Anesthetics

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Anesthesia

- General anesthesia is a reversible state of central nervous system (CNS) depression, causing loss of response to and perception of stimuli.

- For patients undergoing surgical or medical procedures, anesthesia provides five important benefits:

1. Sedation and reduced anxiety
2. Lack of awareness and amnesia
3. Skeletal muscle relaxation
4. Suppression of undesirable reflexes
5. Analgesia

- Patient factors in selection of anesthesia:

1. Status of organ systems: cardiovascular system, respiratory system, liver and kidney, nervous system, pregnancy.
2. Concomitant use of drugs: multiple adjunct agents, concomitant use of drugs.

Stages of Anesthesia

1. Induction:

- General anesthesia in adults is normally induced with an IV agent like propofol, producing unconsciousness in 30 to 40 seconds.
- Additional inhalation and/or IV drugs may be given to produce the desired depth of anesthesia.

2. Maintenance of anesthesia

- Maintenance is commonly provided with volatile anesthetics, which offer good control over the depth of anesthesia.
- Opioids such as fentanyl are used for analgesia along with inhalation agents, because the latter are not good analgesics.

3. Recovery

- Postoperatively, the anesthetic admixture is withdrawn, and the patient is monitored for return of consciousness. For most anesthetic agents, recovery is the reverse of induction. Redistribution from the site of action (rather than metabolism of the drug) underlies recovery.
- If neuromuscular blockers have not been fully metabolized, reversal agents may be used.

Depth of Anesthesia

The depth of anesthesia has four sequential stages characterized by increasing CNS depression as the anesthetic accumulates in the brain

1. Stage I—Analgesia:

Loss of pain sensation results from interference with sensory transmission in the spinothalamic tract. The patient progresses from conscious and conversational to drowsy.

2. Stage II—Excitement:

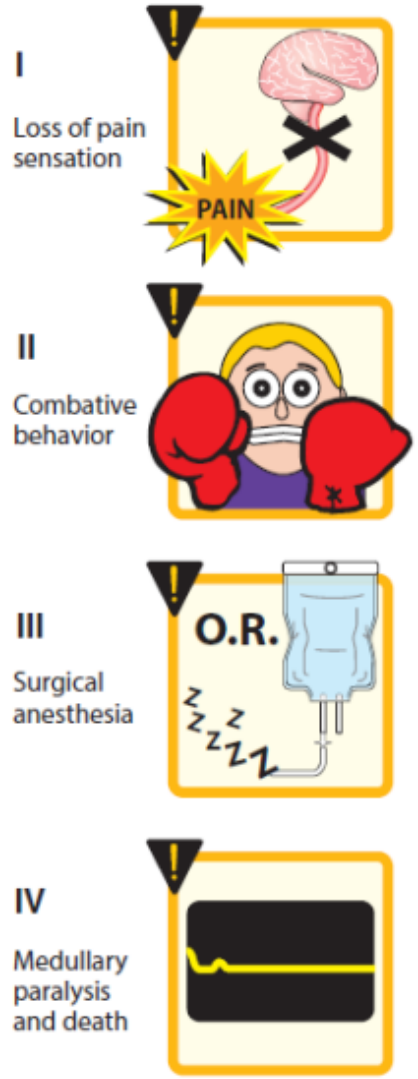
The patient displays delirium and possibly combative behavior. A rise and irregularity in blood pressure and respiration occur, as well as a risk of laryngospasm. To shorten or eliminate this stage, rapid-acting IV agents are given before inhalation anesthesia is administered.

3. Stage III—Surgical anesthesia:

There is gradual loss of muscle tone and reflexes as the CNS is further depressed. Regular respiration and relaxation of skeletal muscles with eventual loss of spontaneous movement occur. This is the ideal stage for surgery. Careful monitoring is needed to prevent undesired progression to stage IV.

4. Stage IV—Medullary paralysis:

Severe depression of the respiratory and vasomotor centers occurs. Ventilation and/or circulation must be supported to prevent death.



Inhalation Anesthetics

- No specific receptor has been identified as the locus of general anesthetic action.

