Chapter 31: Opioid Analgesics & Antagonists

INTRODUCTION

The opioids include natural opiates and semisynthetic alkaloids derived from the opium poppy, pharmacologically similar synthetic surrogates, and endogenous peptides. On the basis of their interaction with opioid receptors the drugs are classified as agonists, mixed agonist-antagonists, and antagonists.

Opioid peptides released from nerve endings modulate transmission in the brain and spinal cord and in primary afferents via their interaction with specific receptors. Many of the pharmacologic actions of opiates and synthetic opioid drugs are effected via their interactions with endogenous opioid peptide receptors.

CLASSIFICATION

The opioid analgesics and related drugs are derived from several chemical subgroups and may be classified in several ways.

A. Spectrum of Clinical Uses

Opioid drugs can be subdivided on the basis of their major therapeutic uses (eg, analgesics, antitussives, and antidiarrheal drugs).

B. Strength of Analgesia

On the basis of their relative abilities to relieve pain, the analgesic opioids may be classified as strong, moderate, and weak agonists. Partial agonists are opioids that exert less analgesia than morphine, the prototype of a strong analgesic, or full agonist.

C. Ratio of Agonist to Antagonist Effects
Opioid drugs may be classified as agonists (full or partial receptor activators), antagonists (receptor blockers), or mixed agonist-antagonists, which are capable of activating one opioid receptor subtype and blocking another subtype.

PHARMACOKINETICS

A. Absorption and Distribution

Most drugs in this class are well absorbed when taken orally, but morphine, hydromorphone, and oxymorphone undergo extensive first-pass metabolism. In most cases, opioids can be given parenterally, and sustained-release forms of some drugs are now available, including morphine and oxycodone. Fentanyl is available as a transdermal patch. Opioid drugs are widely distributed to body tissues. They cross the placental barrier and exert effects on the fetus that can result in both respiratory depression and, with continuous exposure, physical dependence in neonates.

<table>
<thead>
<tr>
<th>High-Yield Terms to Learn</th>
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<tr>
<td><strong>Opiate</strong></td>
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<td><strong>Opioid</strong></td>
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<td><strong>Opioid peptides</strong></td>
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<td><strong>Opioid agonist</strong></td>
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<td><strong>Partial agonist</strong></td>
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<td><strong>Opioid antagonist</strong></td>
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<tr>
<td><strong>Mixed agonist-antagonist</strong></td>
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B. Metabolism

With few exceptions, the opioids are metabolized by hepatic enzymes, usually to inactive glucuronide conjugates, before their elimination by the kidney. However, morphine-6-glucuronide has analgesic activity equivalent to that of morphine, and morphine-3-glucuronide (the primary metabolite) is neuroexcitatory. Codeine, oxycodone, and hydrocodone are metabolized by cytochrome CYP2D6, an isozyme exhibiting genotypic variability. In the case of codeine, this may be responsible for variability in analgesic response because the drug is demethylated by CYP2D6 to form the active metabolite, morphine. The ingestion of alcohol causes major increases in the peak serum levels of several opioids including hydromorphone and oxymorphone. Meperidine is metabolized to normeperidine, which may cause seizures at high plasma levels. Depending on the specific drug, the duration of their analgesic effects ranges from 1–2 h (eg, fentanyl) to 6–8 h (eg, buprenorphine). However, long-acting formulations of some drugs may provide analgesia for 24 h or more. The elimination half-life of opioids increases in patients with liver disease. Remifentanil, a congener of fentanyl, is metabolized by plasma and tissue esterases and has a very short half-life.

MECHANISMS OF ACTION

A. Receptors

Many of the effects of opioid analgesics have been interpreted in terms of their interactions with specific receptors for endogenous peptides in the CNS and peripheral tissues. Certain opioid receptors are located on
primary afferents and spinal cord pain transmission neurons (ascending pathways) and on neurons in the midbrain and medulla (descending pathways) that function in pain modulation (Figure 31–1). Other opioid receptors that may be involved in altering reactivity to pain are located on neurons in the basal ganglia, the hypothalamus, the limbic structures, and the cerebral cortex. Three major opioid receptor subtypes have been extensively characterized pharmacologically: μ, δ, and κ receptors. All 3 receptor subtypes appear to be involved in antinociceptive and analgesic mechanisms at both spinal and supraspinal levels. The μ-receptor activation plays a major role in the respiratory depressant actions of opioids and together with κ-receptor activation slows gastrointestinal transit; κ-receptor activation also appears to be involved in sedative actions; δ-receptor activation may play a role in the development of tolerance.

