Pain

جامعة بيرزيت
BIRZEIT UNIVERSITY

Introduction: pain

- Pain is an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage.
- It 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
  - **Neurogenic pain**: anticonvulsants (e.g pregabalin), tricyclic antidepressants (amitriptyline), or SNRI (duloxetine)
  - For **severe or chronic pain**: opioids are the drug of choice

Introduction: pain

Pain terms and definitions[1]

- **Allodynia:** Pain due to a stimulus that does not normally provoke pain.
- **Hyperalgesia:** Increased pain from a stimulus that normally provokes pain.
- **Central sensitization:** Increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input.
- **Nociceptive pain:** Pain that arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors.
- **Neuropathic pain:** Pain caused by a lesion or disease of the somatosensory nervous system.
- **Nociplastic pain:** Pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain.

Reference:

1. *IASP Terminology. International Association for the Study of Pain. Available at: https://www.iasp-pain.org/Education/Content.aspx?ItemNumber=1698 (Accessed on December 1, 2019).*

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Introduction: 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)

Introduction: opioids

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 40).]
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 vaso-dilatory 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.

Introduction: opioid receptors

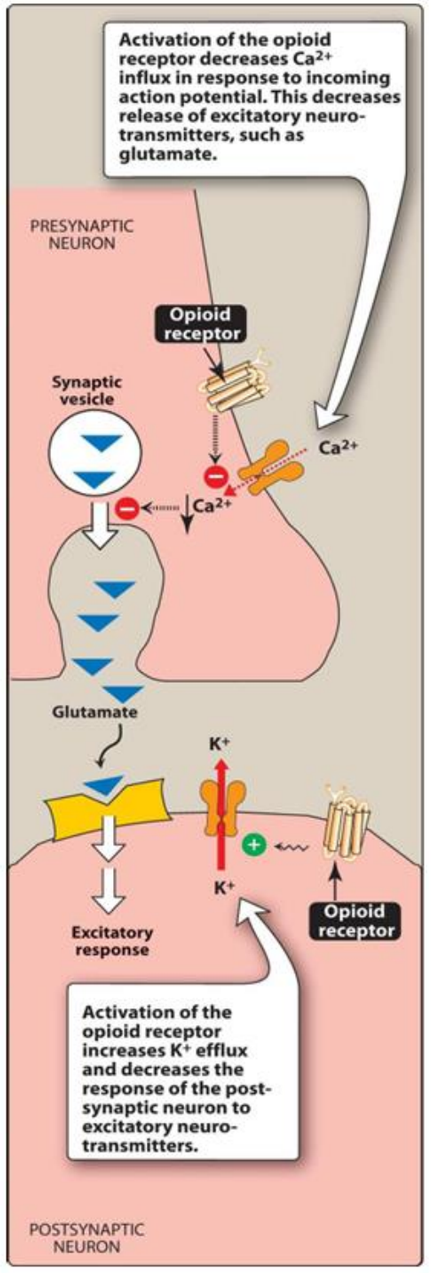
- Three major receptor families **μ (mu), κ (kappa), and δ (delta)**
- G protein–coupled receptor family and inhibit adenylyl cyclase
- Also associated with ion channels, **increasing postsynaptic K+ efflux (hyperpolarization)** or **reducing presynaptic Ca2+ influx**, thus slowing neuronal firing and transmitter release
- The **analgesic properti**es of the opioids are mediated by the μ receptors
- κ receptors in the dorsal horn also contribute (butorphanol & nalbuphine owe their analgesic effect to κ- receptor activation)
- Enkephalins interact more selectively with the δ receptors in the periphery

