the new restrictions were effective in reducing overall opiate use.

Long-acting hydrocodone formulations are sold under the trade names Hysingla and Zohydro. The FDA approved Zohydro (developed by Zogenix) for the treatment of moderate to severe pain, in October 2013. A year later, in November 2014, the FDA also approved Hysingla (made by Purdue Pharma), the second single-entity hydrocodone product for the treatment of moderate to severe pain. The term “single entity” means that each drug contains only hydrocodone, without any other medication, such as acetaminophen. The use of products containing acetaminophen in high doses over long periods of time has the potential for causing liver injury. Hysingla ER was originally approved with abuse deterrent technology. But the initial approval of Zohydro ER was extremely controversial because the original formulation did not contain abuse deterrent technology. In order to prescribe Zohydro ER, clinicians were required to complete a risk assessment and pain management treatment agreement. In January 2015, Zohydro ER was reformulated to contain BeadTek technology, which causes the drug to form a viscous gel when crushed or dissolved in liquids, which makes the hydrocodone difficult to inject. The new formulation of Zohydro ER, which was approved in February 2015, maintains the same pharmacokinetic and efficacy profiles as the older formulations, but includes the abuse deterrent technology.

One agent under development, KP201, is currently under FDA review as an alternative form of hydrocodone. In February 2016, the FDA granted the manufacturer of KP201 combined with acetaminophen (also known as APAP for the active ingredient acetyl-para-aminophenol) priority review status. Clinical studies have not yet been published. Guenther and coworkers (2016) reported KP201 to have similarity in abuse potential to hydrocodone (for example, Norco). In June 2016, this drug, with the trade name Apadaz, received a positive evaluation as an extended release formulation of hydrocodone and acetaminophen, but not with abuse deterrent properties and, as of March 2, 2017, had not been approved by the FDA.

In January 2017, another extended release hydrocodone compound was approved by the FDA. This product, with the trade name Vantrela, was made by the Teva pharmaceutical company. It claims to have abuse deterrent potential whether administered by oral, intranasal, or intravenous routes.

**Oxycodone**

*Oxycodone* (Percodan, OxyContin; Xtampza-ER, Remoxy) is another semisynthetic opioid similar in action to morphine. The short-acting, generic preparation is widely prescribed for the treatment of acute pain. The enzyme CYP3A4 metabolizes oxycodone
to the opioid agonist noroxycodone, which is not very potent, and the enzyme CYP2D6 metabolizes oxycodone to oxymorphone, which is more potent. In most patients, analgesia is primarily due to oxycodone, but data suggests that analgesic effects in individuals with CYP2D6 abnormalities might be different.

The long-acting formulations of oxycodone (OxyContin, Xartemis-XR, Xtampza-ER, Remoxy) contain oxycodone in doses to 80 milligrams (normal acute doses are about 5 to 10 milligrams). Since 1999, OxyContin has been widely abused and responsible for numerous overdose fatalities. Abusers crushed the pill, destroying the time-release mechanisms, and either snorted the powder, smoked the drug, or diluted it in water and injected it. The abuse of OxyContin led to the development of a new formulation approved in April 2010, intended to prevent it from being cut, broken, chewed, crushed, frozen, heated, or dissolved to release more medication. Evidence from human pharmacokinetic studies shows that the drug is not rapidly released if it is dissolved in ethanol or other common drinks or solvents. Two other products, Remoxy and Xtampza-ER, are now available.

The new formulations of oxycodone did successfully reduce abuse liability. A year after the new formula was marketed, it was reported to sell for 28 percent less than the original OxyContin on the black market and abuse fell significantly. However, the use of other opioids, such as fentanyl, heroin, and oxymorphone (Opana; see the next section) increased. While 24 percent of drug users said they found a way around the tamper-proof mechanism, most (66 percent) said they just switched to another opioid (Cicero et al., 2012).

**Hydromorphone and Oxymorphone**

Hydromorphone (Dilaudid, Palladone) and oxymorphone (Numorphan, Opana-ER) are both structurally related to morphine and are 6 to 10 times more potent. They produce somewhat less sedation but equal respiratory depression. Palladone (not to be confused with paliperidone; see Chapter 11) and Exalgo are trade names for two long-acting formulations of hydromorphone that are taken once daily for treatment of chronic pain in patients who have developed a tolerance to opioids and thus can tolerate the high doses of 10 to 32 milligrams per day (the dose of short-acting hydromorphone is about 1 to 2 milligrams). The half-life of both Palladone and Exalgo is about 18 hours, providing analgesia for up to 24 hours (Weinstein, 2009). Palladone is formulated as an immediately dissolving capsule containing controlled-release pellets. Exalgo contains hydromorphone in the OROS osmotic delivery system similar to that used for Concerta (see Chapter 15).

The long-acting formulation of oxymorphone has been controversial. The FDA first approved Opana-ER in 2006. In 2010, following the reformulation of OxyContin, abuse of Opana skyrocketed, since Opana could be crushed and snorted, allowing a full 12-hour dose delivered in minutes. In response, in 2012, the manufacturer developed a crush-resistant formulation similar to that of OxyContin. One adverse effect of injection was the occurrence of thrombotic thrombocytopenic purpura (TTP). TTP is characterized by the occurrence of blood clots in small vessels throughout the body, which can damage organs. Even worse, while the new formulation appeared to deter abuse
by snorting the powdered drug, abusers found they could cook the pills and administer it by injection. This has led to wide abuse and multiple deaths. Indeed, the current street cost of a single Opana pill can be up to $200 depending on the tablet strength. Martin and coworkers (2016) reviewed the technology behind controlled-release formulations for long-acting opioid pain products. Hopefully, as new guidelines for opioid prescribing are implemented, overprescription for these products will decrease (Alford, 2016; Califf et al., 2016).

Propoxyphene

*Propoxyphene* (Darvon) is an analgesic compound that is structurally similar to methadone; it is less potent than codeine but more potent than aspirin. Darvon was marketed in 1957 when there were few alternatives for treating pain, except aspirin and strong opioids. In 2010, the FDA determined that the drug should be removed from commercial sale because of concerns about potentially fatal heart rhythm abnormalities, drug overdose suicide, and overdoses.