**FIGURE 31–1**

Putative sites of action of opioid analgesics. On the left, sites of action on the pain transmission pathway from the periphery to the higher centers are shown. (A) Direct action of opioids on inflamed or damaged peripheral tissues. (B) Inhibition also occurs in the spinal cord. (C) Possible sites of action in the thalamus. Different thalamic regions project to somatosensory (SS) or limbic (L) cortex. Parabrachial nuclei (medulla/pons) project to the amygdala. On the right, actions of opioids on pain-modulating neurons in the midbrain (D), rostral ventral medulla (E), and the locus coeruleus indirectly control pain transmission pathways by enhancing descending inhibition to the dorsal horn. (Adapted, with permission, from Katzung BG, editor: Basic & Clinical Pharmacology, 12th ed. McGraw-Hill, 2012.)

B. Opioid Peptides

Opioid receptors are thought to be activated by endogenous peptides under physiologic conditions. These peptides, which include endorphins such as β-endorphin, enkephalins, and dynorphins, are synthesized in the cell body and are transported to the nerve endings where they accumulate in synaptic vesicles. On release from nerve endings, they bind to opioid receptors and can be displaced from binding by opioid antagonists. Endorphins have highest affinity for μ receptors, enkephalins for δ receptors, and dynorphins for κ receptors. Although it remains unclear whether these peptides function as classic neurotransmitters, they appear to...
modulate transmission at many sites in the brain and spinal cord and in primary afferents. Opioid peptides are also found in the adrenal medulla and neural plexus of the gut.

C. Ionic Mechanisms

Opioid analgesics inhibit synaptic activity partly through direct activation of opioid receptors and partly through release of the endogenous opioid peptides, which are themselves inhibitory to neurons. All 3 major opioid receptors are coupled to their effectors by G proteins and activate phospholipase C or inhibit adenylyl cyclase. At the postsynaptic level, activation of these receptors can open potassium ion channels to cause membrane hyperpolarization (inhibitory postsynaptic potentials). At the presynaptic level, opioid receptor activation can close voltage-gated calcium ion channels to inhibit neurotransmitter release (Figure 31–2). Presynaptic actions result in the inhibition of release of multiple neurotransmitters, including acetylcholine (ACh), norepinephrine, serotonin, glutamate, and substance P.

FIGURE 31–2

Spinal sites of opioid action. The μ, κ, and δ agonists reduce excitatory transmitter release from presynaptic terminals of nociceptive primary afferents. The μ agonists also hyperpolarize second-order pain transmission neurons by increasing K⁺ conductance, evoking an inhibitory postsynaptic potential (IPSP). (Reproduced, with permission, from Katzung BG, editor: Basic & Clinical Pharmacology, 10th ed. McGraw-Hill, 2007.)

ACUTE EFFECTS

A. Analgesia

The opioids are the most powerful drugs available for the relief of pain. They attenuate both emotional and sensory aspects of the pain experience. Strong agonists (ie, those with the highest analgesic efficacy, full agonists) include morphine, methadone, meperidine, fentanyl, levorphanol, and heroin. Drugs with mixed agonist-antagonist actions (eg, buprenorphine, see below) may antagonize the analgesic actions of full agonists and should not be used concomitantly. Codeine, hydrocodone, and oxycodone are partial agonists with mild to moderate analgesic efficacy. They are commonly available in combinations with acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs). Propoxyphene, a very weak agonist drug, is also available combined with acetaminophen.
B. Sedation and Euphoria

These effects may occur at doses lower than those required for maximum analgesia. The sedation is additive with other CNS depressants, but there is little amnesia. Some patients experience dysphoric effects from opioid drugs. At higher doses, the drugs may cause mental clouding and result in a stuporous, or even a comatose, state.

C. Respiratory Depression

Opioid actions in the medulla lead to inhibition of the respiratory center, with decreased response to carbon dioxide challenge. With full agonists, respiratory depression may be seen at conventional analgesic doses. Increased $P_{CO_2}$ may cause cerebrovascular dilation, resulting in increased blood flow and increased intracranial pressure. Opioid analgesics are relatively contraindicated in patients with head injuries.