- Inhaled gases are used primarily for maintenance of anesthesia after administration of an IV agent. Depth of anesthesia can be rapidly altered by changing the inhaled concentration.

- Inhalational agents have very steep dose–response curves and very narrow therapeutic indices, so the difference in concentrations causing surgical anesthesia and severe cardiac and respiratory depression is small. No antagonists exist.

- General anesthetics increase the sensitivity of the γ-aminobutyric acid (GABAA) receptors to the inhibitory neurotransmitter GABA.

- Unlike other anesthetics, nitrous oxide and ketamine do not have actions on GABAA receptors. Their effects are likely mediated via inhibition of the N-methyl-d-aspartate (NMDA) receptors.

- Other receptors are also affected by volatile anesthetics. For example, the activity of the inhibitory glycine receptors in the spinal motor neurons is increased. In addition, they also block excitatory postsynaptic currents of nicotinic receptors.

Isoflurane

- It does not induce cardiac arrhythmias or sensitize the heart to catecholamines. However, like other halogenated gases, it produces dose-dependent hypotension.
- It has a pungent odor and stimulates respiratory reflexes (for example, breath holding, salivation, coughing, laryngospasm) and is therefore not used for inhalation induction.
- With higher blood solubility than desflurane and sevoflurane, isoflurane is typically used only when cost is a factor.

Desflurane

- It provides very rapid onset and recovery due to low blood solubility. This makes it a popular anesthetic for outpatient procedures.
- Like isoflurane, it decreases vascular resistance and perfuses all major tissues very well.
- Because it stimulates respiratory reflexes, desflurane is not used for inhalation induction. It is relatively expensive and thus rarely used for maintenance during extended anesthesia.

Sevoflurane

- It has low pungency, allowing rapid induction without irritating the airways. This makes it suitable for inhalation induction in pediatric patients.
- It has a rapid onset and recovery due to low blood solubility.

Nitrous oxide

- It is a nonirritating potent analgesic but a weak general anesthetic.

- It is frequently used at concentrations of 30 to 50% in combination with oxygen for analgesia, particularly in dentistry.

- Nitrous oxide alone cannot produce surgical anesthesia, but it is commonly combined with other more potent agents.

- Nitrous oxide does not depress respiration and does not produce muscle relaxation.

- When co-administered with other anesthetics, it has moderate to no effect on the cardiovascular system or on increasing cerebral blood flow, and it is the least hepatotoxic of the inhalation agents. Therefore, it is probably the safest of these anesthetics, provided that sufficient oxygen is administered simultaneously.

Intravenous Anesthetics

Propofol

- It is an IV sedative/hypnotic used for induction and/or maintenance of anesthesia.
- It is widely used and has replaced thiopental as the first choice for induction of general anesthesia and sedation.

Onset: Induction is smooth and occurs 30 to 40 seconds after administration.

Actions: It has less of a depressant effect than volatile anesthetics on CNS evoked potentials, making it useful for surgeries in which spinal cord function is monitored.

- It does not provide analgesia, so supplementation with narcotics is required.
- Propofol is commonly infused in lower doses to provide sedation.

Intravenous Anesthetics

Benzodiazepines

- They are used in conjunction with anesthetics for sedation.
- The most commonly used is Midazolam. Diazepam and Lorazepam are alternatives.
- All three facilitate amnesia while causing sedation, enhancing the inhibitory effects of various neurotransmitters, particularly GABA.
- Minimal cardiovascular depressant effects are seen, but all are potential respiratory depressants (especially when administered IV).

Opioids

- Because of their analgesic property, opioids are commonly combined with other anesthetics.
- The most commonly used opioids are fentanyl and its congeners, sufentanil and remifentanil, because they induce analgesia more rapidly than morphine.
- They may be administered intravenously, epidurally, or intrathecally (into the cerebrospinal fluid).
- Opioid effects can be antagonized by naloxone.