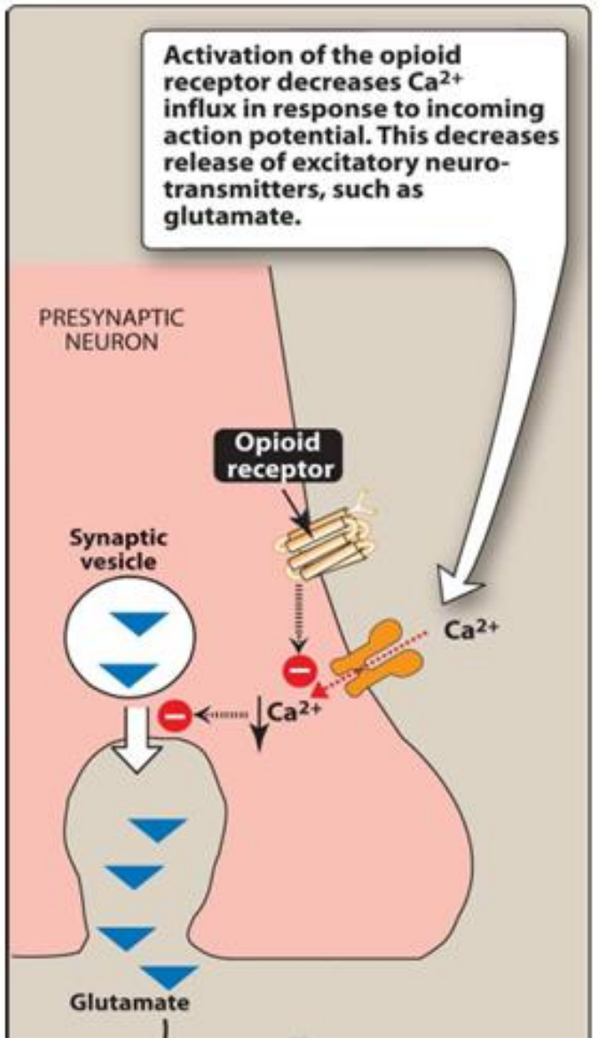
Introduction: opioid receptors

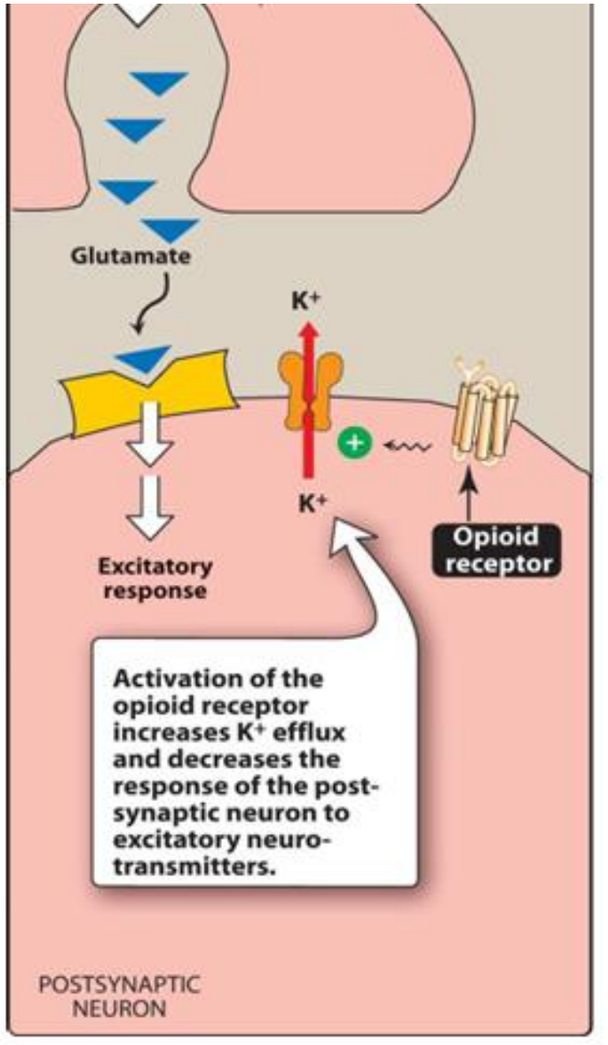
TABLE 31–1

Opioid receptor subtypes, their functions, and their endogenous peptide affinities.

