Opioids

Pain

- Pain is an unpleasant sensation that can be acute or chronic and involves complex neurochemical processes in the peripheral and central nervous system
- Pain is subjective, and the physician must rely on the patients' perception and description of their pain
- For mild to moderate pain NSAIDs like ibuprofen are used
- Neurogenic pain responds best to anticonvulsants (e.g pregabalin), tricyclic antidepressants (amitriptyline), or SNRI (duloxetine)
- For severe or chronic pain **opioids** are the drug of choice

Opioids

- Opioids are natural or synthetic compounds that produce morphine like effects
- “Opiate” is the term used for drugs obtained from opium poppy such as morphine and codeine
- Opioids are used to relieve intense pain, like post-surgery pain or pain caused by diseases like cancer
- Opioids with euphoric effects have abuse potential
- Mechanism of action:
  - Bind to μ opioid receptors relieving pain
  - Mimic the action of endogenous peptide neurotransmitters (endorphins, enkephalins, and dynorphins)

Therapeutic Use	Comments
Analgesia	Morphine 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 diphenoxylate and loperamide (see Chapter 31).]
Relief of cough	Morphine does suppress the cough reflex, but codeine and dextromethorphan are more commonly used.
Treatment of acute pulmonary edema	Intravenous morphine 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.

Figure 14.6
Selected clinical uses of opioids.

Opioid receptors

- Three major receptor families μ (mu), κ (kappa), and δ (delta)
- G protein–coupled receptor family and inhibit adenylyl cyclase
- Also associated with ion channels, increasing postsynaptic K+ efflux (hyperpolarization) or reducing presynaptic Ca^{2+} influx, thus slowing neuronal firing and transmitter release
- The analgesic properties of the opioids are mediated by the μ receptors
- κ receptors in the dorsal horn also contribute (e.g butorphanol and nalbuphine owe their analgesic effect to κ-receptor activation)
- Enkephalins interact more selectively with the δ receptors in the periphery

Opioids

- Strong agonists (High affinity for μ receptors)
  - Morphine
  - Hydromorphone
  - Oxymorphone
  - Heroin
  - Fentanyl
  - Hydrocodone
  - Methadone
  - Oxycodone
  - Meperidine

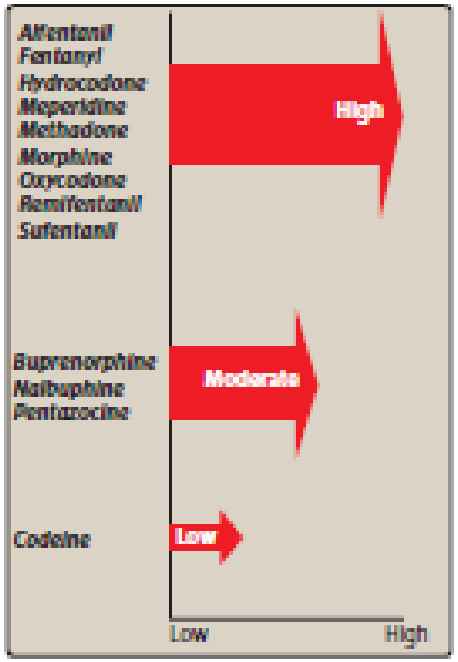


Figure 14.7
A comparison of opioid agonist efficacy.

Opioids and opioid antagonists

- Moderate/low agonists
  - Codeine
- Mixed agonist-antagonists and partial agonists
  - Pentazocine
  - Butorphanol
  - Buprenorphine
  - Nalbuphine
- Antagonists
  - Naloxone
  - Naltrexone
- Other analgesics
  - Tramadol
  - Tapentadol

Strong agonists

Morphine:

