

Opioid Analgesics

Dr.Samaher Jaber Younis

BCPS

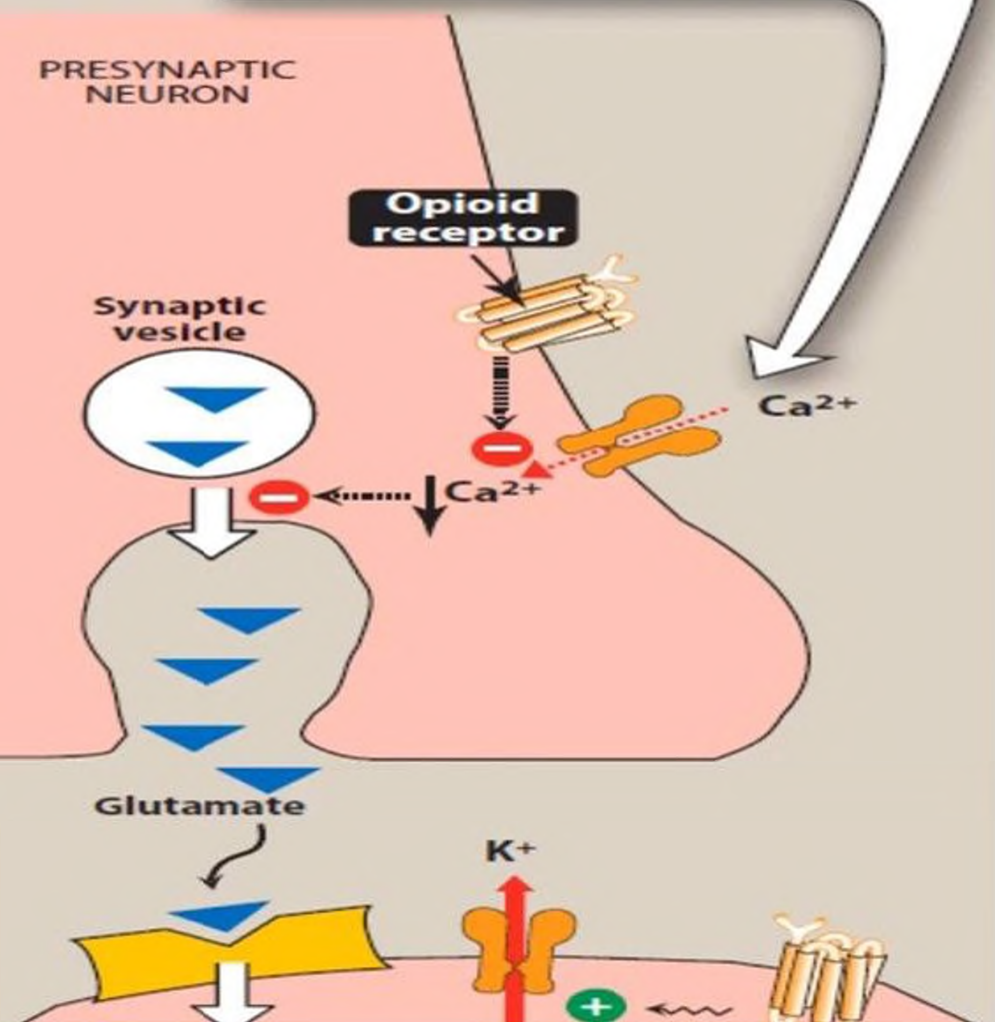
Management of pain is one of clinical medicine's greatest challenges. Pain is defined as an unpleasant sensation that can be either acute or chronic and is a consequence of complex neurochemical processes in the peripheral and central nervous systems (CNS). It is subjective and the clinician must rely on the patient's perception and description of pain. Alleviation of pain depends on the specific type of pain (nociceptive or neuropathic pain). For example, with mild-to-moderate arthritic pain (nociceptive pain), nonopioid analgesics such as nonsteroidal anti-inflammatory drugs are often effective. Neuropathic pain responds best to anticonvulsants, tricyclic antidepressants, or serotonin/norepinephrine reuptake inhibitors. However, for severe acute pain or chronic malignant or nonmalignant pain, opioids can be considered as part of the treatment plan in select patients.