Receptor Subtype	Functions	Endogenous Opioid Peptide Affinity
μ(mu)	Supraspinal and spinal analgesia; sedation; inhibition of respiration; slowed gastrointestinal transit; modulation of hormone and neurotransmitter release	Endorphins > enkephalins > dynorphins
δ(delta)	Supraspinal and spinal analgesia; modulation of hormone and neurotransmitter release	Enkephalins > endorphins and dynorphins
κ(kappa)	Supraspinal and spinal analgesia; psychotomimetic effects; slowed gastrointestinal transit	Dynorphins > > endorphins and enkephalins







Opioids

Strong agonists (High affinity for μ receptors)

- Morphine
- Hydromorphone
- Oxymorphone
- Heroin
- Alfentanyl
- Fentanyl
- Remifentanil
- Sufentanil
- Hydrocodone
- Methadone
- Oxycodone
- Meperidine = Pethidine (Br)

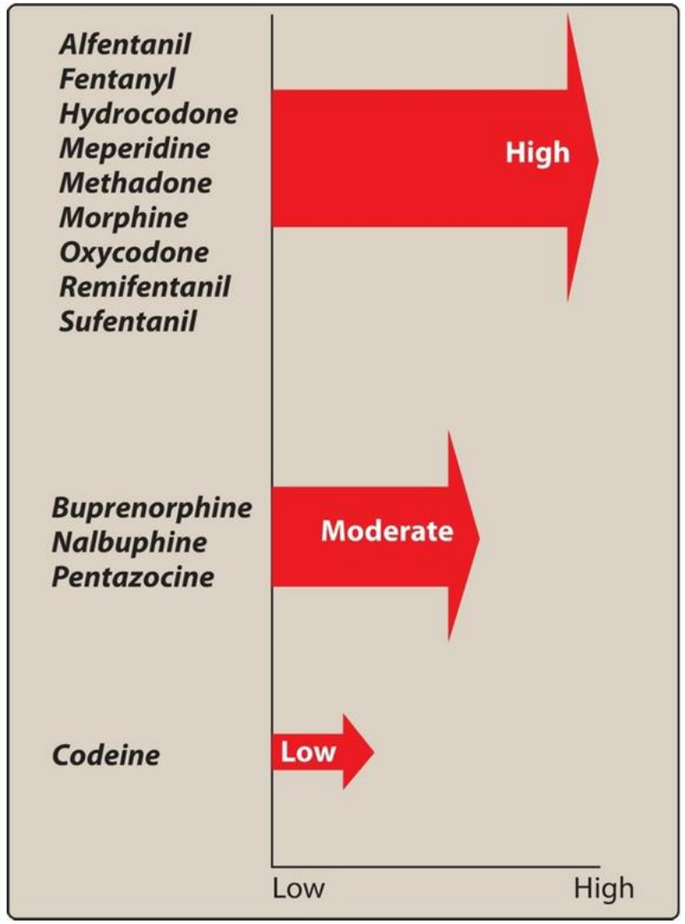


Figure 14.7 A comparison of opioid agonist efficacy.

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

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

Benzmorphan	
Pentazocine	Mixed Agonist/Antagonist
Phenylpiperidines	
Fentanyl	Agonist
Alfentanil	Agonist
Remifentanil	Agonist
Sufentanil	Agonist
Meperidine	Agonist
Diphenylheptane	
Methadone	Agonist
Phenylpropylamines	
Tramadol	Agonist
Tapentadol	Agonist

