# Opioids

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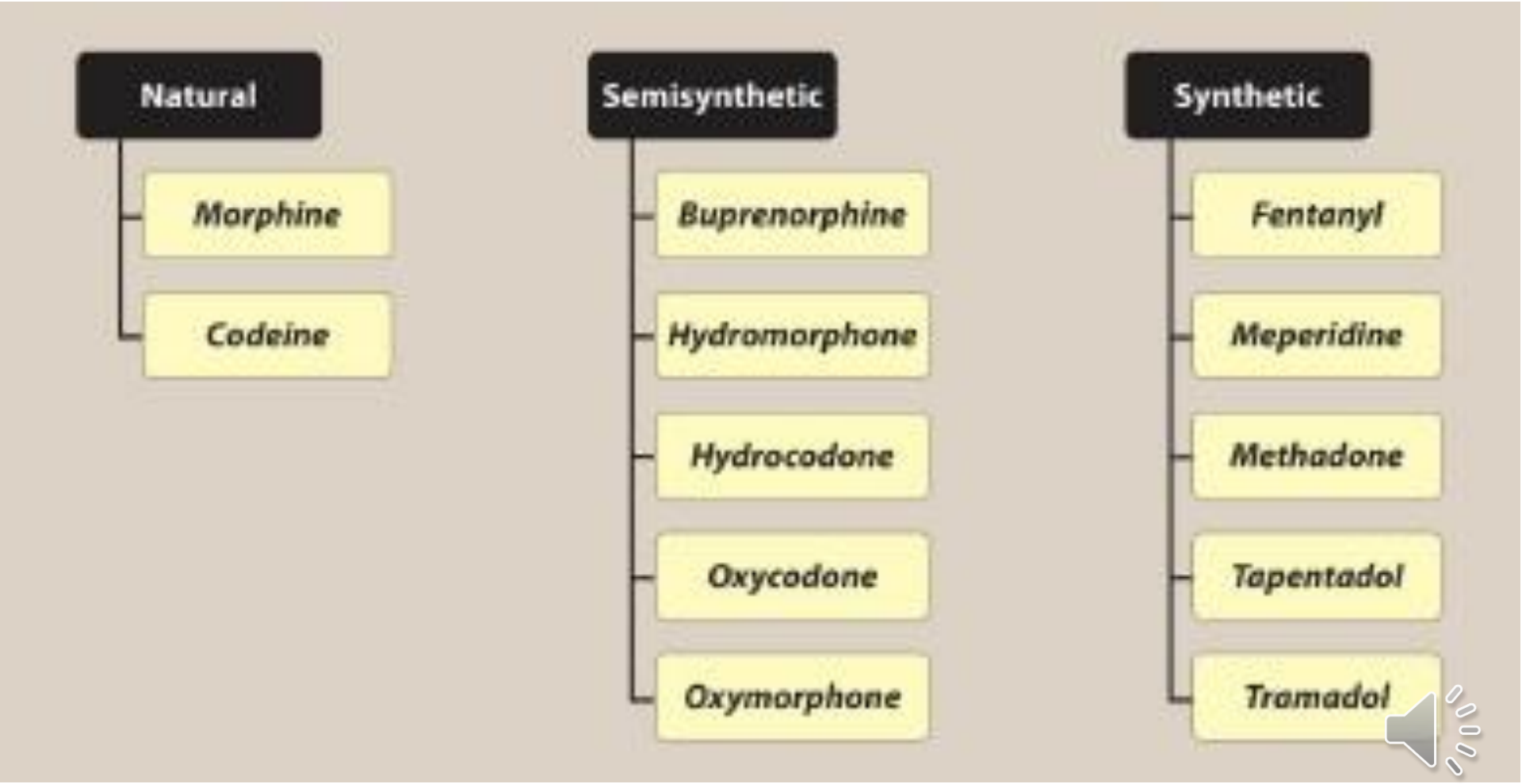
- Management of pain is one of clinical medicine’s greatest challenges.
- Pain is defined as an unpleasant sensation that can be either acute or chronic and is a consequence of complex neurochemical processes in the peripheral and central nervous systems (CNS).
- It is subjective, and the clinician must rely on the patient’s perception and description of pain

# Opioids

- . 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 (NSAIDs) 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.