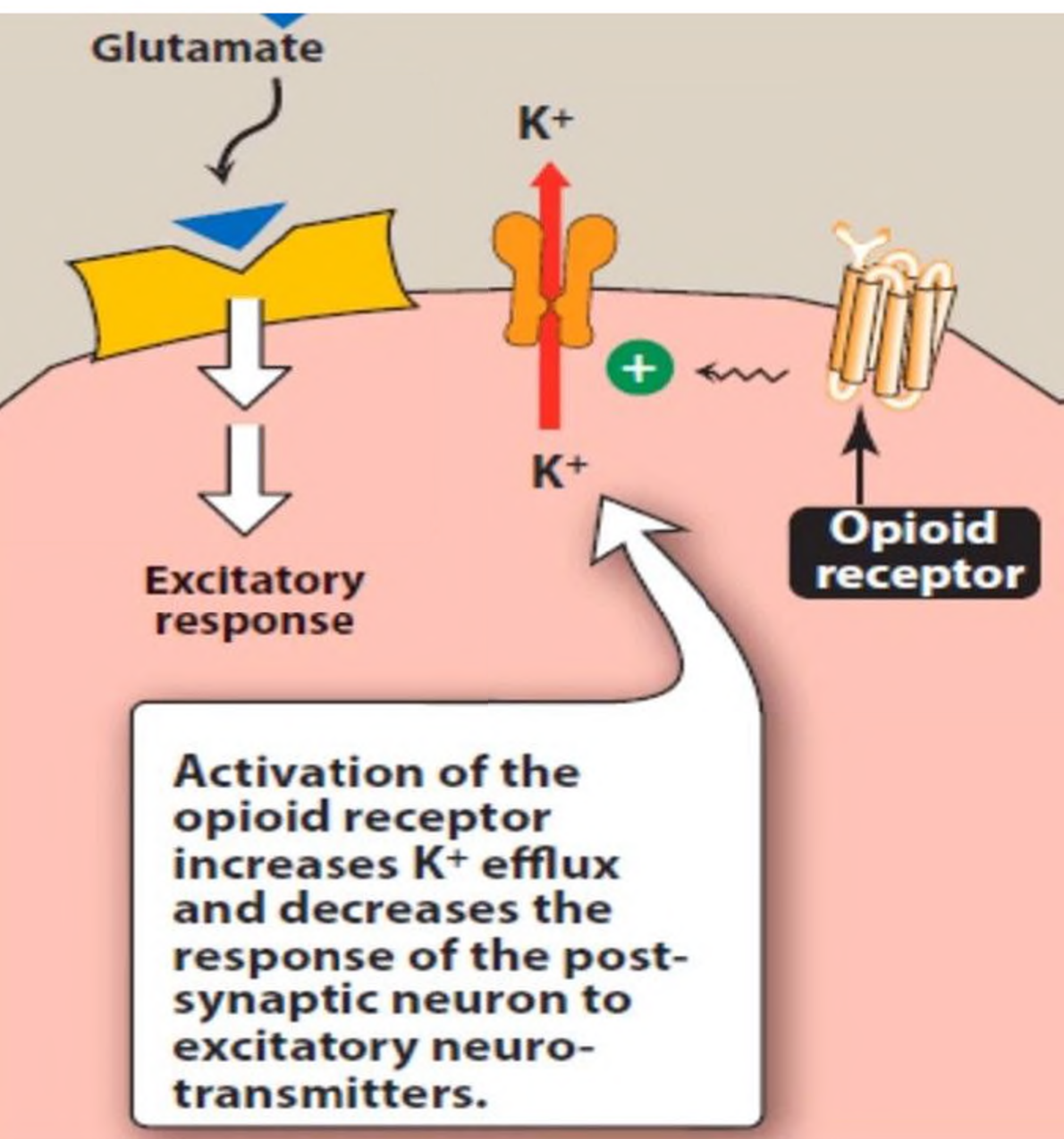
Opioids are natural, semisynthetic, or synthetic compounds that produce *morphine*-like effects. These agents are divided into chemical classes based on their chemical structure. All opioids act by binding to specific opioid receptors in the CNS to produce effects that mimic the action of endogenous peptide neurotransmitters (for example, endorphins, enkephalins, and dynorphins). Although the opioids have a broad range of effects, their primary use is to relieve intense pain that results from surgery, injury, or chronic disease. Unfortunately, widespread availability of opioids has led to abuse of agents with euphoric properties. Antagonists that reverse the actions of opioids are also clinically important for use in cases of overdose.