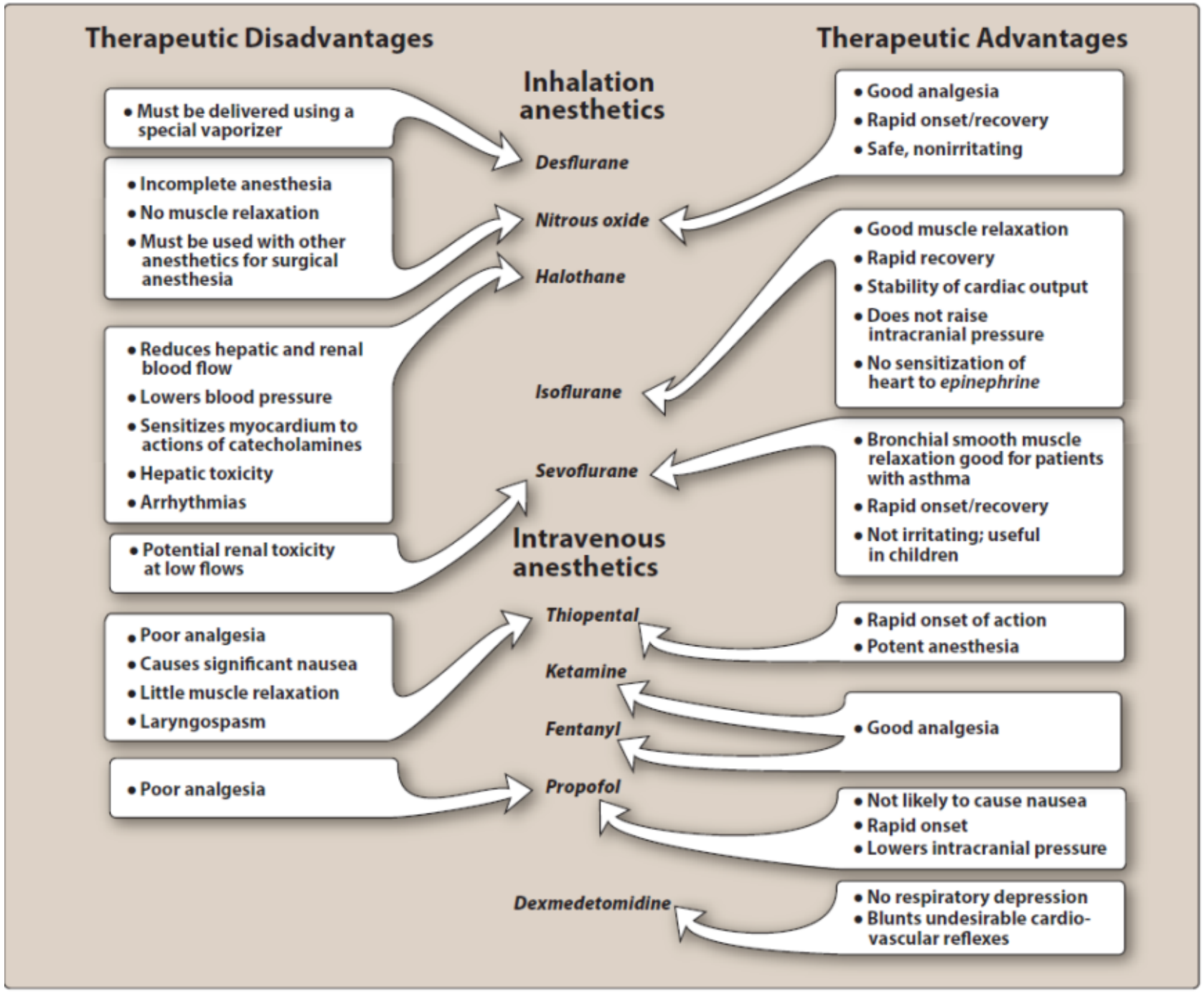
Intravenous Anesthetics

Etomidate

- It is a hypnotic agent used to induce anesthesia, but it lacks analgesic activity.
- Induction is rapid, and the drug is short-acting. Among its benefits are little to no effect on the heart and circulation.
- Etomidate is usually only used for patients with coronary artery disease or cardiovascular dysfunction.