Meperidine

*Meperidine* (Demerol) is a synthetic opioid whose structure differs from that of morphine. Because of this structural difference, meperidine was originally thought to be free of many of the undesirable properties of the opioids. However, meperidine is addictive and it can be substituted for morphine or heroin in addicts. It is one-tenth as potent as morphine, produces a similar type of euphoria, and is equally likely to cause dependence. Meperidine’s side effects differ from morphine’s and include more excitatory effects, such as tremors, delirium, hyperreflexia, and convulsions. These excitatory actions are produced by a metabolite of meperidine (normeperidine). Unlike other opiates, meperidine does not cause pinpoint pupils, but it may dilate the pupils because of an anticholinergic action. Meperidine and normeperidine can accumulate in people who have kidney dysfunction or who use only meperidine for their opioid addiction. Following discontinuation, withdrawal symptoms develop more rapidly than with morphine because of meperidine’s shorter duration of action.

Fentanyl and Its Derivatives

*Fentanyl* (Sublimaze) and three related compounds, *sufentanil* (Sufenta), *alfentanil* (Alfenta), and *remifentanil* (Ultiva) are short-acting, intravenously administered opioid agonists that are structurally related to meperidine. They are meant to be used during and after surgery to relieve surgical pain. Carfentanil, an even more potent compound, is used to immobilize large animals, such as elephants, in veterinary practice. Fentanyl and its derivatives are multiple times more potent than morphine and frequently combined with heroin to increase its potency, usually resulting in fatalities in unsuspecting heroin users.
In addition to its intravenous formulation, fentanyl is also available in numerous other forms: a transdermal skin patch (Durapatch; Ionsys); a dissolvable buccal tablet (Fentora), which is placed between the upper cheek and gum; a fentanyl buccal soluble film (Onsolis); a sublingual tablet (Abstral); a sublingual spray (Subsys); an oral lozenge on a stick (Actiq), which is often referred to as a “lollipop”; and a nasal spray (Lazanda). The transdermal route of drug delivery offers prolonged, rather steady levels of drug in blood; the buccal tablet, the lollipop, and the nasal spray are short-acting products intended for the treatment of breakthrough cancer pain in opioid-dependent patients who are intolerant of injections (Paech et al., 2012). A sublingual, 30 microgram tablet formulation of sufentanil has been developed to treat moderate to severe acute pain. Its administration is restricted to medically supervised situations, to prevent diversion. Although sufentanil is usually given by IV infusion, it is short acting, whereas the new sublingual formulation lasts longer and does not produce a spike in blood levels. On October 12, 2017, the FDA informed the company (AcelRX Pharmaceutical) that it could not approve the drug until certain modifications were made (Minkowitz and Candiotti, 2015).

As an analgesic, fentanyl and its derivatives are 80 to 500 times as potent as morphine and profoundly depress respiration. Death from these agents is invariably caused by respiratory failure. Because they are so lipid soluble, these drugs may accumulate in fat stores, which means they need an extended period of time to leave the body; that is, to move from the fat cells to the blood and then to the liver. Remifentany differs from fentanyl in this regard. Although it is also very lipid soluble, remifentanyl is metabolized quickly outside of the liver, in the blood and tissues. For this reason, the drug is used for rapid, short-acting analgesia, which can be given for long periods but is cleared quickly (Pathan and Williams, 2012).

Fentanyl has been used illicitly under various nicknames (for example, “china white”). Numerous derivatives, such as alpha fentanyl, have been manufactured illegally; they emerge periodically and have been responsible for many fatalities (Lozier et al., 2015). In March 2015, a surge in overdose deaths around the country from heroin laced with fentanyl prompted the Drug Enforcement Agency (DEA) to issue a nationwide alert. Similarly, in September 2016, the DEA also issued a public warning and notified law enforcement agencies about the dangers of carfentanil, a synthetic opioid that is 10,000 times more potent than morphine and 100 times more potent than fentanyl.

**Tapentadol**

*Tapentadol* (Nucynta) was released in 2009 as a Schedule II analgesic, similar to tramadol (discussed below) because it has two types of action. First, it activates the mu opioid receptor and second, it inhibits the reuptake of norepinephrine. Tapentadol is a full mu agonist, but its binding affinity is 18 times less than morphine. Furthermore, it is only two to three times less potent than morphine, presumably because of the noradrenergic reuptake block. It differs from tramadol in that it only slightly inhibits serotonin reuptake. Because it is weakly serotonergic, it is unlikely to result
in serotonin syndrome if administered with SSRI-type antidepressants. Tapentadol is not a prodrug and has no known active metabolites. As a result, it does not have to be metabolized to elicit its therapeutic effects. Consequently, there is less risk of drug–drug and cytochrome P450 interactions. This characteristic is advantageous for patients who are poor metabolizers of CYP3A4 and CYP2D6, and therefore have an unsatisfactory reaction to standard opiates. For control of moderate to severe pain, 75 milligrams of tapentadol is equivalent to 10 milligrams of oxycodone (Raffa et al., 2012; Xiao et al., 2017).

To date, the abuse potential of tapentadol appears to be modest, with abuse being reported significantly less than that of other opioids (Butler et al., 2015; Dart et al., 2016).

An extended-release formulation of tapentadol was approved in 2011 for treatment of severe chronic pain (such as severe low back pain and knee pain) and, in 2014, it became the first opioid approved for patients with diabetic peripheral neuropathy (Vadivelu et al., 2015).

**Methadone**

*Methadone* (Dolophine) is a synthetic mu agonist opioid very similar to morphine. Methadone was first shown to block the effects of heroin withdrawal in 1948. In 1965, it was introduced as a substitute treatment for opioid dependency. The outstanding properties of methadone are its effective analgesic activity, efficacy by the oral route, extended duration of action in suppressing withdrawal symptoms in physically dependent people, and tendency to show persistent effects with repeated administration.

Today, methadone has two primary legitimate uses: (1) as an orally administered substitute for heroin in methadone maintenance treatment programs; and (2) as a long-acting analgesic for the treatment of chronic pain syndromes (Krueger, 2012). This effect is thought to be partly due to an antagonistic activity at the NMDA glutamatergic receptor (see Table 10.1). Federal prescription regulations clearly separate these two uses. Physicians who do not practice in federally licensed methadone treatment programs may not prescribe the drug for the maintenance of opioid dependency; the drug may be prescribed only through licensed methadone maintenance treatment program centers. However, office-based physicians may prescribe methadone for the treatment of either acute or chronic pain. Unfortunately, such prescriptions may have contributed to the recent opioid epidemic. In 2009, only 2 percent of opioid prescriptions were for methadone, but this drug was implicated in about 30 percent of opioid overdose deaths. Although the death rate from methadone overdoses peaked for most demographic groups from 2005 to 2007 and declined thereafter, this was not the case for those aged 55 to 64 years, whose methadone overdose death rates maintained an increase through 2014 (Jones et al., 2016).