# Origin of opioids: natural, semisynthetic, or synthetic.



# Morphine like effects

| System | Effects | Explanation/Comment |
|---|---|---|
| CNS | Analgesia without loss of consciousness | Opioids are more selective for pain than other CNS drugs<br>Other sensory modalities remain intact |
| | Respiratory depression | Direct inhibition of 5-$HT_{4A}$ receptors in the rhythm-generating respiratory neurons in the pre–Boetzinger complex of the brainstem |
| | Miosis | Excitation at the nucleus of the oculomotor nerve. This is pathognomonic of opiate intoxication (so-called pinpoint pupils) |
| | Euphoria | |
| | Antitussive (cough suppressant) | Inhibition of central cough reflex |
| | Nausea and vomiting | Opiates have a direct action on the chemoreceptor trigger zone in the medulla |
| | Warmth and drowsiness | |
| | Itchy nose | |

# Morphine like effects

| | | |
|---|---|---|
| Cardiovascular system | Peripheral vasodilation<br>Inhibition of baroreceptor reflexes<br>Orthostatic hypotension | There is little or no direct effect on the heart |
| GI system | Constipation | Decreased stomach motility, increased tone and nonpropulsive contraction in the small and large intestine, and increased tone of the anal sphincter |
| | Increased biliary tract pressure | |

# Opiate Receptors

- 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

## Opiate Receptors

There are three major categories of opiate receptors: μ (mu), δ (delta), and κ (kappa). The actions of opioids in current use are interpreted with regard to their actions at μ, δ, and κ receptors

Table 13.1 ► **Actions Mediated by Opiate Receptors**

| Opiate Receptor | CNS Location* | Action |
|---|---|---|
| μ | Dorsal horn of the spinal cord, nucleus of the solitary tract, periaqueductal gray region, thalamus, nucleus accumbens, amygdala, cerebral cortex | Supraspinal analgesia<br>Respiratory depression<br>Euphoria<br>Dependence |
| κ | Dorsal horn of the spinal cord, periaqueductal gray region, hypothalamus | Spinal analgesia<br>Miosis (pupillary constriction)<br>Sedation |
| δ | Pontine nucleus, nucleus accumbens, amygdala, cerebral cortex | Involved in affective behaviors (related to feelings or mental state) |

* Opiate receptors are also found in the enteric nervous system, placenta, vas deferens, and immune system.

*Abbreviation:* CNS, central nervous system.

# Summary of opioid analgesics and antagonists .

## STRONG AGONISTS

***Alfentanil*** ALFENTA
***Fentanyl*** ABSTRAL, ACTIQ, DURAGESIC, FENTORA, IONSYS, LAZANDA, SUBSYS
***Heroin*** GENERIC ONLY
***Hydrocodone*** HYSINGLA, LORTAB*, NORCO*, VICODIN*, ZOHYDRO ER
***Hydromorphone*** DILAUDID, EXALGO
***Levorphanol*** GENERIC ONLY
***Meperidine*** DEMEROL
***Methadone*** DOLOPHINE, METHADOSE
***Morphine*** ARYMO ER, KADIAN, MORPHABOND, MS CONTIN
***Oxycodone*** OXAYDO, OXYCONTIN, PERCOCET*, ROXICODONE
***Oxymorphone*** OPANA
***Remifentanil*** ULTIVA
***Sufentanil*** SUFENTA

## MODERATE/LOW AGONISTS

***Codeine*** GENERIC ONLY

## MIXED AGONIST–ANTAGONIST AND PARTIAL AGONISTS

***Buprenorphine*** BELBUCA, BUPRENEX, BUTRANS, PROBUPHINE
***Butorphanol*** GENERIC ONLY
***Nalbuphine*** GENERIC ONLY
***Pentazocine*** TALWIN

## ANTAGONISTS

***Naloxone*** EVZIO, NARCAN
***Naltrexone*** VIVITROL

## OTHER ANALGESICS

***Tapentadol*** NUCYNTA
***Tramadol*** CONZIP, ULTRAM

# Pharmacological classes of opioids and actions on opioid receptors.

| 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 |

# Adverse effects of most mu agonist

- Nausea, vomiting, mental cloudiness, dysphoria, constipation, and increased biliary pressure.
- Severe respiratory depression can occur and may result in death from acute opioid overdose.
- Opioid-induced constipation (OIC) is a common adverse effect.
- Tolerance and dependence. They are characteristics of the opioid drugs.
- Morphine should be used with caution in patients with liver disease and renal dysfunction.