D. Antitussive Actions

Suppression of the cough reflex by unknown mechanisms is the basis for the clinical use of opioids as antitussives. This action can be obtained with the use of doses lower than those needed for analgesia.

E. Nausea and Vomiting

Nausea and vomiting are caused by opioid activation of the chemoreceptor trigger zone and are increased by ambulation.

F. Gastrointestinal Effects

Constipation occurs through decreased intestinal peristalsis, which is probably mediated by effects on opioid receptors in the enteric nervous system. This powerful action is the basis for the clinical use of these drugs as antidiarrheal agents.

G. Smooth Muscle

Opioids (with the exception of meperidine) cause contraction of biliary tract smooth muscle, which can result in biliary colic or spasm, increased ureteral and bladder sphincter tone, and a reduction in uterine tone, which may contribute to prolongation of labor.

H. Miosis

Pupillary constriction is a characteristic effect of all opioids except meperidine, which has a muscarinic blocking action. Little or no tolerance occurs. Miosis is blocked by the opioid antagonist naloxone and by atropine.

I. Miscellaneous

Opioid analgesics, especially morphine, can cause flushing and pruritus through histamine release. They cause release of antidiuretic hormone (ADH) and prolactin but may inhibit the release of luteinizing hormone (LH). Exaggerated responses to opioid analgesics may occur in patients with adrenal insufficiency or hypothyroidism.

**SKILL KEEPER: OPIOID PEPTIDES AND SUBSTANCE P**
These peptides are relevant to understanding the analgesic actions of opioid-analgesic drugs in terms of CNS function (See Chapters 6 and 17). What are the roles of these peptides in peripheral tissues? The Skill Keeper Answers appear at the end of the chapter.

**CHRONIC EFFECTS**

**A. Tolerance**

Marked tolerance can develop to the just-mentioned acute pharmacologic effects, with the exception of miosis and constipation. The mechanism of opioid tolerance development may involve receptor uncoupling. Antagonists of glutamate N-methyl-D-aspartate (NMDA) receptors (eg, ketamine), as well as δ-receptor antagonists, are reported to block opioid tolerance. Although there is cross-tolerance between different opioid agonists, it is not complete. This provides the basis for “opioid rotation,” whereby analgesia is maintained (eg, in cancer patients) by changing from one drug to another.

**B. Dependence**

Physical dependence is an anticipated physiologic response to chronic therapy with drugs in this group, particularly the strong agonists. Physical dependence is revealed on abrupt discontinuance as an abstinence syndrome, which includes rhinorrhea, lacrimation, chills, gooseflesh, muscle aches, diarrhea, yawning, anxiety, and hostility. A more intense state of precipitated withdrawal results when an opioid antagonist is administered to a physically dependent individual.

**CLINICAL USES**

**A. Analgesia**

Treatment of relatively constant moderate to severe pain is the major indication. Although oral formulations are most commonly used, buccal and suppository forms of some drugs are available. In the acute setting, strong agonists are usually given parenterally. Prolonged analgesia, with some reduction in adverse effects, can be achieved with epidural administration of certain strong agonist drugs (eg, fentanyl and morphine). Fentanyl has also been used by the transdermal route providing analgesia for up to 72 h. For less severe pain and in the chronic setting, moderate agonists are given by the oral route, sometimes in combinations with acetaminophen or NSAIDs.

**B. Cough Suppression**

Useful oral antitussive drugs include codeine and dextromethorphan. The latter, an over-the-counter drug, has recently been the subject of FDA warnings regarding its abuse potential. Large doses of dextromethorphan may cause hallucinations, confusion, excitation, increased or decreased pupil size, nystagmus, seizures, coma, and decreased breathing.

**C. Treatment of Diarrhea**

Selective antidiarrheal opioids include diphenoxylate and loperamide. They are given orally.

**D. Management of Acute Pulmonary Edema**

Morphine (parenteral) may be useful in acute pulmonary edema because of its hemodynamic actions; its calming effects probably also contribute to relief of the pulmonary symptoms.
E. Anesthesia

Opioids are used as preoperative medications and as intraoperative adjunctive agents in balanced anesthesia protocols. High-dose intravenous opioids (eg, morphine, fentanyl) are often the major component of anesthesia for cardiac surgery.