- The major analgesic drug contained in crude opium
- Has high affinity for μ receptors
- Mechanism of action:
  - μ-Receptor agonist
  - Opioids cause hyperpolarization of nerve cells, inhibition of nerve firing, and presynaptic inhibition of transmitter release
  - Morphine acts at κ receptors in the dorsal horn of the spinal cord, and decreases the release of substance P, which modulates pain perception in the spinal cord
  - Morphine inhibits the release of many excitatory transmitters from nerve terminals carrying nociceptive (painful) stimuli

Morphine

- Actions:
  - Analgesia (relief of pain without loss of consciousness)
  - Euphoria: powerful sense of contentment and well being
  - Respiratory depression by reduction of the sensitivity of respiratory center neurons to carbon dioxide
    (main cause of death in overdose)
    - Tolerance to this effect develops quickly with repeated dosing, which allows the safe use of morphine for the treatment of pain
  - Depression of cough reflex (antitussive effects)
  - Miosis (Pinpoint pupil; important for diagnosis of morphine abuse)

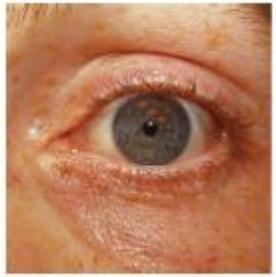


Figure 14.8
Characteristic pinpoint pupil associated with morphine use.

Morphine

- Actions
  - Emesis: due to triggering of chemoreceptor zone
  - GI effects: constipation
  - Cardiovascular: at large doses hypotension and bradycardia may occur
  - Histamine release: Morphine releases histamine from mast cells, causing urticaria, sweating, and vasodilation, can cause bronchoconstriction
  - Hormonal actions: Morphine increases growth hormone release and enhances prolactin secretion, and ADH

Morphine

- Therapeutic uses:
  - Analgesia
  - Treatment of acute pulmonary edema: IV morphine relieves dyspnea by its vasodilatory effect
- Administered IM, SC, IV

(significant first pass effect)

- In case of chronic neoplastic pain, morphine can be administered as extended release tablets or pumps that allow the patient to control pain through self administration

Morphine

- Not used for analgesia during labor
- Infants born of addicted mothers show physical dependence and exhibit withdrawal symptoms if opioids are not administered

Morphine

- Adverse effects
  - Respiratory depression
  - Hypotension
  - Vomiting
  - Tolerance and physical dependence: Repeated morphine use causes tolerance to respiratory depressant, analgesic and euphoric effects
- Detoxification of morphine-dependent individuals is accomplished through the oral administration of methadone, buprenorphine or clonidine
- Morphine should be used cautiously in patients with bronchial asthma, liver failure, or impaired renal function

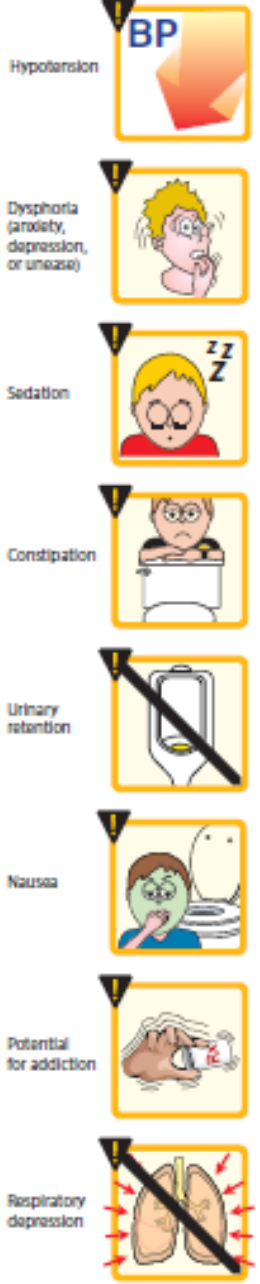


Figure 14.9
Adverse effects commonly observed in individuals treated with opioids.