Selected clinical uses of 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. |

# Opiate Agonists
# Exogenous Opioid Agonists
# Morphine and Related Compounds

- Morphine is the standard for comparison among opioids. Many semisynthetic compounds are made by modifying the morphine molecule.
- — Diacetylmorphine (heroin) is made by acetylation at the three and six carbon positions.
- — Hydromorphone, oxymorphone, oxycodone, and hydrocodone are also made by altering the morphine molecule.
- **Mechanisms of action**
- — Morphine and related compounds act at all opiate receptors, but with the highest affinity at μ receptors. Activation of μ receptors decreases the spontaneous activity of neurons in the gut and in the central nervous system (CNS).

# Opiate Agonists
# Exogenous Opioid Agonists
# Morphine and Related Compounds

- Morphine acts on areas known to be involved in respiration, pain perception, mood, and emotion.
- — At the cellular level, all three subtypes of opiate receptors couple to Gi and Go. Activation of these G proteins by opioid-binding to opiate receptors decrease cyclic adenosine monophosphate levels (cAMP), increase K+ currents, and decrease Ca2+ currents. This results in hyperpolarization and decreased release of neurotransmitters
- — Morphine selectively inhibits the excitatory inputs to neurons involved in transmitting information about noxious stimuli without changing the responses to other types of stimuli.

# Opiate Agonists
# Exogenous Opioid Agonists
# Morphine and Related Compounds

- **Pharmacokinetics**
- — Morphine is readily absorbed from the gastrointestinal (GI) tract, nasal mucosa, and lungs.
- — Bioavailability of oral preparation ranges from 15 to 50% due to first-pass metabolism in the liver.
- — Metabolized by glucuronide conjugation
- — Excreted as a glucuronide conjugate in the urine
- — Diacetylmorphine (heroin) is rapidly deacetylated in the liver to monoacetylmorphine, which is further deacetylated to morphine.

# Opiate Agonists
# Exogenous Opioid Agonists
# Morphine and Related Compounds

- **Uses**
- — Acute relief of pain (symptomatic treatment only)
- — Chronic treatment of pain
- — Antitussives
- — Useful in diarrhea to produce constipation. Small amounts of opium tincture or paregoric are ingested. This effect is of particular use following ileostomy or colostomy and in diarrhea and dysentery.
- **Side effects**. Nausea, vomiting, mental cloudiness, dysphoria, constipation, and increased biliary pressure

# Opiate Agonists
# Exogenous Opioid Agonists
# Morphine and Related Compounds

- **Drug interactions**. Opioid action is potentiated by phenothiazines, monoamine oxidase inhibitors (MAOIs), and tricyclic antidepressants. Some phenothiazines will enhance the sedative effects of morphine while decreasing the analgesic effects.
- **Tolerance and dependence**. They are characteristics of the opioid drugs.
- **Contraindications**
- — It may not be advisable to use opioids in patients with head injury, as mental clouding, vomiting, and miosis may interfere with neurologic assessment of the patient.
- — Caution must be used in patients with lung disease due to respiratory depression

# Meperidine

- — Meperidine is a synthetic opiate.
- — Fentanyl is a meperidine analogue 80 times as potent as morphine.
- — Sufentanil is a meperidine analogue 6000 times as potent as morphine
- May cause CNS excitement at toxic doses (unlike morphine)
- The side effects are the same as for morphine, except there is less constipation

# Meperidine

- **Mechanism of action.** Meperidine acts in the same way as morphine, that is, as an agonist at opiate receptors.
- **Pharmacokinetics.** Meperidine has better bioavailability than morphine: 50% of absorbed
- meperidine escapes first-pass metabolism.
- **Effects**
- — Analgesia
- — May cause CNS excitement at toxic doses (unlike morphine)
- — Respiratory depression
- — Cardiovascular: postural (orthostatic) hypotension but no significant effects
- — Smooth muscle: spasmogenic like morphine, but less intense in relation to its analgesia
- *Note:* Meperidine does not have antitussive or constipating actions.

# Meperidine

- **Side effects**. The side effects are the same as for morphine, except there is less constipation.
- The metabolite normeperidine accumulates with repeated dosing. Normeperidine is not an analgesic, but it produces CNS excitation.
- **Drug interactions**. Meperidine may react with MAOIs, causing excitation, delirium, hyperpyrexia, convulsions, and severe respiratory depression.