The main objectives of methadone maintenance treatment programs are rehabilitation of the dependent person and reduction of diseases associated with needle use, illicit drug use, and crime. Randomized controlled trials have shown that these aims
are generally accomplished. Moreover, long-term use is relatively safe, for example, it does not impair cognitive function. Comparison between methadone patients, opiate users, and normal control persons in laboratory tests showed that cognitive function in methadone maintenance patients improved compared to those dependent on illicit opiates (Wang et al., 2014).

Although there are a number of predictors of the success of a program, the most important is the magnitude of the daily methadone dose. Programs that prescribe average daily doses exceeding 100 milligrams have higher retention rates and lower illicit drug use rates than those in which the average dose is less. Methadone is one of the most well-studied, safe, and effective available medications. Methadone overdose deaths are usually caused by high doses, an increase in dose that occurs too rapidly, or an interaction of methadone with another drug. One report provided risk-reduction suggestions to alleviate these situations (Baxter et al., 2013).

Even where liberal doses are used (sometimes up to 160 milligrams per day or higher), about one-third of the clients regularly experience withdrawal (known as “nonholders”) and two-thirds (known as “holders”) do not experience withdrawal on a once-daily dosing schedule. The generally accepted half-life of methadone is 24 hours.

Multiple CYP hepatic enzymes are required to metabolize methadone. Therefore, methadone is the opioid most susceptible to serious drug interactions resulting from drug-induced enzyme inhibition. For example, some sedatives and antidepressants inhibit methadone’s metabolism, resulting in large elevations in blood concentrations, often resulting in unexpected fatalities (Tennant, 2010).

As well as some methadone maintenance programs may work, they reach only 170,000 of the estimated 810,000 opioid-dependent people in the United States. In recent years, diversion of methadone (from methadone clinic programs and from physicians’ prescriptions for analgesic effects) has become a major problem. When the large doses prescribed for an opioid-dependent person (40 to 100 milligrams) are taken by a nonopioid-dependent person, severe respiratory depression and death frequently result.

**Levo-Alpha Acetylmethadol**

Levo-alpha acetylmethadol (LAAM) is related to methadone. It is an oral opioid analgesic that was approved in mid-1993 for the clinical management of opioid dependence in heroin addicts. LAAM has a slow onset and a long duration of action (about 72 hours). Its primary advantage over methadone is its long duration of action; in maintenance therapy it is administered by mouth three times a week.

In general, LAAM and methadone are of equal efficacy as measured by opioid-free urine samples in heroin-dependent persons. Higher doses of methadone (60 to 100 milligrams) and 75 to 115 milligram doses of LAAM both substantially reduced the use of heroin. Kiselica (2013) reviewed the comparable efficacies of methadone and LAAM in the treatment of opioid addiction. LAAM is currently not available due to possible serious cardiac complications.
PARTIAL AGONISTS

Tramadol

Tramadol is the active ingredient in such brand name opioids as Ultram, Ultrace, ConZip, Ryzolt, and Rybix ODT. Like codeine, tramadol is a prodrug and is converted (metabolized) by both CYP3A4 and CYP2D6 to O-desmethyltramadol, which is the active form of the drug. Patients with deficiencies in CYP2D6 production (that is, poor metabolizers) will tend to get reduced analgesic effects from tramadol. Those who produce increased quantities of CYP2D6 (rapid metabolizers) may experience increased pharmacologic and unexpected adverse effects. Drug interactions with CYP2D6 inhibitors may also reduce the analgesic efficacy of tramadol.

It had been generally assumed that tramadol was less liable to abuse than opioid painkillers. With an increase in tramadol prescriptions, however, came an increase in reported problems with abuse and addiction. After several years, the DEA officially moved tramadol from Schedule V to Schedule IV in 2014, which was comparable to the benzodiazepines. The original designation was based on studies in which the drug was injected and on its benign abuse record in Europe. But it was subsequently realized that taken orally in high doses, tramadol was as prone to abuse as OxyContin, which is one of the most addictive drugs in the United States. Furthermore, withdrawal of tramadol, especially rapid discontinuation, sometimes elicited symptoms unusual for opiate withdrawal, such as hallucinations, paranoia, extreme anxiety, panic attacks, confusion, and unusual sensory experiences, such as numbness and tingling in one or more extremities (Seney et al., 2003). Because it was thought to be safer than other opiates, tramadol was often prescribed to older patients. This cohort, however, accounted for the largest number of emergency room visits associated with this drug, possibly because older adults are often prescribed multiple medicines that can interact with tramadol to produce seizures and the serotonin syndrome (Chapter 12). Nevertheless, the extended-release formulation of tramadol was recently found to be effective in suppressing opiate withdrawal in a small clinical trial (Dunn et al., 2017).

A metabolite of tramadol, O-desmethyltramadol (O-DSMT), has been synthesized and is presently a legal alternative to illegal opioid drugs, packaged as a powder, or combined with other agents. One example, discussed later in the chapter, is marketed as the blend “Krypton,” which consists of powdered kratom leaf (Mitragyna speciosa) laced with O-DSMT. It has been linked to several accidental overdose deaths (Kronstrand et al., 2011).

Buprenorphine

Buprenorphine was developed in about 1980. As a single agent, it had analgesic effects with blunted abuse liability. Indeed, buprenorphine can be used to treat both acute pain (Kumar et al., 2016) and chronic pain (Gimbel et al., 2016). In addition, buprenorphine has become invaluable in helping to reduce opioid cravings in individuals who are addicted to opiates. In its chemical structure, buprenorphine is related to several other opioid agents, including oxycodone, hydromorphone, and oxymorphone.
But buprenorphine works in a different way. It is both, a partial agonist at mu opioid receptors and an antagonist at kappa receptors. The analgesic action is mediated by stimulation of mu opioid receptors, while the kappa receptors are simultaneously blocked. While therapeutic doses provide sufficient analgesia, there is a ceiling that limits respiratory depression and the partial agonistic action plateaus with an increase in dose.