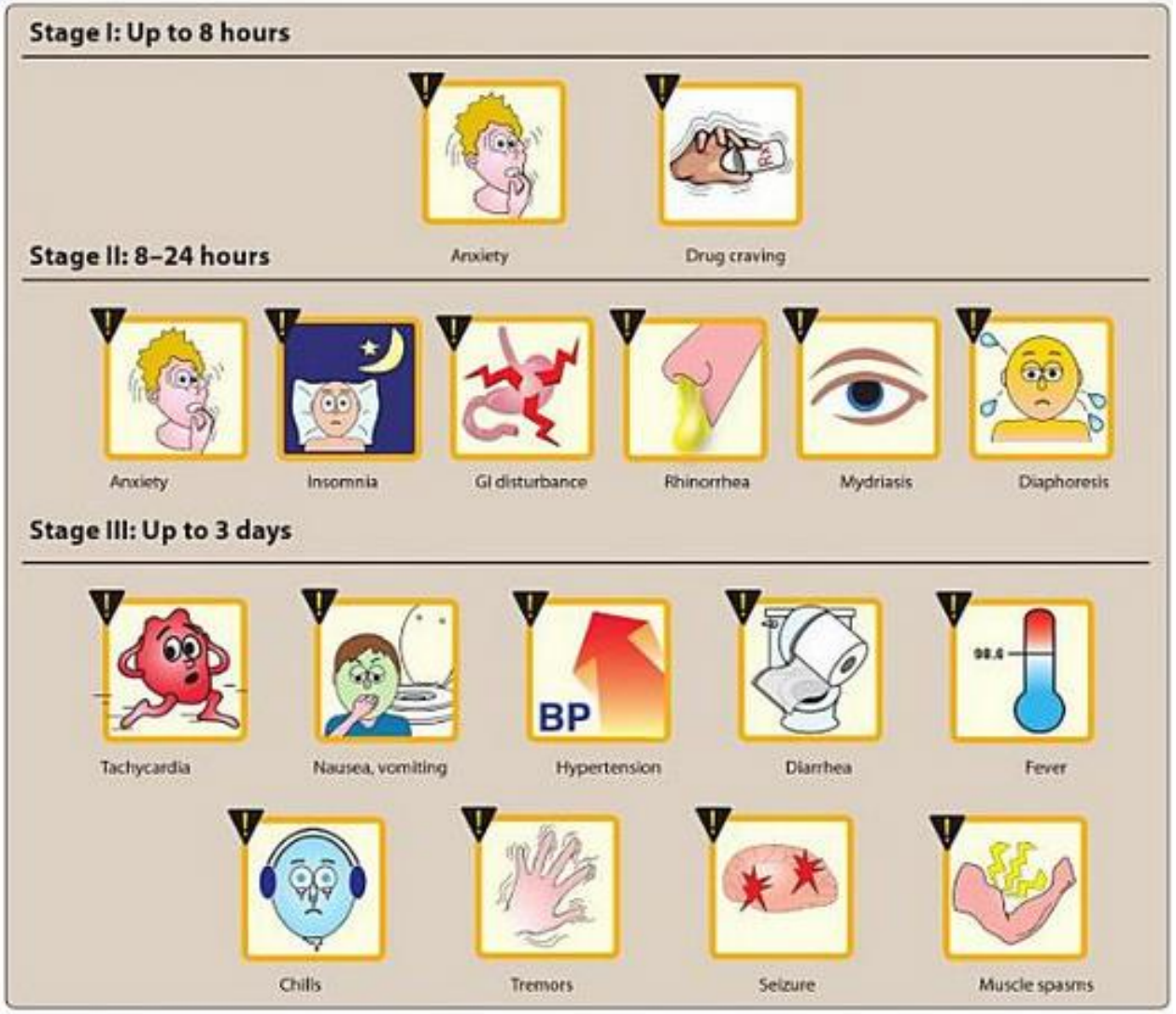
Meperidine

- A synthetic opioid used for acute pain
- Mechanism of action: Meperidine binds to opioid receptors, particularly μ receptors providing analgesia
- Adverse effects
  - Respiratory depression
  - Repeated administration can cause anxiety, tremors, muscle twitches, and rarely convulsions, due to the accumulation of the neurotoxic metabolite normeperidin