OPIOID RECEPTORS

The major effects of the opioids are mediated by three main receptor families, commonly designated as μ (mu, MOR), κ (kappa, KOR), and δ (delta, DOR). Each receptor family exhibits a different specificity for the drug(s) it binds. The analgesic properties of the opioids are primarily mediated by the μ receptors that modulate responses to thermal, mechanical, and chemical nociception. The κ receptors in the dorsal horn also contribute to analgesia by modulating the response to chemical and thermal nociception. The enkephalins interact more selectively with δ receptors in the periphery. All three opioid receptors are members of the G protein–coupled receptor family and inhibit adenylyl cyclase. They are also associated with ion channels, increasing postsynaptic K^+ efflux (hyperpolarization) or reducing presynaptic Ca^{2+} influx, thus impeding neuronal firing and transmitter release in the spinal dorsal horn.

Activation of the opioid receptor decreases Ca^{2+} influx in response to incoming action potential. This decreases release of excitatory neurotransmitters, such as glutamate.





OPIOID AGONISTS

Natural

Morphine

Codeine

Semisynthetic

Buprenorphine

Hydromorphone

Hydrocodone

Oxycodone

Oxymorphone

Synthetic

Fentanyl

Meperidine

Methadone

Tapentadol

Tramadol

Morphine

Morphine is a plant alkaloid isolated from the latex of opium poppy (*Papaver somiferum*). *Morphine* was isolated from opium and named representing the Greek God of Dreams "*Morpheus*." The name "opium" was derived from the Greek word "*opos*," which means *juice*. The compounds derived from *morphine* are generalized as "opiates." The receptor on which morphine acts is called opioid receptors. Endorphins are the endogenous peptide ligands found in the brain for opioid receptors. The addictive liability of compounds associated with opioids and other compounds are generally called narcotics. In the legal context, the Greek word "*narkotikos*" which means "*benumbing*" or the "state of stupor" refers to substances of abuse or substances with addictive liabilities.

Mechanism of action:

Morphine and other opioids exert analgesic effects by interacting stereospecifically with opioid receptors on the membranes of neuronal cells in the CNS and other anatomic structures, such as the smooth muscles of the gastrointestinal (GI) tract and the urinary bladder. *Morphine* is somewhat selective to the μ opioid receptor, but has some affinity for the κ and δ receptors. *Morphine* also inhibits the release of many excitatory transmitters from nerve terminals carrying nociceptive (painful) stimuli.

Actions:

- a. Analgesia: *Morphine* and other opioids relieve pain by raising the pain threshold at the spinal cord level and by altering the brain's perception of pain.
- b. Euphoria: *Morphine* produces a powerful sense of contentment and well-being. Euphoria may be caused by disinhibition of the dopamine-containing neurons of the ventral tegmental area. In normal pain-free individuals, analgesic doses of *morphine* can cause dysphoria.
- c. Respiration: *Morphine* causes respiratory depression by reduction of the responsiveness of medullary respiratory center neurons to carbon dioxide. This can occur with ordinary doses of *morphine* in patients who are opioid-naïve and can be accentuated as the dose is increased, until ultimately respiration ceases. Respiratory depression is the most common cause of death in acute opioid overdoses. Tolerance to this effect develops with repeated dosing, which allows for the safer use of *morphine* for the treatment of pain when the dose is correctly titrated.

d. Depression of cough reflex: Both *morphine* and *codeine* have antitussive properties. In general, cough suppression does not correlate closely with analgesic and respiratory depressant properties of opioid drugs. The receptors involved in the antitussive action appear to be different from those involved in analgesia.

e. Miosis: The pinpoint pupil characteristic of *morphine* results from stimulation of μ and κ receptors at the Edinger–Westphal nucleus. There is little tolerance to this effect. [Note: This is important diagnostically, because many other causes of coma and respiratory depression produce dilation of the pupil.]

f. Emesis: *Morphine* directly stimulates the chemoreceptor trigger zone in the area postrema that causes vomiting.

g. GI tract: *Morphine* relieves diarrhea by decreasing the motility and increasing the tone of the intestinal circular smooth muscle. *Morphine* also increases the tone of the anal sphincter. *Morphine* and other opioids produce constipation, with little tolerance developing. *Morphine* can also increase biliary tract pressure due to contraction of the gallbladder and constriction of the biliary sphincter (sphincter of Oddi). It can aggravate biliary colic pain to multiple folds. This *morphine*-induced biliary pain is relieved partially by the administration of *atropine* and completely by opioid antagonists such as *naloxone* and other smooth muscle relaxants such as *papaverine*.