Although methadone has long been the mainstay of opiate dependence treatment, it is subject to diversion, and the federal government requires patients to receive the drug daily in federally licensed clinics. This makes it difficult for patients with full-time jobs and those who live at a distance to participate. The situation changed dramatically with the approval of *buprenorphine* and then a *buprenorphine-naloxone* (Suboxone) combination product for use in the treatment of opioid addiction. Buprenorphine as a single agent is now available in multiple preparations, each under a different trade name:

1. Buprenex was marketed in the United States in 1985 for the treatment of moderate to severe pain as an injectable buprenorphine formulation.
2. Subutex, a sublingual tablet, was approved in 2002 as a treatment for opioid addiction, especially during the initial therapeutic period. Additionally, it has an off-label application in chronic pain patients who cannot tolerate long-acting, full opioid agents or for whom such agents are inappropriate. Because of abuse problems, the manufacturer discontinued sale in 2011, but not for reasons of safety or effectiveness. Therefore, it is still available in generic form.
3. Bunavail, Suboxone, and Zubsolv: These three trade-named products are transmucosal films to be placed under the tongue from where the medication is absorbed. Each product, with Suboxone being the most popular, is formulated in conjunction with the opioid antagonist naloxone. These are treatments for dependence on any opioid, both at the beginning of opioid withdrawal and for maintenance therapy.
4. Butrans is a transdermal patch, which is approved for pain treatment that is not sufficiently alleviated by other drugs, and therefore warrants around-the-clock, long-term opioid administration. Available doses range from 5 to 20 micrograms per hour; however, for opioid-naive patients, only the 5 micrograms per hour dose is recommended. This formulation is also indicated for maintaining opioid abstinence. Butrans patches should remain on for a week before they are removed.
5. Belbuca, similar to Butrans, is indicated for around-the-clock treatment of pain that is not sufficiently relieved with alternative drugs. It is a newer formulation, available as a buccal film in doses of 75 to 900 micrograms, each lasting about 12 hours. This formulation was developed to adhere to the buccal mucosa and dissolve completely within 30 minutes. The time to peak concentration is 2.5 to 3 hours and the elimination half-life is 27.6 hours.
6. The first buprenorphine implant for maintenance treatment of opioid dependence was approved by the FDA in 2016. This formulation, Probuphine, releases a constant, low-level amount of the drug for 6 months in patients who have been stabilized on low to moderate doses of another buprenorphine agent. This alleviates the
need to take daily medication, and may increase patient compliance. This product consists of four 1-inch rods which are implanted under the skin on the inside of the upper arm, providing treatment for 6 months. No data is yet available on misuse, diversion, or reimplantation after the initial 6 months.

The most common side effects of buprenorphine are flulike symptoms, including headache, sweating, sleeping difficulties, nausea, vomiting, and mood swings. Rosenthal and coworkers (2016), in a carefully controlled trial, compared sublingual buprenorphine (90 persons) with the implanted buprenorphine pellets (Probuphine, 87 persons). About 90 percent of each group achieved a good response over a 6-month period. Modestly more (85 versus 72 percent) maintained opioid abstinence with the implant. New formulations continue to be developed. RBP-6000, developed by Indivior, is a buprenorphine formulation that is injected once a month for the treatment of adults with opiate addiction. It was effective in producing greater rates of abstinence than placebo and was generally well tolerated. The most common side effects included fatigue, constipation, headache, nausea and vomiting, and itching and pain at the injection site. The FDA approved this formulation, as Sublocade on November 30, 2017 (see Nasser et al., 2016).

A weekly, subcutaneous buprenorphine depot formulation, CAM2038, is also in development (Walsh et al., 2017). It was recently tested in adults with moderate to severe opioid use disorder, and doses of 24 and 32 milligrams were well tolerated and effective in blocking the positive subjective effects of the opiate agonist, hydromorphone, and in suppressing withdrawal symptoms. The depot formulation has the benefit of stabilizing the patient undergoing withdrawal and minimizing the likelihood of diversion. Schuckit (2016) reviewed the treatment of opioid use disorders with buprenorphine.

In addition to its indication for analgesia and addiction treatment at low doses, buprenorphine has also been reported to have an antisuicidal benefit in patients who do not have substance abuse problems (Yovell et al., 2015). It was also more effective than opioids alone in improving symptoms of PTSD in veterans with chronic pain who also have an opioid-use disorder (Seal et al., 2016).

**Use of Buprenorphine for the Treatment of Opioid Dependence**

In July 2016, the Substance Abuse and Mental Health Services Administration (SAMHSA) announced regulations that increased access to buprenorphine and the combination buprenorphine and naloxone (Suboxone) medications in office-based settings. The new rules permitted practitioners to dispense or prescribe Schedule III, IV, or V controlled substances already approved by the FDA without requiring a separate registration to dispense narcotic maintenance and detoxification drugs. Qualified practitioners who filed an initial notification of intent (NOI) were also allowed to treat a maximum of 30 patients at a time. After 1 year, practitioners may file a second NOI indicating an intent to treat up to 100 patients at a time, while the final rule (July 2016) expanded this access to medication-assisted treatment (MAT) for up to 275 patients. The final rule also incorporates efforts to provide all aspects of evidence-based MAT and to reduce the likelihood that the drugs are misused or diverted. These rules mean, unlike methadone, a physician in his or her office can prescribe Suboxone for
the treatment of opioid dependence. Also, patients can take the drug home instead of appearing at a clinic every day. The buprenorphine-naloxone combination (in a 4:1 ratio) is less liable to abuse, not only because buprenorphine is a partial agonist, but also because the naloxone causes withdrawal if Suboxone is crushed and injected. When used correctly, however, the naloxone is not well absorbed through the GI tract or mucosa and has a minimal effect. Currently, only physicians may prescribe the drug. The proposed 2017 federal budget also includes a proposal for a buprenorphine demonstration program that would allow advanced practice providers (for example, nurse practitioners) to prescribe buprenorphine. SAMHSA will also review formulations newly approved by the FDA, developed to treat opioid use disorder.

Results are already available. For example, Tanum and colleagues (2017) compared monthly intramuscular injections of extended-release naltrexone with the oral buprenorphine-naloxone formulation in opioid-dependent patients. During the 12-week trial, the treatments were comparable in maintaining abstinence. Similarly, Lee and colleagues (2017) compared monthly intramuscular injections of extended-release naltrexone with daily, self-administered, sublingual buprenorphine-naloxone over 24 weeks in opioid-dependent patients. They found that more patients were unable to be “initiated” into the naltrexone treatment than into the buprenorphine-naloxone treatment. For those who could successfully tolerate naltrexone, however, the results for abstinence were comparable to the results of the buprenorphine plus naloxone treatment. SAMHSA strongly supports creative ways to increase access to medication-assisted treatment.