Opioids

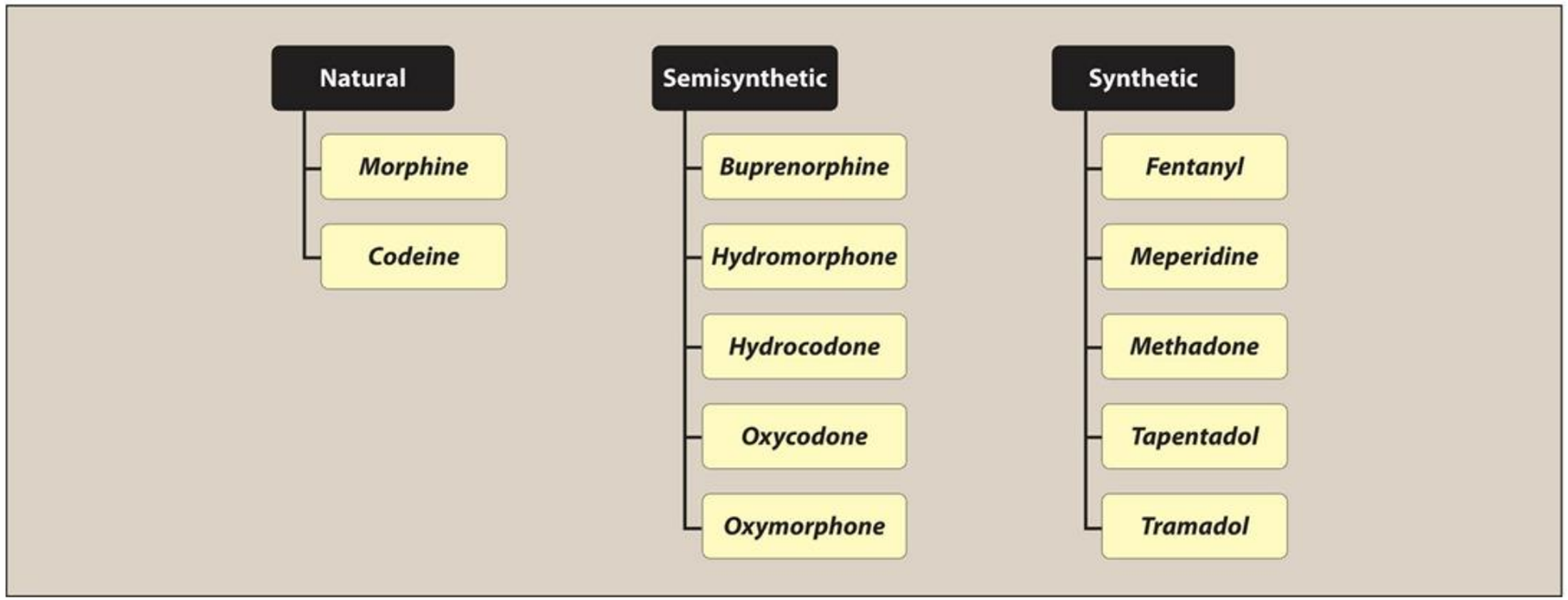


Figure 14.2 Origin of opioids: natural, semisynthetic, or synthetic.

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)

Morphine

- Actions:
  - Emesis: due to triggering of chemoreceptor zone
  - GI effects: constipation
  - Urinary retention
  - 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
    - Prolonged use of morphine may lead to opioid- induced androgen deficiency (decreased testosterone)

Morphine

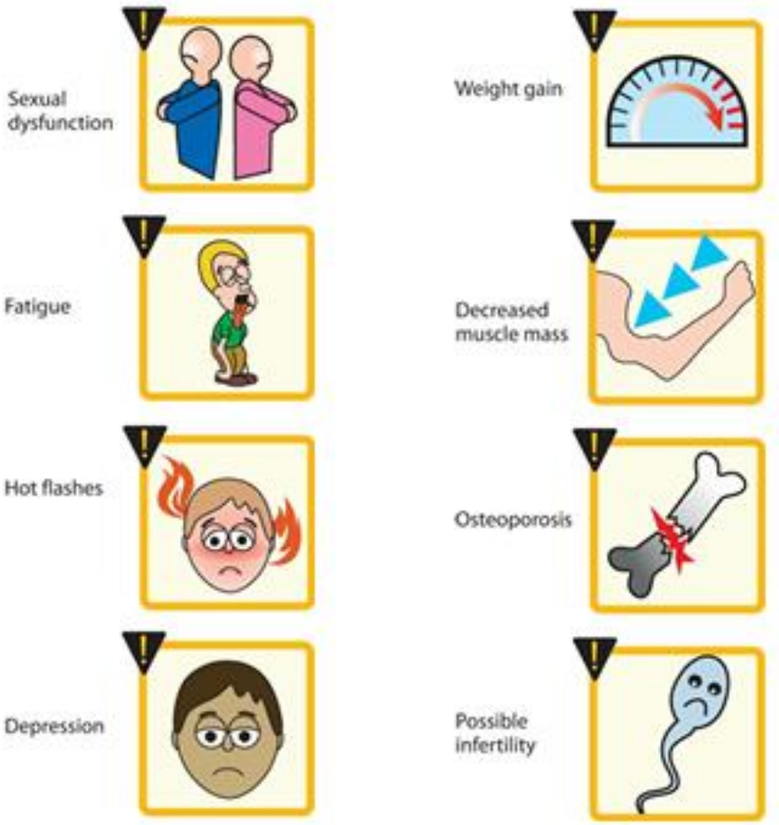


Figure 14.9 Clinical symptoms associated with opioid-induced androgen deficiency (OPIAD).

