Opioid analgesics

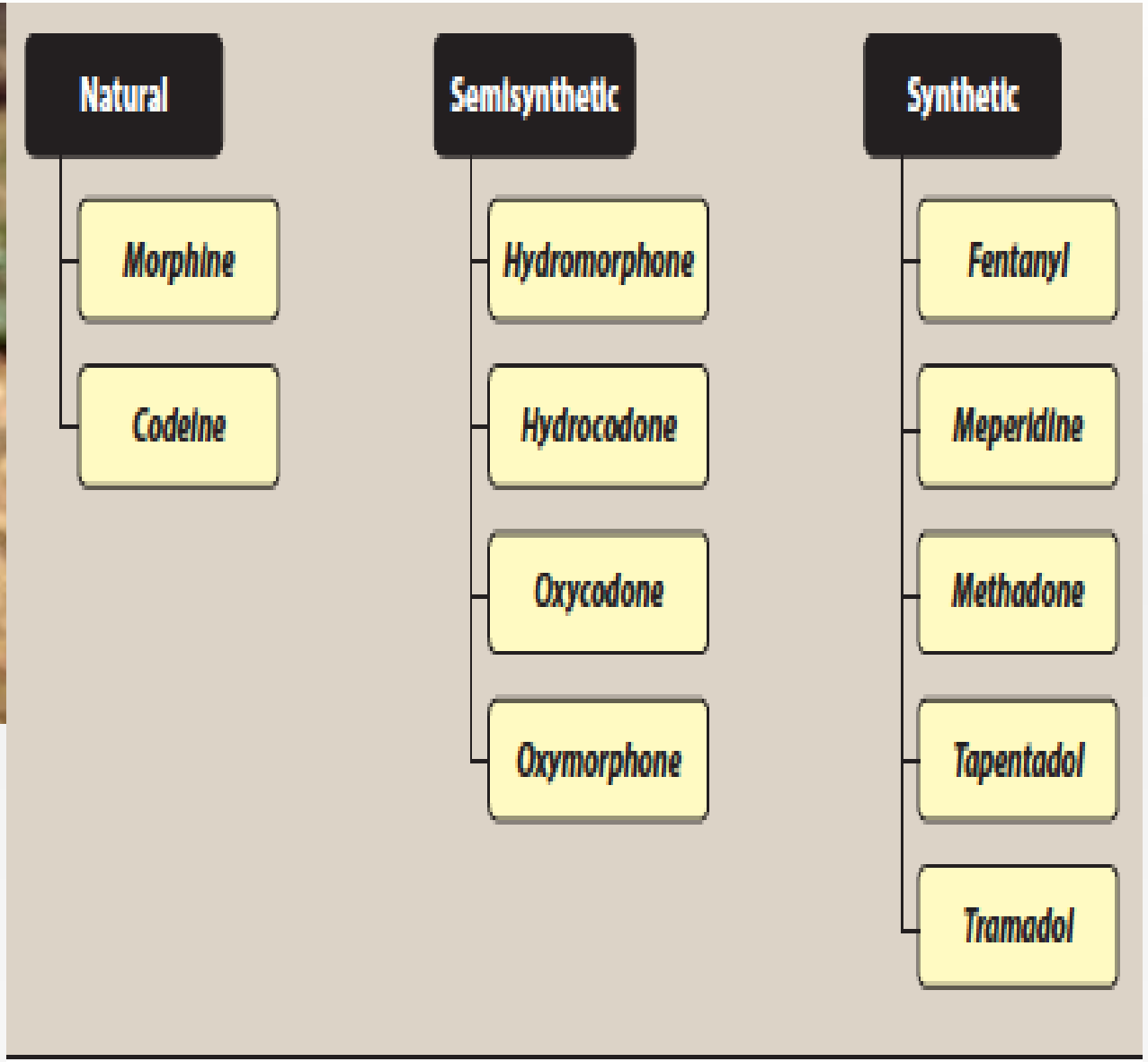
Dr. Laila M. Matalqah
Dr. Romany H Thabet

Alleviation of pain depends on its type;

1. Headaches or mild to moderate arthritic pain nonsteroidal anti-inflammatory agents (NSAIDs) are effective.

2. Neurogenic pain responds best to anticonvulsants, tricyclic antidepressants (for example, *amitriptyline*), or serotonin/norepinephrine reuptake inhibitors (for example, *duloxetine*) rather than NSAIDs or opioids.