Since the introduction of buprenorphine for opioid dependence, it has become clear that this drug is not a panacea. Buprenorphine itself can be abused by intravenous injection. It was thought that adding naloxone to the tablet would precipitate withdrawal if it was crushed and injected. However, it turns out that the effect of naloxone is short lived, and the overall effect is more like taking buprenorphine alone. Both buprenorphine and buprenorphine-naloxone may be diverted and misused (for example, intravenously injected or intranasally administered). Likewise, when illicitly injected, both can cause infectious complications as well as result in death from overdose. Moreover, even though buprenorphine alone has a ceiling effect, the risk of death with buprenorphine overdose is increased if either benzodiazepines or sedative-hypnotics are taken at the same time. In fact, the use of sustained-release naltrexone pellets have been used for treatment of buprenorphine dependence (Jhugroo et al., 2014). Sansone and Sansone (2015) review issues concerning buprenorphine for opiate addiction, and Sontag (2013) describes the history of this treatment and the real-world consequences of attempts to overcome opiate addiction with buprenorphine.

**Buprenorphine and Pregnancy**

Opioid abuse during pregnancy increases negative outcomes for both mother and infant, not only because of the biological actions of the drug, but also because of the accompanying medical, mental health, and related social problems associated with illicit drug use (Wilder and Winhusen, 2015). Methadone had been a mainstay of maintenance therapy of opioid treatment for nearly 50 years and has been shown to be safe and effective in pregnant females compared with the use of heroin or
prescription opioids. Recently, buprenorphine has become the first-line treatment for many opioid-dependent pregnant women (Brogly et al., 2015). Comparisons between methadone and buprenorphine indicate moderately strong evidence for lower risk of preterm birth, increased birth rate and larger head circumference with buprenorphine, and no greater harm (Zedler et al., 2016). Both drugs were nearly equivalent regarding the extent of neonatal abstinence syndrome following delivery. While some minor birth abnormalities can be seen, maltreatment, physical abuse, and medical neglect appear to be the greatest problems associated with postnatal care of the newborns (Kivisto et al., 2015).

**MIXED AGONIST-ANTAGONIST OPIOIDS**

Four approved drugs are classified as mixed agonist-antagonist opioids: pentazocine, butorphanol, nalbuphine, and dezocine. Dezocine (Dalgan) was discontinued in the United States as of 2011. Each of these drugs binds with varying affinity to the mu and kappa receptors. The drugs are weak mu antagonists; most of their limited analgesic effectiveness results from their stimulation of kappa receptors (see Table 10.1). Low doses cause moderate analgesia; higher doses produce little additional analgesia. In opioid-dependent people, these drugs precipitate withdrawal. A high incidence of adverse psychotomimetic side effects (dysphoria, anxiety reactions, hallucinations, and so on) is associated with these agents, limiting their therapeutic use.

*Pentazocine* (Talwin) and *butorphanol* (Stadol) are prototypical mixed agonist-antagonists. Neither has much potential for producing respiratory depression or physical dependence. In 1993, butorphanol, previously available for use by injection, became available as a nasal spray (Stadol NS), the first analgesic so formulated. After it is sprayed into the nostrils, peak plasma levels (and maximal effect) are achieved in 1 hour, with duration of 4 to 5 hours. Use of the nasal spray can result in euphoria and abuse of butorphanol spray can occur, but has not been a major problem. The brand name *Stadol* was discontinued by the manufacturer, so that only the generic formulations are available.

Pentazocine was first approved for use in the United States in 1967 and is still available, but not often used. Pentazocine abuse developed, particularly when the drug was combined with tripelennamine, an antihistamine. This combination of drugs, called “Ts and blues,” caused serious medical complications, including seizures, psychotic episodes, skin ulcerations, abscesses, and muscle wasting. (The latter three effects are caused by the repeated injections rather than by the drugs themselves.) Following recognition of this abuse, pentazocine was combined with naloxone to prevent injection misuse and the reported incidence of misuse declined precipitously.

*Nalbuphine* (Nubain) is primarily a kappa agonist of limited analgesic effectiveness. Because it is also a mu antagonist, it is not likely to produce either respiratory depression or patterns of abuse. It is only available in an injectable formulation. It is currently mainly used as a treatment for morphine-induced pruritus (itching), which is a common side effect of mu agonist opioids. Abuse of nalbuphine is unusual.
Chapter 10  OPIOID ANALGESICS

PURE OPIOID ANTAGONISTS

Three opioid antagonists are clinically available: naloxone, naltrexone, and nalmefene. Each is a structural derivative of oxymorphone, a pure opioid agonist. All three have an affinity for opioid receptors (especially mu); however, after binding, they exert no agonistic effects of their own. Therefore, they antagonize the effects of opioid agonists.

Naloxone (Narcan) is the prototype pure opioid antagonist: it has no effect when injected into people who do not use opioids, but it rapidly precipitates withdrawal when injected into opioid-dependent people. Naloxone is neither analgesic nor subject to abuse. Because naloxone is neither absorbed from the GI tract nor the oral mucosa, it must be given by injection. Naloxone injection was first approved in 1971 for reversing opiate intoxication or overdose, and generic versions have been available since 1985 in two doses: 0.4 milligram per milliliter and 1 milligram per milliliter. Naloxone's duration of action is very brief, in the range of 15 to 30 minutes. Thus, for continued opioid antagonism, it must be reinjected at short intervals to avoid return of the depressant effects caused by the longer-acting agonist opioid. Naloxone is used to reverse the respiratory depression that follows acute opioid intoxication (overdoses) and to reverse opioid-induced respiratory depression in newborns of opioid-dependent mothers.

Enteen and coworkers (2010) studied opioid overdose deaths in San Francisco from 2003 through 2009 as well as results of the DOPE (Drug Overdose and Prevention and Education) project. Over 1900 persons were trained and prescribed take-home naloxone and 11 percent reported using naloxone to treat an overdose. Of 399 overdose events, 89 percent of overdoses were successfully treated with naloxone injection to prevent deaths.

In 2013, some federal agencies suggested that access to naloxone should be increased, in particular, for those prescribed opiate drugs. This was prompted by the observation that, although twice as many people died from prescription opioid overdose, more than 80 percent of naloxone was used for treating heroin overdose. In that year, a toolkit for overdose prevention was packaged by SAMHSA for use by clinicians treating patients at risk of overdose. A year later, the first autoinjector formulation, Evzio, received fast-track FDA approval. This was a fixed-dose single injection product developed so that people without medical expertise could reverse an opiate overdose. The first nasal spray formulation (a 4 milligram dose) was fast-tracked in 2015, followed by a second 2 milligram dose (also marketed as Narcan) in January 2017. Before then, naloxone injections of 1 milligram per milliliter had commonly been used off label with an atomizer for nasal delivery. Each of these products—two injection doses, Narcan nasal spray and the Evzio auto-injector—essentially has one supplier. Although the FDA has approved three manufacturers for injections of the 0.4 milligrams per milliliter dose, most are sold by Hospira, which has raised the price by 129 percent since 2012; the Evzio package cost $690 in 2014 but was $4500 in 2016 (Gupta et al., 2016; Wermeling, 2015). For a life-saving drug, the expense of this medication has been extremely controversial.