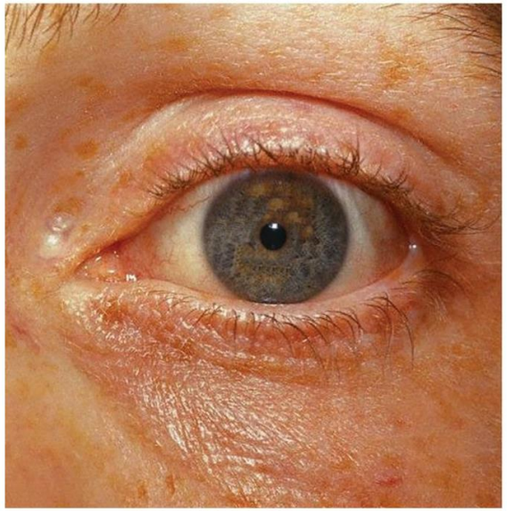


Figure 14.8 Characteristic pinpoint pupil associated with *morphine* use.

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
- Morphine may prolong the second stage of labor by transiently decreasing the strength, duration, and frequency of uterine contractions

- Infants born of addicted mothers show physical dependence and exhibit withdrawal symptoms if opioids are not administered

Morphine

- **Adverse effects**
  - Respiratory depression
  - Constipation
  - 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

Morphine

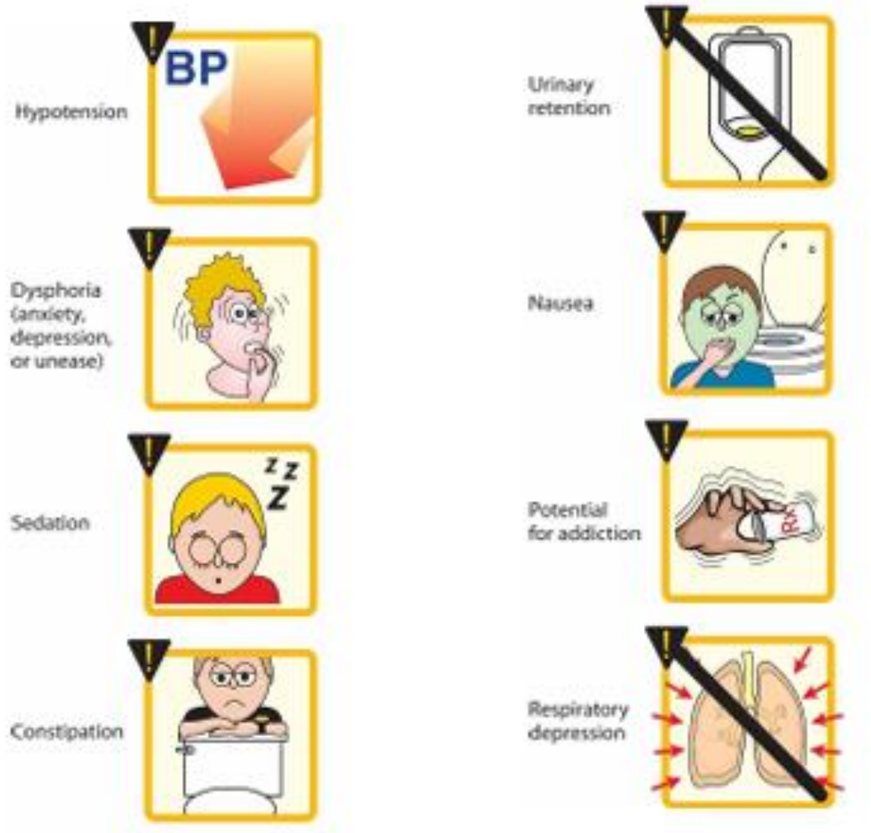


Figure 14.10 Adverse effects commonly observed in individuals treated with opioids.

Morphine

Drug interactions:

- The depressant actions of morphine are enhanced by coadministration with CNS depressant medications such as phenothiazines, MAOIs, benzodiazepines
- Avoid simultaneous prescribing of opioids and benzodiazepines.
- A boxed warning also has been included on the labeling of both opioids and benzodiazepines to alert prescribers of this dangerous combination.
- Serious breathing difficulties have also been noted with the coadministration of opioids and gabapentin and pregabalin

Mepridine

= Pethidine (Br.)