F. Opioid Dependence

Methadone, one of the longer acting opioids, is used in the management of opioid withdrawal states and in maintenance programs for addicts. In withdrawal states, methadone permits a slow tapering of opioid effect that diminishes the intensity of abstinence symptoms. Buprenorphine (see later discussion) has an even longer duration of action and is sometimes used in withdrawal states. In maintenance programs, the prolonged action of methadone blocks the euphoria-inducing effects of doses of shorter acting opioids (eg, heroin, morphine).

TOXICITY

Most of the adverse effects of the opioid analgesics (eg, nausea, constipation, respiratory depression) are predictable extensions of their pharmacologic effects. In addition, overdose and drug interaction toxicities are very important.

A. Overdose

A triad of pupillary constriction, comatose state, and respiratory depression is characteristic; the latter is responsible for most fatalities. Diagnosis of overdosage is confirmed if intravenous injection of naloxone, an antagonist drug, results in prompt signs of recovery. Treatment of overdose involves the use of antagonists such as naloxone and other therapeutic measures, especially ventilatory support.

B. Drug Interactions

The most important drug interactions involving opioid analgesics are additive CNS depression with ethanol, sedative-hypnotics, anesthetics, antipsychotic drugs, tricyclic antidepressants, and antihistamines. Concomitant use of certain opioids (eg, meperidine) with monoamine oxidase inhibitors increases the incidence of hyperpyrexic coma. Meperidine has also been implicated in the serotonin syndrome when used with selective serotonin reuptake inhibitors.

AGONIST-ANTAGONIST DRUGS

A. Analgesic Activity

The analgesic activity of mixed agonist-antagonists varies with the individual drug but is somewhat less than that of strong full agonists like morphine. Buprenorphine, butorphanol, and nalbuphine afford greater analgesia than pentazocine, which is similar to codeine in analgesic efficacy.

B. Receptors

Butorphanol, nalbuphine, and pentazocine are κ agonists, with weak μ-receptor antagonist activity. Butorphanol may act as a partial agonist or antagonist at the μ receptor.

Buprenorphine is a μ-receptor partial agonist with weak antagonist effects at κ and δ receptors. These characteristics can lead to decreased analgesia, or even precipitate withdrawal symptoms, when such drugs are
used in patients taking conventional full μ-receptor agonists. Buprenorphine has a long duration of effect, binding strongly to μ receptors. Although prolonged activity of buprenorphine may be clinically useful (eg, to suppress withdrawal signs in dependency states), this property renders its effects resistant to naloxone reversal, since the antagonist drug has a short half-life. In overdose, respiratory depression caused by nalbuphine may also be resistant to naloxone reversal. Naloxone is included in some formulations of these agonist-antagonist drugs to discourage abuse.

C. Effects

The mixed agonist-antagonist drugs often cause sedation at analgesic doses. Dizziness, sweating, and nausea may also occur, and anxiety, hallucinations, and nightmares are possible adverse effects. Respiratory depression may be less intense than with pure agonists but is not predictably reversed by naloxone. Tolerance develops with chronic use but is less than the tolerance that develops to the full agonists, and there is minimal cross-tolerance. Physical dependence occurs, but the abuse liability of mixed agonist-antagonist drugs is less than that of the full agonists.

D. Miscellaneous

Tramadol is a weak μ-receptor agonist only partially antagonized by naloxone. Its analgesic activity is mainly based on blockade of the reuptake of serotonin; it is a weak norepinephrine reuptake blocker. Tramadol is effective in treatment of moderate pain and has been used as an adjunct to opioid analgesics in chronic pain syndromes. The drug is relatively contraindicated in patients with a history of seizure disorders, and there is risk of the serotonin syndrome if it is co-administered with SSRIs. No significant effects on cardiovascular functions or respiration have been reported.

Tapentadol has strong norepinephrine reuptake-inhibiting activity (blocked by α antagonists) and only modest μ-opioid receptor affinity. It is less effective than oxycodone in the treatment of moderate to severe pain but causes less gastrointestinal distress and nausea. Tapentadol has been implicated in the serotonin syndrome and should be used with caution in seizure disorders.