Naltrexone (ReVia) became clinically available in 1985 as the first orally absorbed, pure opioid antagonist approved for the treatment of heroin dependence. An extended release injectable formulation taken once a month is marketed under the trade name Vivitrol. The actions of naltrexone resemble those of naloxone, but naltrexone is well...
absorbed orally and has a long duration of action, necessitating only a single oral daily dose of about 40 to 100 milligrams. In people who take naltrexone daily, injection of an opioid agonist such as heroin is ineffective. Naltrexone can cause nausea (which can be quite severe in some people) and dose-dependent liver toxicity (Substance Abuse and Mental Health Services Administration, 2016). One problem with naltrexone is that the drug must be taken in order to be effective. Trite as that sounds, the opioid-dependent person must choose between taking naltrexone or returning to heroin use. Therefore, only highly motivated addicts take the drug. A recent trial of extended release naltrexone was disappointing in keeping criminal addicts from relapsing (Lee et al., 2016).

Today, naltrexone is used primarily to treat alcoholism. Naltrexone reportedly decreases heavy drinking, the number of days that alcohol is consumed, and the total amount of alcohol consumed, although the overall benefit has been described as “modest.” The mechanism is believed to be due to antagonism of endorphin, elicited by drinking alcohol, rather than from an as-yet unidentified action outside the opioid system.

Naltrexone has also been reported to have benefits in some other medical conditions, for example, a preventive role in reducing self-injurious behaviors. Effects, however, are weak.

Nalmefene (Selincro) is a pure opioid antagonist. Developed in the early 1970s, it is used mainly to treat alcohol dependence and has been investigated for the treatment of other addictions such as pathological gambling. Compared to naltrexone, the advantages of nalmefene include longer half-life, greater oral bioavailability, and no reported dose-dependent liver toxicity. If given to people who are dependent on opiates or postoperatively for reversal of surgically administered opioids, nalmefene can precipitate acute withdrawal symptoms.

**Agonist-Antagonist Combinations**

One option for addressing opiate addiction is to make opiate pain medications resistant to tampering. The development of abuse-deterrent formulations is an ongoing effort, supported by the federal government, and there are numerous approaches under evaluation. One solution is to combine an agonist with an antagonist. In late 2009, the FDA approved the first of these types of medications, a combination of morphine and naltrexone (Embeda-ER). Embeda extended-release capsules are for oral use and contain pellets of morphine sulfate that surround a core of naltrexone. The naltrexone does not interfere with the analgesic action of morphine, but morphine's abuse potential is considerably reduced. Different dosing regimens are commercially available, all with a morphine-to-naltrexone ratio of 100:4. Embeda was the first FDA-approved long-acting opioid designed to reduce recreational abuse when tampered with by crushing or chewing.

As discussed earlier in this chapter, an abuse-deterrent version of OxyContin was introduced in 2010, which, when combined with water, produced a gellike substance that was hard to inject. Misuse by injecting, snorting, and smoking fell by two-thirds within 2 years. Another combination product using extended release oxycodone and naloxone was marketed in 2014 under the trade name Targiniq-ER. With this formulation, the oxycodone provides analgesic action, but the naloxone remains in the
Opioid analgesics

intestine (not being absorbed when taken orally) and blocks the constipating effect of the oxycodone. When crushed, and subsequently injected, the oxycodone remains active but some naloxone is absorbed, which antagonizes the opiate. This product is meant to deter, but not prevent, abuse.

A combination of oxycodone and low-dose naltrexone was developed by the same company that made Embeda. The new drug, Troxyca, was approved in August 2016. The capsules contain pellets in which a core of naltrexone is surrounded by extended-release oxycodone hydrochloride. When used as directed, the oxycodone is released as intended while the naltrexone remains sequestered. If the pellets are crushed in an effort to abuse the opiate, naltrexone is released and blocks the effect of the oxycodone. If the dose of naltrexone in the product is sufficient and if the drug is abused by injection, the antagonist would precipitate withdrawal symptoms. Taylor and coworkers (2014) reviewed several oxycodone-naloxone products.

Another approach to preventing oral misuse is to develop a prodrug, which would be inactive until swallowed. In the gut, digestion would release the opiate, but this would not happen if the drug was injected. A hydromorphone prodrug (see the next section) is under development (Dolgin 2015).

NOVEL OPIOID-BASED COMPOUNDS UNDER DEVELOPMENT

In 2012, Moorman-Li and coworkers reviewed abuse-deterrent and novel opioids for the treatment of chronic pain. Four years later, Gudin and Nalamachu (2016) reviewed the development of opiate prodrugs (see below) as abuse deterrents. Here, we describe novel options for pain relief, claimed to have lower side effects and less abuse potential of currently available opioids.

- **HS665** is a pure kappa agonist (Guerrieri et al., 2015; Spetea et al., 2012). Clinical trials with HS665 have not yet been reported. Being devoid of mu receptor agonism, abuse liability should be low, although analgesic activity may also be low. As a kappa agonist, this drug appears to resemble nalbuphine, an older, mixed agonist-antagonist with prominent kappa agonist activity. A recent review updates the current status of kappa agonist analgesics and describes experimental agents that have greater selectivity and potency (Erli et al., 2017).

- **CR845** (difelikefalin) and nalfurafine are two other kappa receptor agonists that appear to possess both analgesic and antipuritic (anti-itch) activity (Cowan et al., 2015; Inui, 2012). CR845 poorly crosses the blood–brain barrier and thus its analgesic and antipuritic actions are restricted to the periphery, bypassing many of the abuse and side effect issues of centrally acting agents. Clinical trials have not been published and, as of January 2017, CR845 was still undergoing Phase II clinical testing.

  The lack of scientific publications for this drug has been the topic of an extensive critical review of its developmental history. According to Hesselink (2017), “[a]lthough the clinical development phase started in 2008, primary scientific data on CR845 in peer reviewed journals to date are absent. The only sources
for information and valuation of the company available are some abstracts and posters, written by company employees, and many press releases of CARA Therapeutics.”