Dexmedetomidine

- It is a sedative used in intensive care settings and surgery.
- It is relatively unique in its ability to provide sedation without respiratory depression.
- Like clonidine, it is an α2 receptor agonist in certain parts of the brain.
- It has sedative, analgesic, sympatholytic, and anxiolytic effects that blunt many cardiovascular responses.
- It reduces volatile anesthetic, sedative, and analgesic requirements without causing significant respiratory depression.

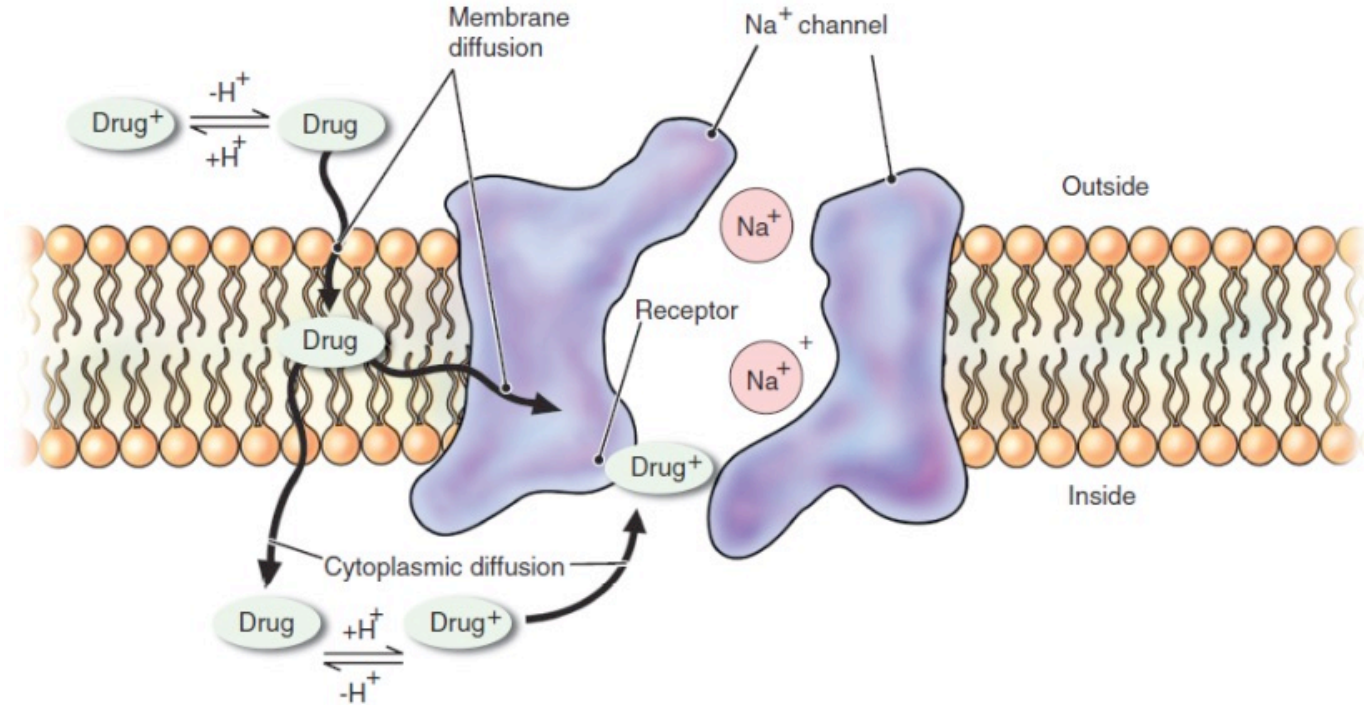

Therapeutic Disadvantages
Therapeutic Advantages
Inhalation anesthetics
• Must be delivered using a special vaporizer
• Good analgesia
• Rapid onset/recovery
• Safe, nonirritating
Desflurane
• Incomplete anesthesia
• No muscle relaxation
• Must be used with other anesthetics for surgical anesthesia
Nitrous oxide
Halothane
• Good muscle relaxation
• Rapid recovery
• Stability of cardiac output
• Does not raise intracranial pressure
• No sensitization of heart to epinephrine
• Reduces hepatic and renal blood flow
• Lowers blood pressure
• Sensitizes myocardium to actions of catecholamines
• Hepatic toxicity
• Arrhythmias
Isoflurane
Sevoflurane
• Bronchial smooth muscle relaxation good for patients with asthma
• Rapid onset/recovery
• Not irritating; useful in children
• Potential renal toxicity at low flows
Intravenous anesthetics
Thiopental
• Rapid onset of action
• Potent anesthesia
• Poor analgesia
• Causes significant nausea
• Little muscle relaxation
• Laryngospasm
Ketamine
Fentanyl
• Good analgesia
• Poor analgesia
Propofol
• Not likely to cause nausea
• Rapid onset
• Lowers intracranial pressure
Dexmedetomidine
• No respiratory depression
• Blunts undesirable cardiovascular reflexes

Local Anesthetics

bupivacaine, lidocaine, chloroprocaine, mepivacaine, procaine, ropivacaine, and tetracaine

- Local anesthetics block nerve conduction of sensory impulses and, in higher concentrations, motor impulses from the periphery to the CNS.

- Na^+ ion channels are blocked to prevent the transient increase in permeability of the nerve membrane to Na^+ that is required for an action potential.



Summary of pharmacologic properties of some local anesthetics

DRUG	POTENCY	ONSET	DURATION
Procaine	Low	Rapid	Short
Chloroprocaine	Low	Rapid	Short
Tetracaine	High	Slow	Long (spinal)
Lidocaine	Low	Rapid	Intermediate
Mepivacaine	Low	Moderate	Intermediate
Bupivacaine	High	Slow	Long
Ropivacaine	High	Moderate	Long