OPIOID ANTAGONISTS

Naloxone, nalmefene, and naltrexone are pure opioid receptor antagonists that have few other effects at doses that produce marked antagonism of agonist effects. These drugs have greater affinity for μ receptors than for other opioid receptors. A major clinical use of the opioid antagonists is in the management of acute opioid overdose. Naloxone and nalmefene are given intravenously. Because naloxone has a short duration of action (1–2 h), multiple doses may be required in opioid analgesic overdose. Nalmefene has a duration of action of 8–12 h. Naltrexone has a long elimination half-life, blocking the actions of strong agonists (eg, heroin) for up to 48 h after oral use. Naltrexone decreases the craving for ethanol and is approved for adjunctive use in alcohol dependency programs. Unlike the older drugs, two new antagonists, methylnaltrexone and alvimopan, do not cross the blood-brain barrier. These agents block adverse effects of strong opioids on peripheral μ receptors, including those in the gastrointestinal tract responsible for constipation, with minimal effects on analgesic actions and without precipitating an abstinence syndrome.

QUESTIONS

Questions 1 and 2. A 63-year-old man is undergoing radiation treatment as an outpatient for metastatic bone cancer. His pain has been treated with a fixed combination of oxycodone plus acetaminophen taken orally. Despite increasing doses of the analgesic combination, the pain is getting worse.

1. The most appropriate oral medication for his increasing pain is
2. It is possible that this patient will have to increase the dose of the analgesic as his condition progresses as a result of developing tolerance. However, tolerance will not develop to a significant extent with respect to

- (A) Biliary smooth muscle
- (B) Emesis
- (C) Pupillary constriction
- (D) Sedation
- (E) Urinary retention

3. You are on your way to take an examination and you suddenly get an attack of diarrhea. If you stop at a nearby drugstore for an over-the-counter opioid with antidiarrheal action, you will be asking for

- (A) Codeine
- (B) Dextromethorphan
- (C) Diphenoxylate
- (D) Loperamide
- (E) Nalbuphine

4. An emergency department patient with severe pain thought to be of gastrointestinal origin received 80 mg of meperidine. He subsequently developed a severe reaction characterized by tachycardia, hypertension, hyperpyrexia, and seizures. Questioning revealed that the patient had been taking a drug for a psychiatric condition. Which drug is most likely to be responsible for this untoward interaction with meperidine?

- (A) Alprazolam
- (B) Bupropion
- (C) Lithium
- (D) Phenelzine
- (E) Mirtazapine

5. Genetic polymorphisms in certain hepatic enzymes involved in drug metabolism are established to be responsible for variations in analgesic response to
Questions 6 and 7. A young male patient is brought to the emergency department in an anxious and agitated state. He informs the attending physician that he uses “street drugs” and that he gave himself an intravenous “fix” approximately 12 h ago. He now has chills and muscle aches and has also been vomiting. His symptoms include hyperventilation and hyperthermia. The attending physician notes that his pupil size is larger than normal.

6. What is the most likely cause of these signs and symptoms?
   - (A) The patient had injected dextroamphetamine
   - (B) The patient has hepatitis B
   - (C) The patient has overdosed with an opioid
   - (D) The signs and symptoms are those of the opioid abstinence syndrome
   - (E) These are early signs of toxicity due to contaminants in “street heroin”

7. Which drug will be most effective in alleviating the symptoms experienced by this patient?
   - (A) Buprenorphine
   - (B) Codeine
   - (C) Methadone
   - (D) Naltrexone
   - (E) Tramadol

8. Which statement about nalbuphine is accurate?
   - (A) Activates μ receptors
   - (B) Does not cause respiratory depression
   - (C) Is a nonsedating opioid
   - (D) Pain-relieving action is not superior to that of codeine
   - (E) Response to naloxone in overdose may be unreliable

9. Which drug does not activate opioid receptors, has been proposed as a maintenance drug in treatment programs for opioid addicts, and with a single oral dose, will block the effects of injected heroin for up to 48 h?
   - (A) Buprenorphine
   - (B) Codeine
   - (C) Fentanyl
   - (D) Methadone
   - (E) Tramadol
○ (A) Fentanyl

○ (B) Nalbuphine

○ (C) Naloxone

○ (D) Naltrexone

○ (E) Propoxyphene

10. Which drug is a full agonist at opioid receptors with analgesic activity equivalent to morphine, a longer duration of action, and fewer withdrawal signs on abrupt discontinuance than morphine?