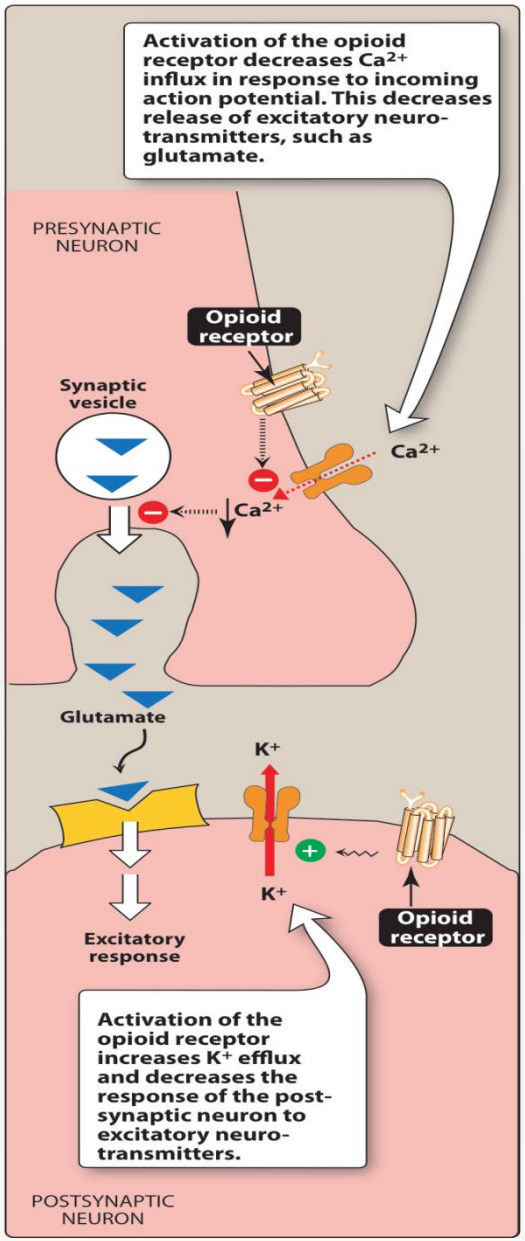
3. However, for severe or chronic malignant pain, opioids are usually the drugs of choice