- A synthetic opioid used for acute pain
- Mechanism of action: Meperidine binds to opioid receptors, μ and k 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 normeperidine
  - Has anticholinergic effects (higher risk of delirium)

Methadone

- μ-Receptor agonist
- NMDA receptor antagonist
- Norepinephrine and serotonin reuptake inhibitor
- Useful in treatment of nociceptive & neuropathic pain
- Causes less euphoria and less dependence than morphine
- Better bioavailability than morphine
- Uses:
  - Analgesia
  - Controlling withdrawal symptoms of dependent abusers of morphine and heroin
- Can prolong QT intervals (Requires ECG monitoring)

Fentanyl

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

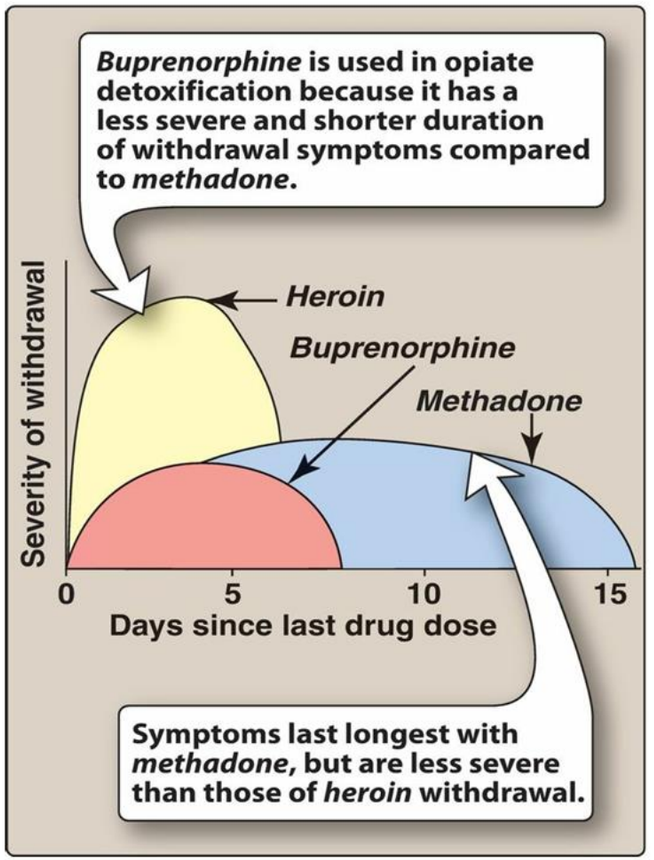


Figure 14.11 Severity of opioid withdrawal symptoms after abrupt withdrawal of equivalent doses of *heroin*, *buprenorphine*, and *methadone*.

Oxycodone and oxymorphone

- Oxycodone
  - Orally active and is sometimes formulated with aspirin or acetaminophen or ibuprofen
  - Twice more potent than morphine
  - Used to treat moderate to severe pain
  - Metabolized to oxymorphone by CYP2D6

- Oxymorphone
  - Administered orally, three times the potency of morphine.
  - No drug interactions with CYP system

Hydrocodone and Hydromorphone

- Hydromorphone
  - Oral hydromorphone is 4-7 times more potent than oral morphine as
  - an analgesic and is used most often to treat severe pain
  - Preferred to morphine in patients with renal dysfunction due to less accumulation of metabolites

- 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
  - Metabolized to Hydromorphone via CYP2D6

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

- Dextromethorphan is a synthetic cough depressant that has relatively no analgesic action and much lower potential for abuse in usual antitussive doses. It is preferred over codeine in most situations where cough suppression is needed.

Mixed agonists-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

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

Pentazocine

- Acts as an agonist on κ receptors and a partial agonist at μ 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

Nalbuphine and butorphanol

- Limited role in the treatment of chronic pain.
- Butorphanol is available in a nasal spray that has been used for severe headaches, but it has been associated with misuse.
- Both products are available in an injectable formulation.
- Less psychotomimetic effects than pentazocine.
- Nalbuphine does not affect the heart or increase blood pressure.