h. Cardiovascular: *Morphine* has no major effects on blood pressure or heart rate at lower dosages, but hypotension and bradycardia may occur at higher doses. Because of respiratory depression and carbon dioxide retention, cerebral vessels dilate and increase cerebrospinal fluid pressure. *Morphine* is usually contraindicated in individuals with head trauma or severe brain injury

- i. Histamine release: *Morphine* releases histamine from mast cells causing urticaria, sweating, and vasodilation. Because it can cause bronchoconstriction, *morphine* should be used with caution in patients with asthma.
- j. Hormonal actions: Prolonged use of *morphine* may lead to opioid-induced androgen deficiency due to suppression of the hypothalamic-pituitary-gonadal axis (HPA). This results in decreased production of sex hormones, especially testosterone, resulting in many clinical symptoms.
- k. Labor: *Morphine* may prolong the second stage of labor by transiently decreasing the strength, duration, and frequency of uterine contractions.
- l. Thermoregulation: *Morphine* decreases the body temperature slightly due to its effect on hypothalamus heat-regulating mechanisms. In opioid withdrawal, elevated body temperature has been observed.
- m. Immune system: *Morphine* shows both direct and indirect effects (through centrally mediated neuronal mechanisms) on the immune system. Opioids in general cause moderate immunosuppression which makes the recipient susceptible for infections and tumor metastasis.

Therapeutic Use	Comments
Analgesia	<i>Morphine</i> is the prototype opioid agonist. Opioids are used for pain in trauma, cancer, and other types of severe pain.
Treatment of diarrhea	Opioids decrease the motility and increase the tone of intestinal circular smooth muscle. [Note: Agents commonly used include <i>diphenoxylate</i> and <i>loperamide</i> (see Chapter 31).]
Relief of cough	<i>Morphine</i> does suppress the cough reflex, but <i>codeine</i> and <i>dextromethorphan</i> are more commonly used.
Treatment of acute pulmonary edema	Intravenous <i>morphine</i> dramatically relieves dyspnea caused by pulmonary edema associated with left ventricular failure, possibly via the vasodilatory effect. This, in effect, decreases cardiac preload and afterload, as well as anxiety experienced by the patient.
Anesthesia	Opioids are used as pre-anesthetic medications, for systemic and spinal anesthesia, and for postoperative analgesia.

Pharmacokinetics:

- a. Administration: *Morphine* has a linear pharmacokinetic profile; however, absorption of morphine after oral administration is slow and erratic. Extended-release oral preparations provide more consistent plasma levels. Because significant first-pass metabolism of *morphine* occurs in the liver, subcutaneous and IV injections produce the most reliable response.
- b. Distribution: *Morphine* rapidly enters all body tissues, including the fetuses of pregnant women. It should not be used for analgesia during labor. Infants born to addicted mothers show physical dependence on opioids and exhibit withdrawal symptoms if opioids are not administered. Only a small percentage of *morphine* crosses the blood–brain barrier, because *morphine* is the least lipophilic of the common opioids. By contrast, the more lipid-soluble opioids, such as *fentanyl* and *methadone*, readily penetrate the CNS.

c. Fate: *Morphine* is conjugated with glucuronic acid in the liver to two active metabolites (morphine-6-glucuronide [M6G] and morphine-3-glucuronide [M3G]) which are renally excreted. M6G is a very potent analgesic, and morphine glucuronide metabolites undergo enterohepatic circulation. M3G does not have analgesic activity, but is believed to cause neuroexcitatory effects. The duration of action of *morphine* is 4 to 5 hours when administered systemically to opioid-naive individuals, but considerably longer when injected epidurally because the low lipophilicity prevents redistribution from the epidural space.

Adverse effects:

Many adverse effects are common across the entire opioid class. With most μ agonists, severe respiratory depression can occur and may result in death from acute opioid overdose. Respiratory drive may be suppressed in patients with respiratory disorders such as obstructive sleep apnea, emphysema, or cor pulmonale, so close monitoring is necessary when using opioids. Opioid-induced constipation (OIC) is a common adverse effect.