Since 2009, nalfurafine (Remitch) has been used intravenously in several countries to treat uremic itching (see Inui, 2015, for this indication). In October 2017, information regarding a clinical trial of nalfurafine for this condition was updated on the site clinicaltrials.gov. Some data, however, suggest that this drug might have additional therapeutic benefit. Both oxycodone and nalfurafine elicited an analgesic effect in animal studies, and the combination of the two drugs was additive. Yet nalfurafine also decreased the reinforcing and respiratory depressant effect of oxycodone, suggesting that it might have some important selective actions (Townsend et al., 2017).

• NKTR-181 is a mu opioid agonist analgesic with a very slow rate of entry into the CNS. Its analgesic effect is purportedly similar to that of oxycodone, with a 90 percent slower delivery rate into the brain. Because of this, its abuse and euphoric effects are thought to be low. In addition, respiratory depression should be lower compared to other mu agonists. The drug is in early clinical trials. The FDA has now granted fast-track status for NKTR-181. As of September 2017, however, only one clinical trial had been completed, successfully reducing lower back pain in humans. It may possibly be on the market by 2019.

• PF329 (ER hydromorphone) is a prodrug that is converted in the body to hydromorphone. When PF329 reaches the small intestine, an amino acid that was bonded to the hydromorphone is cleaved off by the digestive enzyme trypsin, which then activates controlled release of the drug. The molecular bonds cannot be severed by crushing or dissolving. This makes the half-life of the drug slower than that of hydromorphone. Positive results were reported by Fisher and coworkers (2012). A newer agent, PF614, is an extended-release oxycodone prodrug, for which a Phase I clinical trial was initiated in November 2016. Evidence of its deterrence potential was reported by Kirkpatrick and colleagues (2017).

• UMB-425 is a mixed mu agonist–delta antagonist that theoretically results in potent analgesic effects without tolerance liabilities (Healy et al., 2013). Results in mice were encouraging; studies in humans have not been reported. As of May 2017, studies of toxicity and pharmacokinetics had not yet been conducted.

FUTURE PHARMACOTHERAPY OF OPIOID DEPENDENCE

In 1994, Goldstein reviewed more than 20 years of administering methadone maintenance therapy to heroin addicts in New Mexico. More than half the patients were traced and analyzed. Of these 5001 patients, more than one-third had died from violence, overdose, or alcoholism. About one-quarter were still enmeshed in the criminal justice system. Another one-quarter had gone on and off methadone maintenance. Data indicated that opioid dependence is a lifelong condition for a considerable fraction of the addict population.
Similarly, in 2001, Hser and coworkers reported a remarkable 33-year follow-up of 581 male heroin addicts who were first identified in the early 1960s. At follow-up in 1996–1997, 284 were dead and 242 were interviewed; the mean age at interview was 57 years. Of the 242, 20 percent tested positive for heroin (an additional 9.5 percent refused to provide a urine sample and 14 percent were incarcerated, so urinalysis was unavailable); 22 percent were daily alcohol drinkers; 67 percent smoked; many reported illicit drug use (heroin, cocaine, marijuana, and amphetamines). The group also reported high rates of physical health, mental health, and criminal justice problems. Although long-term heroin abstinence was associated with less criminality, morbidity, and psychological distress, and with higher employment, only a minority of people who were dependent on opioids attained this goal.

Other ways of dealing with opiate addiction continue to be explored. One approach now employed is to try to mitigate the likelihood of overdose death by distributing naloxone to heroin users. Nasal naloxone is representative of such an attempt.

Another approach, which has also been applied to nicotine and cocaine addiction, is the development of a heroin vaccine. While positive results can be demonstrated in rats, human research is fraught with difficulties.

Other research has, in fact, suggested that the immune system might hold the key to preventing opiate addiction (Hutchinson et al., 2012). Investigators have reported that opiate drugs, in addition to binding classic opiate receptors, also attach to a type of receptor associated with the immune system, called TLR4 (which stands for Toll-Like Receptor 4), which activates a biochemical pathway called MyD88. When the TLR4 receptor was blocked by the “unnatural” isomer of naloxone—(+)-naloxone (dextro-naloxone)—in laboratory animals, the rewarding effects of opiate drugs were reduced. The animals no longer made the effort to get opiate injections and they no longer preferred the location where they used to get the opiate. These results suggest a new direction for development of addiction treatments.

Opiate overdose deaths are caused by the respiratory depression produced when the drugs activate opiate receptors in the brain stem. Development of an opiate that would provide potent analgesia without this lethal reaction has been a long-term pharmaceutical goal. In November 2017, the drug company Trevena submitted an intravenous opioid called oliceridine (Olinvo) for FDA approval, which may produce such a selective effect. Oliceridine is one of a number of novel opiate compounds called “biased agonists.”

This new phenomenon occurs when typical opiate agonists bind to the mu receptor and activate G-proteins to produce their effects. But such stimulation also activates another intracellular protein, β-arrestin2, which reduces G-protein action so that it does not remain activated indefinitely. β-arrestin2 also mediates opioid-induced respiratory depression and constipation, albeit the mechanism is not yet clear. Nevertheless, opioid drugs that bind to receptors in such a way that they activate the G-protein, but do not stimulate β-arrestin2 as much, might provide pain relief without the unwanted side effects. Thus, oliceridine represents the first of a new class of opiate that has a “bias” toward such selective activation. Although it remains to be seen if such drugs induce less tolerance, or are less likely to produce addiction and dependence, they represent a significant advance in opioid pain therapy (Waldman, 2017).
In addition to the abuse of prescription opiates, the current abuse problems with opioid drugs include several substances that are not prescribed medications.

**Desomorphine**

*Desomorphine* (dihydrodesoxymorphine) is an opiate-derived compound, developed in the United States in 1932. It can be synthesized from codeine with other ingredients such as gasoline, paint thinner, hydrochloric acid, iodine, and red phosphorus (from the striking pads of matchboxes), in a manner similar to the production of methamphetamine from pseudoephedrine. This designer drug began to appear in Russia several years ago after first showing up in Siberia in 2002, perhaps because codeine is commonly sold over the counter in Russia. Unfortunately, this homemade mixture has many contaminants, is very toxic, and, when injected, can produce severe tissue damage (for example, phlebitis and gangrene) that can sometimes require limb amputation. The addict’s skin becomes greenish and scaly at the injection site because the blood vessels burst and the tissue dies; this has led to the street name of “krokodil” or “crocodile” in English.

**Kratom**

*Kratom* (also known as “thang,” “kakuam,” “thom,” “ketum,” and “biak”) comes from the leaves of the medicinal plant *Mitragyna speciosa*, which is native to Southeast Asia and used for thousands of years by chewing, smoking, brewing in a tea, and oral ingestion. In low doses, kratom has a stimulant action, but high doses produce sedation and opiate effects. Despite the isolation of over 40 other alkaloids, most research has been conducted on the predominant alkaloid mitragynine, which was first isolated in 1921 (Adkins et al., 2011; Troy, 2013).