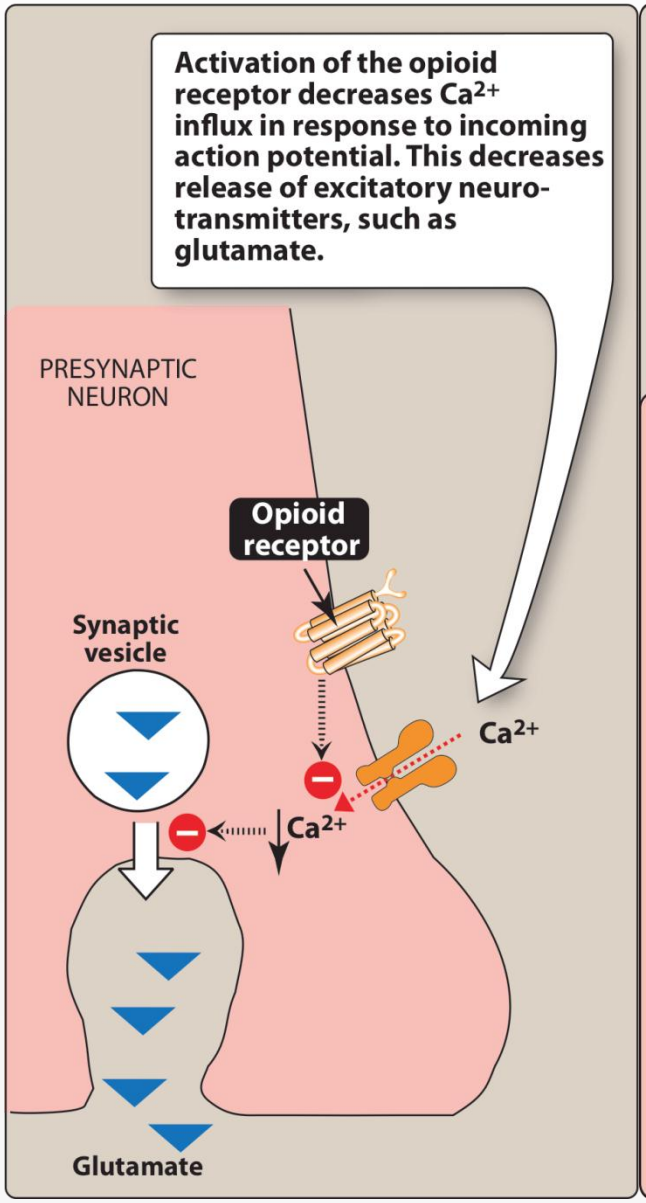

Natural
Morphine
Codeine
Semisynthetic
Hydromorphone
Hydrocodone
Oxycodone
Oxymorphone
Synthetic
Fentanyl
Meperidine
Methadone
Tapentadol
Tramadol

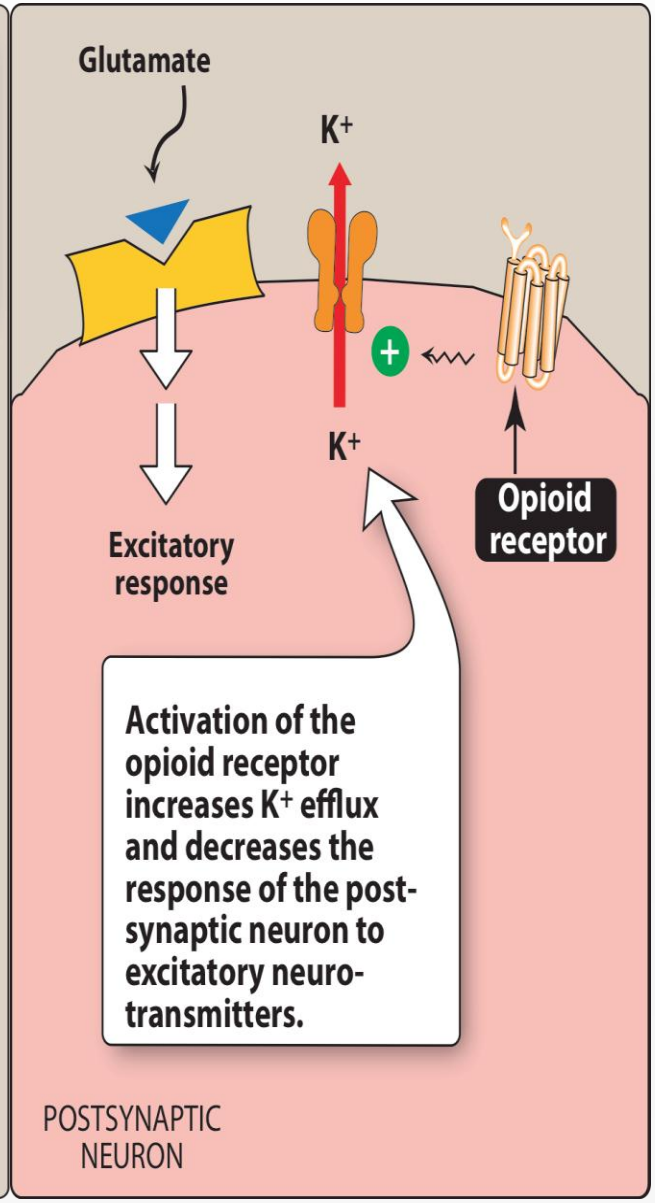
Opioid receptors

Receptor subtype	Functions
μ (mu)	**Analgesia** **Sedation** **Inhibition of respiration** **Slowed gastrointestinal** Modulation of hormone and neurotransmitter release
δ (delta)	**Analgesia** Modulation of hormone and neurotransmitter release
K (kappa)	**Analgesia** Psychotomimetic effect Slowed gastrointestinal transit

Opioid receptors







- The analgesic properties of the opioids are primarily mediated by the μ receptors; however, the Ќ(kappa) receptors in the dorsal horn also contribute.