Methadone

- μ-Receptor agonist
- NMDA receptor antagonist, useful in treatment of neurogenic pain
- Causes less euphoria and less dependence than morphine
- Uses:
  - Analgesia
  - Controlling withdrawal symptoms of dependent abusers of morphine and heroin

Opioids withdrawal syndrome



Fentanyl

- μ-Receptor agonist
- Has 100-fold the analgesic potency of morphine
- Used in anesthesia
- Administered IV, epidurally or intrathecally
- Epidural fentanyl is used to induce anesthesia and for analgesia post-operatively and during labor
- Can cause hypoventilation
- Sufentanil, alfentanil, and remifentanil are related to fentanyl

Heroin

- Synthetic derivative of morphine
- 3 times more potent than morphine
- Causes more euphoria than morphine
- **No medical use**

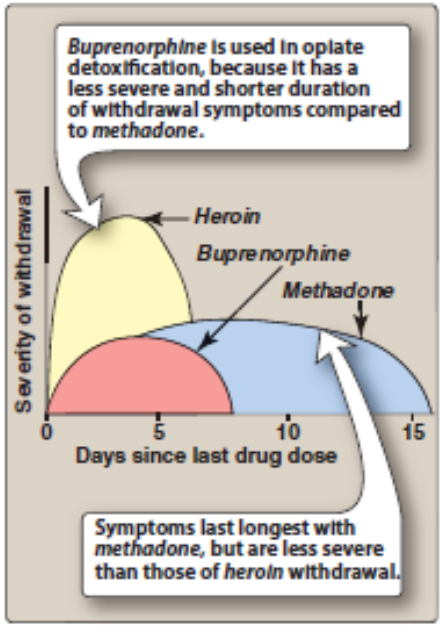


Figure 14.11
Severity of opioid withdrawal symptoms after abrupt withdrawal of equivalent doses of *heroin*, *buprenorphine*, and *methadone*.

Opioids

- Oxycodone
  - Orally active and is sometimes formulated with aspirin or acetaminophen
  - Used to treat moderate to severe pain Oxymorphone
- Oxymorphone
  - Narcotic analgesic
- Hydromorphone
  - Oral hydromorphone is 8–10 times more potent than oral morphine as an analgesic and is used most often to treat severe pain
- Hydrocodone
  - Analgesic potency of oral hydrocodone is approximately that of morphine
  - Hydrocodone is often combined with acetaminophen or ibuprofen to treat moderate-to-severe pain

Codeine

- Moderate/low agonist
- Good antitussive activity at doses that do not cause analgesia
- Metabolized to morphine in the body by CYP2D6 causing analgesic effects (30% that of morphine)
- Causes euphoria
- Lower abuse potential than morphine at commonly used doses

Mixed agonist–antagonists & partial agonists

- Mixed agonist–antagonists: Drugs that stimulate one receptor but block another

- The effects of these drugs depend on previous exposure to opioids
  - In individuals who have not recently received opioids (naïve patients), mixed agonist–antagonists show agonist activity and are used to relieve pain
  - In patient with opioid dependence, the agonist–antagonist drugs may show primarily blocking effects and produce withdrawal symptoms

Pentazocine

- Acts as an agonist on κ receptors and a weak antagonist at μ and δ receptors
- Pentazocine promotes analgesia by activating receptors in the spinal cord, and it is used to relieve moderate pain
- Produces less euphoria than morphine
- Causes respiratory depression at higher doses
- High doses increase blood pressure and can cause hallucinations, nightmares, dysphoria, tachycardia, and dizziness
- In angina, pentazocine increases the mean aortic pressure and pulmonary arterial pressure increasing the work of the heart
- Does not antagonize the respiratory depression of morphine
- Tolerance and dependence develop on repeated use