# Methadone and Levo-α-acetylmethadol (LAAM)

- Mechanism of action. These agents are synthetic, long-acting opiate agonists with similar
- pharmacological effects as morphine.
- **Pharmacokinetics**
- — Long half-life (1–1.5 days)
- **Uses**
- — Analgesia (equally as potent as morphine)
- — Treatment of opioid withdrawal symptoms
- **Side effects**
- — Constipation and biliary spasm

# Propoxyphene (Darvon)

- **Mechanism of action.** Propoxyphene is an agonist at opiate receptors.
- **Pharmacokinetics.** It is not as potent or effective as codeine, but it does have less potential for dependence.
- **Uses**
- — Previously used as an analgesic agent but has recently been removed from the market.

# Mixed Opiate Agonist-Antagonists Pentazocine

- **Mechanism of action**. Pentazocine is a μ-receptor antagonist and a δ- and κ-receptor agonist.
- **Effects**
- — Produces analgesia, sedation, and respiratory depression
- — May block the analgesia produced by morphine
- **Uses**
- — Primarily used as an analgesic, but not effective against severe pain
- **Side effects**
- — Respiratory depression
- — May cause confusion and hallucinations

# Mixed Opiate Agonist-Antagonists Pentazocine

- **Tolerance, dependence, and withdrawal**
- — Originally thought to have less potential for abuse and released for general use, but then drug abusers combined pentazocine and tripelennamine as a substitute for heroin.
- Talwin Nx™ (pentazocine and naloxone) includes naloxone to prevent intravenous (IV) use.
- — May precipitate withdrawal symptoms in patients who have been receiving opioids

# Mixed Opiate Agonist-Antagonists Buprenorphine

- **Mechanism of action.** Buprenorphine is a partial agonist at μ receptors.
- **Pharmacokinetics**
- — Given IM or IV
- **Uses**
- — Analgesia
- **Side effects**
- — Respiratory depression

# 13.3 Opiate Antagonists
# Naloxone, Naltrexone, and Nalmefene

- **Mechanism of action**. These antagonists bind with high affinity to all opiate receptors but have highest affinity for μ receptors. They act as competitive inhibitors.
- **Pharmacokinetics**
- — Naloxone and nalmefene are only effective IV, with nalmefene having a longer duration of action (10 hours versus 1 hour for naloxone).
- — Naltrexone is effective orally.
- **Uses**
- — Naloxone and nalmefene are used to treat opioid poisoning
- — Naltrexone has been tested for treating drug and alcohol addictions
- Withdrawal. In patients dependent on opiates, antagonists will induce withdrawal symptoms.

# Related Compounds

- **Dextromethorphan**
- Dextromethorphan is an opioid analogue that is available over the counter but has no analgesic or addictive properties.
- Mechanism of action
- — Unclear, but may involve μ and κ receptors
- Uses
- — Antitussive

# Related Compounds
# Tramadol

- Tramadol is chemically unrelated to opioids.
- Mechanism of action. Tramadol is a weak opiate receptor agonist. It also inhibits norepinephrine and 5-hydroxytryptamine (5-HT) reuptake. It is only partially inhibited by naloxone.
- It is equal to or less effective than codeine plus aspirin or to codeine plus acetaminophen.
- Uses
- — Neuropathic pain
- Side effects
- — Constipation, nausea, vomiting, dizziness, and drowsiness

# Related Compounds
# Ziconotide

- Ziconotide is not an opioid.
- Mechanism of action. Ziconotide is a peptide blocker of neuronal N-type Ca2+ channels.
- **Pharmacokinetics**
- — Given by intrathecal infusion
- **Uses**
- — Management of severe chronic pain
- **Side effects**
- — Severe psychiatric symptoms, such as hallucinations, paranoia, and delirium. Drunklike reactions
- also occur (e.g., dizziness, sleepiness, confusion, incoordination, and mental slowness).
- These symptoms take days or weeks to resolve after discontinuation.
- — Bacterial meningitis

# Summary of the primary indications for the opioid analgesics.

| Opioid | Indications |
|---|---|
| Morphine and related compounds | Acute pain<br>Chronic pain<br>Cough (codeine)*<br>Diarrhea |
| Meperidine and analogues | Analgesia<br>Regional analgesia (fentanyl)<br>Preanesthetic (fentanyl) |
| Methadone and LAAM | Opioid withdrawal |
| Pentazocine | Analgesia for moderate pain |
| Buprenorphine | Analgesia |
| Naloxone and nalmefene | Opioid poisoning |
| Dextromethorphan | Cough* |
| Tramadol | Neuropathic pain |
| Ziconotide | Severe chronic pain |