- For example, *butorphanol* and *nalbuphine* primarily owe their analgesic effect to K-receptor activation.

- The enkephalins interact more selectively with the delta receptors in the periphery.

Morphine

Has diverse effects:

- Analgesia,
- Drowsiness,
- Mood changes,
- Respiratory depression,
- Reduced GI motility,
- Vomiting,
- Endocrine and ANS changes.

Pharmacological Actions of morphine

Analgesia:

- ***without the loss of consciousness*** (raising the pain threshold at the spinal cord level and altering the brain's perception of pain).

- Patients treated with *morphine* are still aware of the presence of pain, but the sensation is not unpleasant.

- However, when given to an individual free of pain, its effects may be unpleasant and may cause nausea and vomiting.

- **Euphoria:** may be caused by disinhibition of the ventral tegmentum.

- **Respiration:** respiratory depression by reduction of the sensitivity of respiratory center neurons to carbon dioxide. This occurs with ordinary doses of *morphine* and is accentuated as the dose increases until, ultimately, respiration ceases.

- **Emesis:** directly stimulates the chemoreceptor trigger zone that causes vomiting.

- **Depression of cough reflex:** Both *morphine* and *codeine* have antitussive properties. The receptors involved in the antitussive action appear to be different from those involved in analgesia.

- **Miosis:** The pinpoint pupil, characteristic of *morphine* use, results from stimulation of μ and kappa receptors (excites the Edinger-Westphal nucleus of the oculomotor nerve, which causes enhanced parasympathetic stimulation to the eye). There is ***little tolerance to this effect.***

- **Gastrointestinal tract:**

produces constipation **(**by decreasing the motility and increasing the tone of the intestinal circular smooth muscle. Also, increases the tone of the anal sphincter).

Little tolerance developing.

It can also increase biliary tract pressure due to contraction of the gallbladder and constriction of the biliary sphincter.

- **Cardiovascular:** no major effects on the blood pressure or heart rate except at large doses, when hypotension and bradycardia may occur. Because of respiratory depression and carbon dioxide retention, cerebral vessels dilate and increase CSF pressure. (= contraindicated in individuals with severe brain injury).

- **Histamine release:** causing urticaria, sweating, and vasodilation (= contraindicated in asthmatics)

- **Hormonal actions:**

1. Inhibits release of gonadotropin-releasing hormone and corticotropin-releasing hormone,
2. Decreases the concentration of luteinizing hormone, follicle-stimulating hormone, adrenocorticotropic hormone.
3. Testosterone and cortisol levels decrease.
4. Increases growth hormone release and enhances prolactin secretion.
5. Increases antidiuretic hormone (leads to urinary retention).

- **Labor:** may prolong the second stage of labor by transiently decreasing the strength, duration, and frequency of uterine contractions.

Therapeutic uses

- **Analgesia**
- **Treatment of diarrhea**
- **Relief of cough (***Codeine* has greater antitussive action than *morphine)*
- **Treatment of acute pulmonary edema:** Intravenous *morphine* dramatically relieves dyspnea caused by pulmonary edema associated with left ventricular failure possibly by its vasodilatory effect.

Pharmacokinetics

- Absorption of *morphine* from the gastrointestinal tract is ***slow and erratic (****Codeine* is well absorbed when given by mouth)

- Significant hepatic first-pass metabolism (therefore, intramuscular, subcutaneous, or IV injections produce the most reliable responses).

- **Distribution:** *Morphine* rapidly enters all body tissues, including the fetuses of pregnant women (should not be used for analgesia during labor)

- Only a small percentage of *morphine* crosses the blood-brain barrier (despite *fentanyl, methadone*, and *heroin*, which readily penetrate into the brain).