○ (A) Fentanyl

○ (B) Hydromorphone

○ (C) Methadone

○ (D) Nalbuphine

○ (E) Oxycodone

ANSWERS

1. In most situations, pain associated with metastatic carcinoma ultimately necessitates the use of an opioid analgesic that is equivalent in strength to morphine, so hydromorphone, oxymorphone, or levorphanol would be indicated. Pentazocine or the combination of codeine plus salicylate would not be as effective as the original drug combination. Propoxyphene is even less active than codeine alone. Buprenorphine, a mixed agonist-antagonist, is not usually recommended for cancer-associated pain because it has a limited maximum analgesic effect (“ceiling”) and because of possible dysphoric and psychotomimetic effects. The answer is C.

2. Chronic use of strong opioid analgesics leads to the development of tolerance to their analgesic, euphoric, and sedative actions. Tolerance also develops to their emetic effects and to effects on some smooth muscle, including the biliary and the urethral sphincter muscles. However, tolerance does not develop significantly to the constipating effects or the miotic actions of the opioid analgesics. The answer is C.

3. Codeine and nalbuphine could decrease gastrointestinal peristalsis, but not without marked side effects (and a prescription). Dextromethorphan is a cough suppressant. The other 2 drugs listed are opioids with antidiarrheal actions. Diphenoxylate is not available over the counter because it is a constituent of a proprietary combination that includes atropine sulfate (Lomotil). The answer is D.

4. Concomitant administration of meperidine and monoamine oxidase inhibitors such as isocarboxazid or phenelzine has resulted in life-threatening hyperpyrexic reactions that may culminate in seizures or coma. Such reactions have occurred even when the MAO inhibitor was administered more than a week after a patient had been treated with meperidine. Note that concomitant use of selective serotonin reuptake inhibitors and meperidine has resulted in the serotonin syndrome, another life-threatening drug interaction (see Chapter 16). The answer is D.

5. Codeine, hydrocodone, and oxycodone are metabolized by the cytochrome P450 isoform CYP2D6, and variations in analgesic response to these drugs have been attributed to genotypic polymorphisms in this isozyme. In the case of codeine, this may be especially important since the drug is demethylated by
CYP2D6 to form the active metabolite, morphine (see Chapter 5). The answer is B.

6. The signs and symptoms are those of withdrawal in a patient physically dependent on an opioid agonist. They usually start within 6–10 h after the last dose; their intensity depends on the degree of physical dependence, and peak effects usually occur at 36–48 h. Mydriasis is a prominent feature of the abstinence syndrome; other symptoms include rhinorrhea, lacrimation, piloerection, muscle jerks, and yawning. The answer is D.

7. Prevention of signs and symptoms of withdrawal after chronic use of a strong opiate like heroin requires replacement with another strong opioid analgesic drug. Methadone is most commonly used, but other strong μ-receptor agonists would also be effective. Acetaminophen and codeine will not be effective. Beneficial effects of diazepam are restricted to relief of anxiety and agitation. The antagonist drug naltrexone may exacerbate withdrawal symptoms. The answer is C.

8. Nalbuphine and butorphanol are κ agonists, with weak μ-receptor antagonist activity. They have analgesic efficacy superior to that of codeine, but it is not equivalent to that of strong opioid receptor agonists. Although these mixed agonist-antagonist drugs are less likely to cause respiratory depression than strong μ activators, if depression does occur, reversal with opioid antagonists such as naloxone is unpredictable. Sedation is common. The answer is E.

9. The opioid antagonist naltrexone has a much longer half-life than naloxone, and its effects may last 2 d. A high degree of client compliance would be required for naltrexone to be of value in opioid dependence treatment programs. The same reservation is applicable to the use of naltrexone in alcoholism. The answer is D.

10. Fentanyl, hydromorphone, and methadone are full agonists with analgesic efficacy similar to that of morphine. When given intravenously, fentanyl has a duration of action of just 60–90 min. Hydromorphone has poor oral bioavailability. Methadone has the greatest bioavailability of the drugs used orally, and its effects are more prolonged. Tolerance and physical dependence develop, and dissipate, more slowly with methadone than with morphine. These properties underlie the use of methadone for detoxification and maintenance programs. The answer is C.