Initial management includes a nonprescription stimulant laxative such as *senna*. Peripherally acting μ -opioid receptor antagonists such as *methylnaltrexone*, *naloxegol*, and *naldemedine* are prescription drugs available for the treatment of OIC. [Note: *Lubiprostone* is a chloride channel activator that is indicated for OIC and irritable bowel syndrome. *Morphine* should be used with caution in patients with liver disease and renal dysfunction.

Tolerance and physical dependence:

Repeated use produces tolerance to the respiratory depressant, analgesic, euphoric, emetic, and sedative effects of *morphine*. Tolerance usually does not develop to miosis (constriction of the pupils) or constipation. Physical and psychological dependence can occur with *morphine* and other agonists. Withdrawal produces a series of autonomic, motor, and psychological responses such as goosebumps, muscle spasms, hyperalgesia, lacrimation, rhinorrhea, yawning, sweating, restlessness, dilated pupils, anorexia, irritability, tremors, diarrhea, and flushing that can be severe. The abstinence withdrawal peaks at 48 to 72 hours, though generally it is not life threatening except in neonates and the severely debilitated. Administration of an opioid antagonist may precipitate a severe withdrawal reaction.

Drug interactions: Drug interactions with *morphine* are possible. The depressant actions of *morphine* are enhanced by coadministration with CNS depressant medications such as phenothiazines, monoamine oxidase inhibitors (MAOIs), and benzodiazepines. Guidelines for opioid prescribing urge clinicians to avoid simultaneous prescribing of opioids and benzodiazepines. A black box warning also has been included on the labeling of both opioids and benzodiazepines to alert prescribers of this dangerous combination.

Opioid	Equivalence to 5 mg IV Morphine
PO Morphine	15 mg
PO Hydromorphone	3 mg
PO Hydrocodone	10-15 mg
PO Oxycodone	7.5-10 mg
PO Codeine	100 mg
PO Tramadol	60 mg
IV Morphine	5 mg
IV Fentanyl	0.05 mg (50 mcg)
IV Hydromorphone	0.7 mg

Phenanthrenes	Action on Opioid Receptors
<i>Morphine</i>	Agonist
<i>Codeine</i>	Agonist
<i>Oxycodone</i>	Agonist
<i>Oxymorphone</i>	Agonist
<i>Hydromorphone</i>	Agonist
<i>Hydrocodone</i>	Agonist
<i>Levorphanol</i>	Agonist
<i>Buprenorphine</i>	Partial agonist/Antagonist
<i>Nalbuphine</i>	Mixed agonist/Antagonist
<i>Butorphanol</i>	Mixed agonist/Antagonist
<i>Naloxone</i>	Antagonist
Benzmorphan	
<i>Pentazocine</i>	Mixed agonist/Antagonist

Phenylpiperidines	
<i>Fentanyl</i>	Agonist
<i>Alfentanil</i>	Agonist
<i>Remifentanyl</i>	Agonist
<i>Sufentanil</i>	Agonist
<i>Meperidine</i>	Agonist
Diphenylheptane	
<i>Methadone</i>	Agonist
Phenylpropylamines	
<i>Tramadol</i>	Agonist
<i>Tapentadol</i>	Agonist

Opioid	Routes of Administration	Comments
<i>Morphine</i>	PO (IR and ER), PR, IM, IV, SC, IA, SL, EA	• For all drugs listed: opioid class side effects (Figure 14.9). Metabolism through conjugation in liver and P-glycoprotein. • Active metabolites are renally eliminated and accumulate in renal impairment. • Metabolite M3G has no analgesic action, but can be neuroexcitatory. • Metabolite M6G is two to four times more potent than parent drug; accumulation can cause oversedation and respiratory depression. • Abuse deterrent formulations available.
<i>Methadone</i>	PO, IV, IM, SC	• No active metabolites. • Racemic mixture • Metabolized by many CYP450 isoenzymes: High risk of drug interactions. • Substrate of P-glycoprotein • Long and variable half-life increases risks of overdose. • Very lipophilic and redistributes to fat stores. • Duration of analgesia is much shorter than elimination half-life. Repeated dosing can lead to accumulation. • Can prolong QTc interval and cause torsades de pointes. • Warning: Conversion to and from <i>methadone</i> and other opioids should be done with great care, since equianalgesic dosing varies dramatically.