Adverse effects

- Severe respiratory depression occurs and can result in death
- Vomiting
- Dysphoria
- Allergy-enhanced hypotensive effects.
- The elevation of intracranial pressure, particularly in head injury, can be serious.

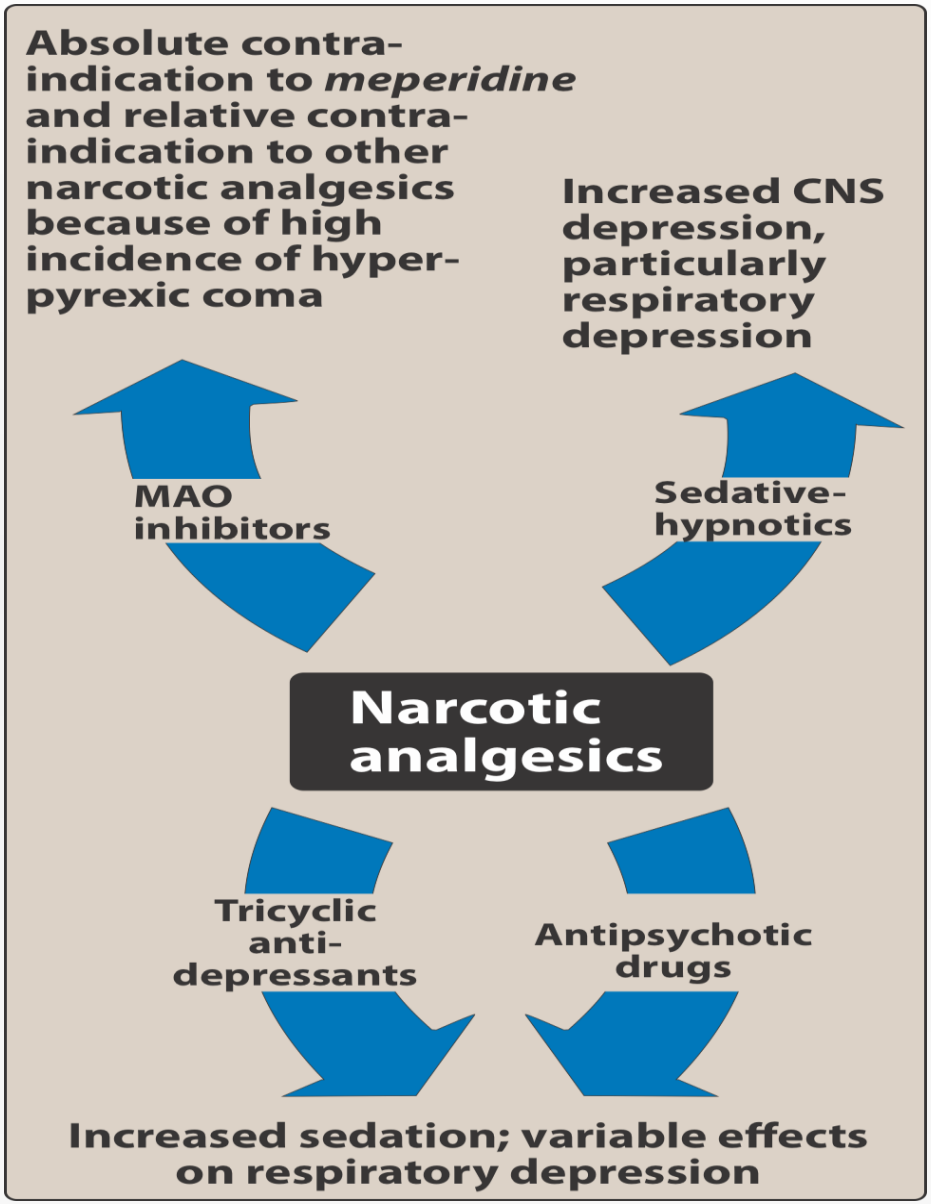
- Acute urinary retention in benign prostatic hyperplasia.
- Patients with adrenal insufficiency or myxedema may experience extended and increased effects from the opioids.
- *Morphine* should be used with cautiously in patients with bronchial asthma or liver failure.
- **Drug interactions:** The depressant actions of *morphine* are enhanced by phenothiazines, monoamine oxidase inhibitors, and tricyclic antidepressants