Opioids

Opioid Receptors

- The major effects of the opioids are mediated by three receptor families, which are commonly designated as μ (mu), κ (kappa), and δ (delta).
- 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.

Common adverse effects in individuals treated with opioids

Hypotension

Urinary retention

Dysphoria (anxiety, depression, or unease)

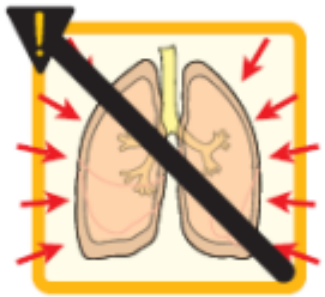
Nausea

Sedation

Potential for addiction

Constipation

Respiratory depression



Opioid Agonists

1. **Morphine:** is the major analgesic drug contained in crude opium and is the prototype strong μ receptor agonist.

- **Mechanism of action:** Morphine and other opioids exert their major effects by interacting stereospecifically with opioid receptors on the membranes of certain cells in the CNS and other anatomic structures, such as the gastrointestinal (GI) tract and the urinary bladder.

- Morphine also acts at κ receptors in lamina I and II of the dorsal horn of the spinal cord. It decreases the release of substance P, which modulates pain perception in the spinal cord.

- Morphine also appears to inhibit the release of many excitatory transmitters from nerve terminals carrying nociceptive (painful) stimuli.

Morphine

Actions:

1. Analgesia: Morphine and other opioids cause analgesia (relief of pain without the loss of consciousness) and relieve pain both by raising the pain threshold at the spinal cord level and, more importantly, by altering the brain's perception of pain.
2. Euphoria: Morphine produces a powerful sense of contentment and well-being.
3. Respiration: Morphine causes respiratory depression by reduction of the sensitivity of respiratory center neurons to carbon dioxide.
4. Depression of cough reflex: Both morphine and codeine have antitussive properties.
5. Miosis: The pinpoint pupil characteristic of morphine use results from stimulation of μ and κ receptors.
6. Emesis: Morphine directly stimulates the chemoreceptor trigger zone in the area postrema that causes vomiting.
7. Cardiovascular: Morphine has no major effects on the blood pressure or heart rate at lower dosages.

Morphine

Actions:

8. Histamine release: Morphine releases histamine from mast cells causing urticaria, sweating, and vasodilation.

9. Hormonal actions: Morphine increases growth hormone release and enhances prolactin secretion. It increases antidiuretic hormone and leads to urinary retention.