**SKILL KEEPER ANSWERS: OPIOID PEPTIDES AND SUBSTANCE P**

1. Precursor molecules that release opioid peptides are found at various peripheral sites, including the adrenal medulla and the pituitary gland and in some secretomotor neurons and interneurons in the enteric nervous system (See Chapters 6 and 17). In the gut these peptides appear to inhibit the release of ACh, presumably from parasympathetic nerve endings, and thereby inhibit peristalsis. In other tissues, opioid peptides may stimulate the release of transmitters or act as neurohormones.

2. Substance P, an undecapeptide, is a member of the tachykinin peptide group. It is an important sensory neuron transmitter in the enteric nervous system and in primary afferents involved in nociception. Substance P contracts intestinal and bronchiolar smooth muscle but is an arteriolar vasodilator (possibly via nitric oxide release). It may also play a role in renal and salivary gland functions.

**CHECKLIST**

*When you complete this chapter, you should be able to:*

- [ ] Identify 3 opioid receptor subtypes and describe 2 ionic mechanisms that result from such activation.
- Name the major opioid agonists, rank them in terms of analgesic efficacy, and identify specific dynamic or kinetic characteristics.

- Describe the cardinal signs and treatment of opioid drug overdose and of the withdrawal syndrome.

- List acute and chronic adverse effects of opioid analgesics.

- Identify an opioid receptor antagonist and a mixed agonist-antagonist.

- Identify opioids used for antitussive effects and for antidiarrheal effects.

**DRUG SUMMARY TABLE: OPIOIDS, OPIOID SUBSTITUTES, & OPIOID ANTAGONISTS**

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<tr>
<th>Subclass</th>
<th>Mechanism of Action (Receptors)</th>
<th>Clinical Applications</th>
<th>Pharmacokinetics &amp; Interactions</th>
<th>Toxicities</th>
</tr>
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<tbody>
<tr>
<td><strong>Strong agonists</strong></td>
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<tr>
<td>Fentanyl, hydromorphone, meperidine, morphine, methadone, oxymorphone</td>
<td>Strong μ agonists• variable δ and κ agonists</td>
<td>Severe pain, anesthesia (adjunctive) • dependence maintenance (methadone)</td>
<td>Hepatic metabolism • duration: 1–4 h (methadone 4–6 h)</td>
<td>Respiratory depression, constipation, addiction liability</td>
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<tr>
<td><strong>Partial agonists</strong></td>
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<tr>
<td>Codeine, hydrocodone</td>
<td>As above, but lower affinity</td>
<td>Mild-to-moderate pain; cough (codeine) • analgesic combinations with NSAIDs and acetaminophen</td>
<td>Genetic variations in metabolism</td>
<td>As above, but weaker</td>
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<tr>
<td><strong>Mixed agonist-antagonist</strong></td>
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<tr>
<td>Buprenorphine</td>
<td>Partial μ agonist and κ antagonist</td>
<td>Moderate-to-severe pain • dependence maintenance, reduces craving for alcohol (buprenorphine)</td>
<td>Buprenorphine (long duration) • Nalbuphine (parenteral only)</td>
<td>Like strong agonists but can antagonize their effects</td>
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<tr>
<td>Nalbuphine</td>
<td>κ agonist and μ antagonist</td>
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<tr>
<td><strong>Antagonists</strong></td>
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<tr>
<td>Naloxone, naltrexone, nalmefene</td>
<td>Antagonists at all opioid receptors</td>
<td>Opioid overdose • dependence maintenance (naltrexone)</td>
<td>Duration: naloxone 2 h • naltrexone and nalmefene &gt;10 h</td>
<td>Rapid antagonism of all opioid actions</td>
</tr>
<tr>
<td><strong>Antitussives</strong></td>
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<tr>
<td>Codeine, dextromethorphan</td>
<td>Mechanism uncertain • Weak μ agonist • inhibits norepinephrine and 5-HT transporters</td>
<td>Acute debilitating cough</td>
<td>Duration: 0.5–1 h</td>
<td>Reduce cough reflex • toxic in overdose</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Moderate pain • adjunctive</td>
<td></td>
<td>Toxic in</td>
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Favorite Table | Print
Tramadol

Weak μ agonist, blocks serotonin reuptake to opioids in chronic pain states

Duration: 4–6 h

overdose (seizures)

NSAIDs, nonsteroidal anti-inflammatory drugs.

undefined

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