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

Other analgesics

- Oliceridine
- Oliceridine is a novel synthetic, centrally and peripherally acting μ-opioid agonist.
- It preferentially binds to the G protein–coupled pathway with reduced β-arrestin post-receptor recruitment. Activation of β-arrestin contributes to respiratory depression and gastrointestinal dysfunction. Therefore, reducing activation of βarrestin has the potential to reduce these effects, as compared with traditional opioids like morphine.

- Only available in an IV formulation and is indicated for moderate-to-severe acute pain.
- It possesses a more rapid onset and shorter duration and half-life and is relatively five times as potent as compared with IV morphine.
- Respiratory depression may still occur with this agent. Other adverse effects include dizziness, headache, nausea, vomiting, and constipation.

Opioid withdrawal

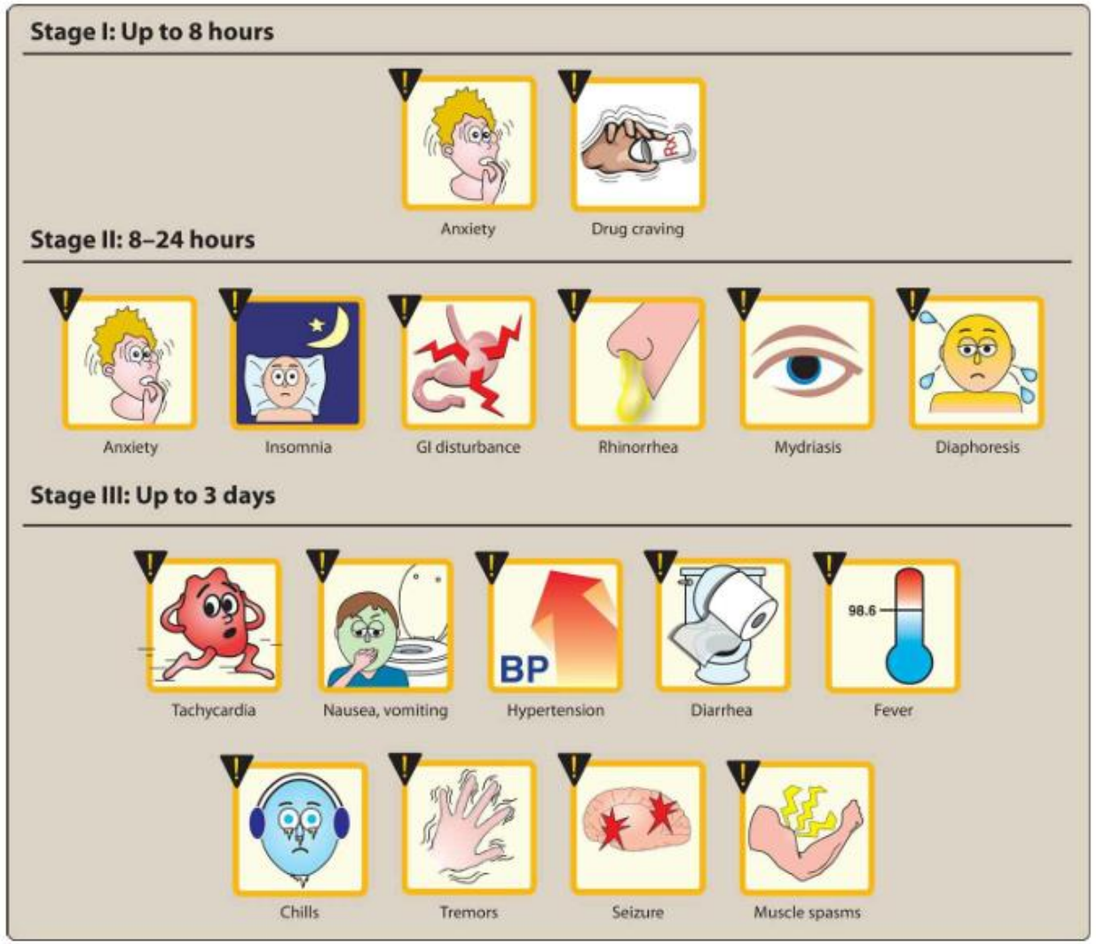


Figure 14.12 Opiate withdrawal syndrome. GI = gastrointestinal.

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 (30-90 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