Morphine – Drug interactions

- Rare

- Mostly about the depressant actions with:

- MAO inhibitors
- Tricyclic antidepressants (TCAs)
- Sedative hypnotics
- Antipsychotic drugs



Tolerance and physical dependence

- **Tolerance to;**

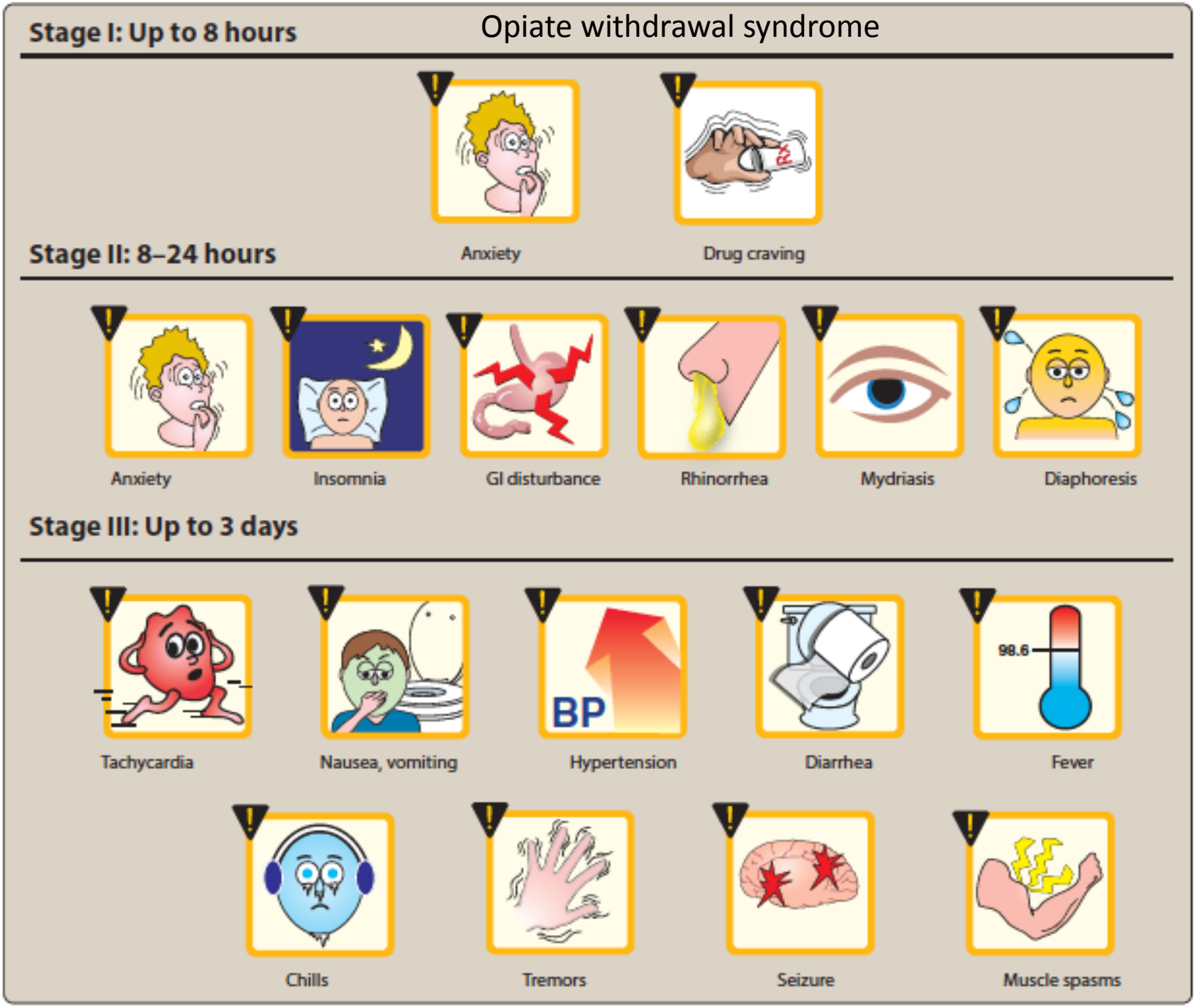
1. The respiratory depressant,
2. Analgesic,
3. Euphoric, and
4. Sedative effects.