Fentanyl	IV, EA, IA, TD, OTFC, SL, Buccal, Nasal	• No active metabolites; option for patients with renal dysfunction but should be used with caution. • Metabolized by CYP3A4. • 100 times more potent than <i>morphine</i>. • Less histamine release, sedation, and constipation in comparison to <i>morphine</i>.
Oxycodone	PO (IR and CR)	• Metabolized by CYP2D6 and CYP3A4. • Black box warning: CYP3A4 drug interactions. • Less histamine release and nausea in comparison to <i>morphine</i>. • Abuse-deterrent formulation available.
Oxymorphone	PO (IR and ER), IV	• Immediate release has longer duration of action and elimination half-life (8 hours) compared to other immediate-release opioids. • Oral bioavailability increases with food. • Should be administered 1 to 2 hours after eating. • Bioavailability increased with coadministration of alcohol.
Hydromorphone	PO (IR and ER), PR, IV, SC, EA, IA	• Metabolized via glucuronidation to H6G and H3G which are renally eliminated and can cause CNS side effects in patients with renal insufficiency. • Abuse-deterrent formulation available.
Hydrocodone	PO (IR and ER)	• Active metabolite is <i>hydromorphone</i>. • Metabolized by CYP2D6 and CYP3A4. • Abuse-deterrent formulations available.
Tapentadol	PO (IR and ER)	• Centrally acting analgesic; μ agonist activity along with inhibition of norepinephrine reuptake. • Efficacy in treating nociceptive and neuropathic pain. • Metabolized predominately by glucuronidation; no CYP450 interactions. • Seizures and serotonin syndrome can occur in predisposed patients.

Tramadol	PO (IR, ODT, and ER), Topically	- Metabolized by Phase 1 and 2. CYP2D6, CYP2B6, and CYP3A4 involved in metabolism; watch drug interactions. - Serotonin syndrome can occur due to drug interactions. - CI for treatment of pain in children < 12 y/o. - CI in children < 18 y/o after removal of tonsils/adenoids. - Recommended not to use in 12-18 y/o who are obese, severe lung disease, or sleep apnea. - Use is not recommended in breastfeeding mothers due to adverse reactions in breastfed infants. - Warning: - Renal impairment dosing required. - Review dosing recommendations in severe hepatic impairment.
Codeine	PO, SC	- Prodrug: Metabolized by CYP2D6 to the active drug <i>morphine</i>. - Rapid and poor metabolizers of CYP2D6 can experience toxicity. - Inhibitors of CYP2D6 will prevent conversion of <i>codeine</i> to <i>morphine</i>, thereby preventing pain control. - Do not use in patients with renal dysfunction. - Use only for mild or moderate pain. - CI in treatment of pain or cough in children < 12 years old. - CI in children < 18 years old after removal of tonsils/adenoids. - Recommended not to use in 12-18 years old who are obese, have severe lung disease, or have sleep apnea. - Use is not recommended in breastfeeding mothers due to adverse reactions in breastfed infants.
Meperidine	PO, IV, SC, EA, IA	- Not recommended as first-line opioid choice. - Active metabolite normeperidine accumulates with renal dysfunction, leading to toxicity. <i>Naloxone</i> does not antagonize the effects of normeperidine; could worsen seizure activity. - Do not use in elderly, patients with renal dysfunction, or for chronic pain management.
Buprenorphine	SL, TD, IM, IV, Buccal (transmucosal), Implant	- Long duration of action; very lipophilic. - Incompletely reversible by <i>naloxone</i>. - Drug interactions: contraindicated with <i>atazanavir</i>, <i>conivaptan</i>, MAO inhibitors; metabolized by primarily by CYP3A4. - Can prolong QTc interval. - Avoid use in patients with hypokalemia, atrial fibrillation, or unstable heart failure, or other predisposing factors increasing QT abnormalities. - Transdermal patch is applied every 7 days. - Abuse-deterrent formulations available.

CI = contraindicated; CR = controlled-release; EA = epidural anesthesia; IA = intrathecal anesthesia; IM = intramuscular; IR = immediate release; IV = intravenous; OTFC = oral transmucosal fentanyl citrate; PO = orally PR = rectally; SC = subcutaneous; SL = sublingual; TD = transdermal; M3G = morphine-3-glucuronide; M6G = morphine-6-glucuronide; NMDA = N-methyl-D-aspartate; H6G = hydromorphone-6-glucuronide; H3G = hydromorphone-3-glucuronide Note: Many different acronyms may be used to indicate a medication is extended-release. Examples include CR (controlled-release), LA (long-acting), ER (extended-release)