Buprenorphine

- Partial μ receptor agonist
- Acts like morphine in naive patients
- Can precipitate withdrawal in morphine users
- Used in opiate detoxification, has less severe and shorter duration of withdrawal symptoms compared to methadone
- Has a long duration of action because of its tight binding to the μ receptor
- Adverse effects
  - Respiratory depression that cannot easily be reversed by naloxone
  - Nausea
  - Dizziness

Other analgesics

Tramadol

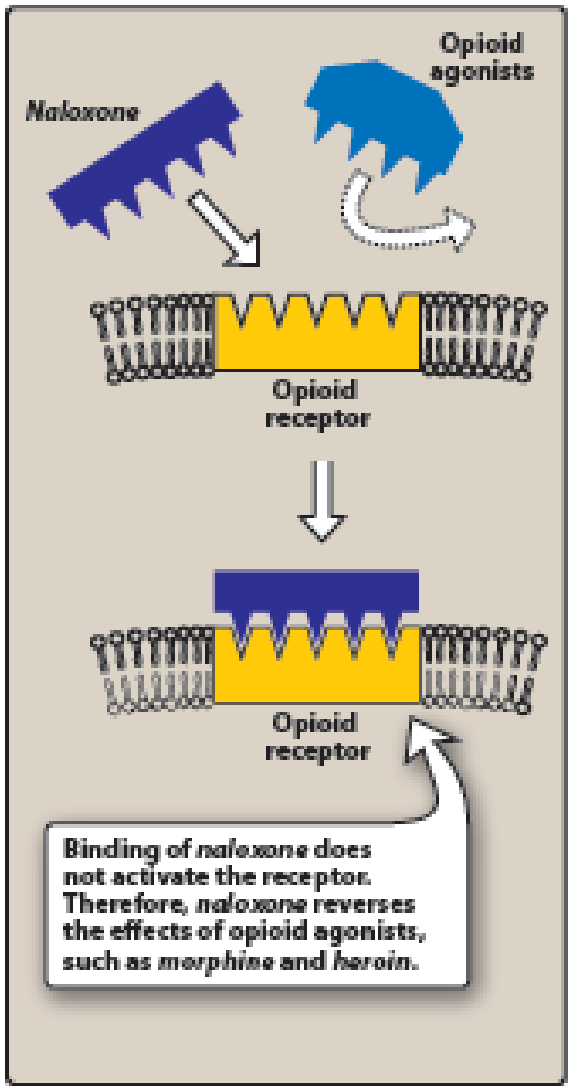
- Centrally acting analgesic that binds to μ-opioid receptor
- Weakly inhibits reuptake of norepinephrine and serotonin
- Used to manage moderate to moderately severe pain
- Less respiratory depression than morphine
- Anaphylactoid reactions have been reported
- Toxicity through drug-drug interactions with medications, such as SSRIs and TCAs or in overdose leads to CNS excitation and seizures
- Tramadol should be avoided in patients taking MAOIs

Tapentadol

- Centrally acting analgesic that binds the μ-opioid receptor and is also a norepinephrine reuptake inhibitor
- Used to manage moderate to severe pain

Opioid antagonists

- Bind with high affinity to opioid receptors but fail to activate the receptor-mediated response
- Administration of opioid antagonists produces no profound effects in normal individuals
- In patients dependent on opioids, antagonists rapidly reverse the effect of agonists, such as morphine or any full μ-agonist causing symptom of opiate withdrawal



Naloxone

- Used to reverse the coma and respiratory depression of opioid overdose
- Rapidly displaces all receptor-bound opioid molecules reversing their effects
- Within 30 seconds of IV injection of naloxone the respiratory depression and coma characteristic of high doses of morphine are reversed causing the patient to be revived and alert
- Naloxone is a competitive antagonist at μ, κ, and δ, receptors
- Short half life (30-80 min)
- Can cause withdrawal symptoms in opioid abusers

Naltrexone

- Similar effects to naloxone with a longer duration of action
- A single oral dose can block Heroin effects for up to 48 hours
- Can cause hepatotoxicity