- **However, tolerance usually does not develop to the**

1. Pupil-constricting and
2. Constipating effects of the drug.

- **Physical and psychological dependence** readily occur with *morphine* and with some of the other agonists.
- Withdrawal produces a series of autonomic, motor, and psychological responses (begins 6-10 h. after the last dose)

Opiate withdrawal syndrome



Fentanyl

- Very potent analgesic (100-fold of morphine) → used in anaesthesia.
- Very lipophilic
- Rapid onset and short duration of action (15 – 30 min), less than morphine
- Uses:
  - **Anaesthesia** (pre-aesthetic and induction and maintenance of anaesthesia) for its analgesic and sedative effects
  - **Analgesia**, postoperative pain and during cardiac surgery because it has no effect on myocardial contraction

Fentanyl

- Sublingual tablet
- Oral buccal tablets: mainly used for a breakthrough pain in cancer patients tolerant to opioids:
- Epidurally–combined with local anesthetics for labor and postoperative pain
- Intrathecally – analgesia
- Injection (IV): anaesthesia and analgesia
- Transdermal film (patch): Should not be used used for acute and postoperative pain
  - Onset of action is delayed at least 12 hours and the offset is prolonged.

Methadone

- Synthetic, orally effective opioid
- Approximately equal in potency to *morphine*
- Induces less euphoria
- Has a somewhat longer duration of action
- **Mechanism of action:** are mediated by μ receptors.
- Increases biliary pressure and is also constipating

- **Therapeutic uses:** analgesic, in the controlled withdrawal of dependent abusers from *heroin* and *morphine*.

- *Methadone* causes a withdrawal syndrome that is milder but more protracted (days to weeks) than that of other opioids.

- **Adverse effects:** can produce physical dependence like that of *morphine*.

Heroin

- Does not occur naturally.
- It is produced by diacetylation of *morphine*, which leads to a three-fold increase in its potency.
- Its greater lipid solubility allows it to cross the blood-brain barrier more rapidly than *morphine*, causing a more ***exaggerated euphoria*** when the drug is taken by injection.
- It has no accepted medical use in the United States

Codeine

- The analgesic actions of *codeine* are due to its conversion to morphine
- Whereas the drug's antitussive effects are due to *codeine* itself.
- Has a higher oral effectiveness.
- *Codeine* shows good antitussive activity at doses that do not cause analgesia
- At commonly used doses, the drug has a lower potential for abuse than *morphine*, and it rarely produces dependence.
- *Codeine* produces less euphoria than *morphine*.

Other agonists

- Oxycodone: For moderate to severe pain

Twofold more effective than morphine

Orally, could be used in combination with aspirin and paracetamol

- Oxymorphone:

More potent than morphine (parentrally; orally

- Hydromorphone:

  - 8-10 more potent than morphine
  - Hydromorphine in patients with renal dysfunction: less accumulation of active metabolies however some metabolites can cause CNS side effects (preferable over morphine for those patients).

Mixed Agonist-Antagonists and Partial Agonists

- Drugs that stimulate one receptor but block another are termed mixed agonist-antagonists.
- The effects of these drugs depend on previous exposure to opioids.