Mitragynine is believed to be an agonist at the mu opiate receptor and an antagonist at the delta opiate receptor. Váradi and colleagues (2016) were able to show in mice that mitragynine pseudoindoxyl, a semisynthetic opioid obtained from the mitragynine found in kratom, was a more effective pain reliever than morphine and produced less tolerance, addiction, and dependence usually associated with opioids. Furthermore, kratom did not suppress their breathing and did not seem to produce constipation.

In humans, kratom appears to have analgesic effects and has been used to treat opioid addiction (Boyer et al., 2007). According to the American Kratom Association, an organization founded in 2014 to represent kratom users, it may help people with addiction, depression, anxiety, and PTSD. Swogger and colleagues (2015) have published a qualitative review of descriptions provided by kratom users. Nevertheless, addiction to kratom itself has also been reported.

The sale of kratom cannot be restricted by the FDA. This is because the substance is designated as a botanic dietary supplement and, in order to be banned, it would have to be proved dangerous, or producers would have to claim it was medically useful. The importation of kratom into the United States, however, was
banned in 2014; the federal government seized 25,000 pounds of kratom that year from a storage site in Los Angeles. In the summer of 2016, the CDC a report calling the plant “an emerging public-health threat,” noting a surge in kratom-related calls to poison control centers (660 calls over a 5-year period) with such symptoms as tachycardia, agitation, drowsiness, nausea, and hypertension. The DEA reported that 15 kratom-related deaths had occurred between 2014 and 2016 (although 14 of those included an additional substance). In August 2016, the DEA announced its plan to temporarily ban the substance. By October, however, following weeks of complaints, the DEA withdrew that plan and instead invited the public to submit their testimonies about using the product. By the December 1 deadline, more than 22,000 people had responded, mostly telling stories about how they relied on the plant for easing their anxiety, PTSD, chronic pain, or struggles with opioid withdrawal, and how restricting access to it would destroy their lives. In November 2017, the FDA released a public health advisory related to potential concerns regarding risks associated with the use of kratom or any of its active ingredients (mitragynine and 7-hydroxymitragynine). For now, kratom remains legal in the United States with the exception of a few states.

In addition to exerting its own opiate effect, as discussed earlier in the chapter, kratom is often combined with another mu agonist, O-desmethyltramadol, the active metabolite of tramadol (a combination referred to as “krypton”).

**Synthetic Fentanyl Derivatives**

Although numerous fentanyl analogs have been synthesized, we still do not know a great deal about their effects, in spite of the fact that their structure activity relationships have been characterized (Vardanyan and Hruby, 2014). Drug dealers have added semilegal versions of fentanyl to increase the potency of heroin on the street since the 1970s. During that period, an analog known as alpha-methylfentanyl was identified in heroin that was found in users who had overdosed. Although alpha-methylfentanyl was placed into the Schedule I category in the United States in 1981, it was detected in contaminated amounts of heroin until the 1990s, accompanied by another, even more potent analog, 3-methyl-fentanyl (TMF). TMF had been made illegal in 1986, but continued to show up intermittently for a number of years. At least 10 more unique analogs of fentanyl have now been identified by toxicologists. The DEA banned a rare type of fentanyl, acetylfentanyl, in 2015, two years after it was first detected in Maine. In early 2016, the DEA placed two other analogs into emergency scheduling, butyrylfentanyl and beta-hydroxythiofentanyl. At the same time, the DEA emergency scheduled a weak synthetic opioid, AH-7921, after noting increased interest in online chat rooms. However, a legal substitute, furanyl-fentanyl, was already gaining attention; since the beginning of 2016, this drug has been identified in 10 overdose deaths in Pennsylvania and it has recently been responsible for an emergency room incident involving two North Dakota high school students. Later, in September 2016, a nationwide warning to the public and law enforcement, was issued by the DEA in regard to carfentanyl (4-carbomethoxyfentanyl), a synthetic opioid that is 10,000 times more potent than morphine, which was first synthesized in 1974.
carfentanyl's street name, “elephant tranquilizer”—a significant number of overdose deaths across the United States have been connected with this drug.

**U-47700**

U-47700 (3,4-dichloro-N-[2-(dimethylamino)cyclohexyl]-N-methylbenzamide) is a synthetic opioid that was patented by the Upjohn Company in 1978 as an analgesic, although studies in humans had not been published. U-47700, which is known on the street as “pink,” “pinky,” and “U4,” has 7.5 times greater binding affinity for mu opioid receptors than morphine. Effects are said to be very similar to those of morphine and heroin. Information linking U-47700 to at least 46 overdose deaths in 2015 and 2016 has been acknowledged by the DEA. Citing “an imminent hazard to the public safety,” the DEA classified U-47700, which was freely available on the Internet, as a Schedule I substance in November 2016.

**W-18**

In February 2016, while raiding a suspected drug dealer, police in Florida confiscated 2.5 pounds of a potent, albeit legal, synthetic fentanyl-like opioid called W-18. This substance is approximately 10,000 times more potent than morphine and 1000 times more potent than fentanyl. Although it was developed in Alberta, Canada, as an alternative painkiller, it was not manufactured and sold until a Chinese chemist discovered the formula. Nonmedical use—there is no medical use—of W-18 by individuals without opiate tolerance is extremely dangerous and has resulted in numerous deaths. It is potentially fatal at high dosages and even opiate tolerant users are at high risk for overdoses. Because we do not know if the opioid antagonist naloxone also blocks W-18, it may be difficult to counteract the drug’s effect after it has been taken.

**STUDY QUESTIONS**

1. How are pain impulses transmitted and modulated within the central nervous system?

2. Describe the opioid receptors. What are the endogenous ligands for those receptors? What happens when an opiate agonist activates its receptor?

3. Define an opioid agonist, antagonist, mixed agonist-antagonist, and partial agonist. Give an example of each and how they are therapeutically useful.

4. In addition to analgesia, what are the major physiological effects of opioid drugs?

5. How have opiate analgesics been reformulated to reduce undesirable side effects?

6. How have opiate analgesics been reformulated to reduce their abuse potential?

7. Discuss the various options for the pharmacological management of opioid dependence and relapse.
8. What are some of the new opiate approaches to pain relief?
9. What are krocodil, kratom, and krypton? What other opiates are now being abused?

REFERENCES


REFERENCES