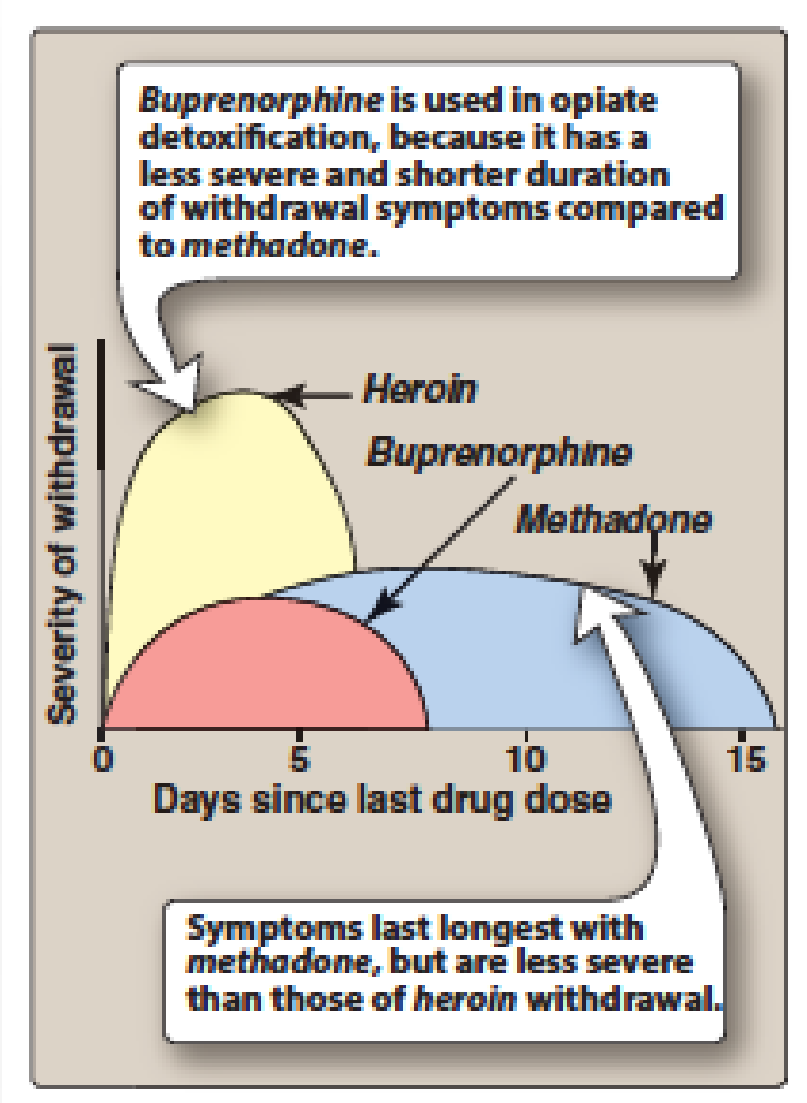
1. In individuals who have not recently received opioids; mixed agonist-antagonists show agonist activity and are used to relieve pain.
2. In the patient with opioid dependence, the agonist-antagonist drugs may show primarily blocking effects that is, produce withdrawal symptoms.

- ***Examples; Pentazocine, Buprenorphine, Nalbuphine***

Buprenorphine

- MOA: **partial agonist at μ receptors,** forming strong bonds → long duration of action
- Incompletely reversible by naloxone
- Precipitate withdrawal in users of morphine or other full opioid agonists
- Side effects: little sedation, respiratory depression, hypotension, nausea and dizziness.
- Main use:

1. opioid detoxification: For opioid withdrawal: sublingual tablet or film, bupronorphine alone or with naloxone
2. analgesia for moderate to severe pain
   - Dosage forms for analgesia: I.V injection, sublingually and transdermal film



- Buprenorphine widely used opioid detoxification than methadone (has shorter and less severe withdrawal symptoms compared to methadone)
- Naloxone can be added to prevent the abuse of buprenorphine via IV administration

Other analgesics - Tramadol

- μ-Opioid receptor weak agonist, centrally
- Weak inhibitor of norepinephrine and serotonin reuptake
- Analgesic for moderate to severe pain
- Only partially antagonised by naloxone
- Respiratory depression less than morphine
- Drug-drug interactions: antidepressants → selective serotonine reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs) and MAO inhibitors
- Anaphylactic reactions
- Associated with misuse and abuse

Antagonists

- Administration of opioid antagonists produces no profound effects in normal individuals.
- However, in patients dependent on opioids, antagonists rapidly reverse the effect of agonists, such as *heroin*, and precipitate the symptoms of opiate withdrawal.
- ***Naloxone, Naltrexone***