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

Codeine

- Codeine is a naturally occurring opioid that is a weak analgesic compared to morphine. It should be used only for mild to moderate pain.
- Codeine is commonly used in combination with acetaminophen for management of pain.
- Codeine exhibits good antitussive activity at doses that do not cause analgesia.

Oxycodone and oxymorphone

- Oxycodone is a semisynthetic derivative of morphine.
- It is orally active and is sometimes formulated with aspirin or acetaminophen. Its oral analgesic effect is approximately twice that of morphine.
- Oxymorphone is a semisynthetic opioid analgesic.
- When given parenterally it is approximately ten times more potent than morphine. The oral formulation has a lower relative potency and is about three times more potent than oral morphine.

Hydromorphone and hydrocodone

- Hydromorphone and hydrocodone are orally active, semisynthetic analogs of morphine and codeine, respectively.
- Oral hydromorphone is approximately 8 to 10 times more potent than morphine. It is preferred over morphine in patients with renal dysfunction due to less accumulation of active metabolites.
- Hydrocodone is the methyl ether of hydromorphone, but is a weaker analgesic than hydromorphone, with oral analgesic efficacy comparable to that of morphine.
- This agent is often combined with acetaminophen or ibuprofen to treat moderate to severe pain. It is also used as an antitussive.

Fentanyl

- Fentanyl, a synthetic opioid chemically related to meperidine, has 100-fold the analgesic potency of morphine and is used for anesthesia.
- The drug is highly lipophilic and has a rapid onset and short duration of action (15 to 30 minutes).
- Fentanyl is combined with local anesthetics to provide epidural analgesia for labor and postoperative pain.
- The oral transmucosal preparation is used in the treatment of cancer patients with breakthrough pain who are tolerant to opioids.

Sufentanil, alfentanil, and remifentanil

- Sufentanil, alfentanil, and remifentanil are three synthetic opioid agonists related to fentanyl.
- Sufentanil is even more potent than fentanyl, whereas the other two are less potent and shorter acting.
- These agents are mainly used for their analgesic and sedative properties during surgical procedures requiring anesthesia.

Methadone

- Methadone is a synthetic, orally effective opioid that has variable equianalgesic potency compared to that of morphine.
- Methadone induces less euphoria and has a longer duration of action.
- The actions of methadone are mediated by μ receptors. In addition, methadone is an antagonist of the N methyl-d-aspartate (NMDA) receptor and a norepinephrine and serotonin reuptake inhibitor. Thus, it has efficacy in the treatment of both nociceptive and neuropathic pain.
- Methadone is also used in the controlled withdrawal of dependent abusers from opioids and heroin.
- Oral methadone is administered as a substitute for the opioid of abuse, and the patient is then slowly weaned from methadone.

Meperidine

- Meperidine is a lower-potency synthetic opioid structurally unrelated to morphine.
- It is used for acute pain and acts primarily as a κ agonist, with some μ agonist activity also. Meperidine is very lipophilic and has anticholinergic effects, resulting in an increased incidence of delirium as compared to other opioids.
- The duration of action is slightly shorter than that of morphine and other opioids.
- Due to the short duration of action and the potential for toxicity, meperidine should only be used for short-term (≤48 hours) management of pain.

Partial agonists and mixed agonist–antagonists

Buprenorphine

- Buprenorphine is classified as a partial agonist, acting at the μ receptor. It acts like morphine in naïve patients, but it can also precipitate withdrawal in users of morphine or other full opioid agonists.
- A major use is in opioid detoxification, because it has shorter and less severe withdrawal symptoms compared to methadone.
- In contrast to methadone, which is available only at specialized clinics when used for detoxification or maintenance, buprenorphine is approved for office-based detoxification or maintenance.
- Buprenorphine tablets are indicated for the treatment of opioid dependence and are also available in a combination product containing buprenorphine and naloxone.
- Naloxone was added to prevent the abuse of buprenorphine via IV administration.
- The injectable form and the once-weekly transdermal patch are indicated for the relief of moderate to severe pain.

Partial agonists and mixed agonist–antagonists

Pentazocine

- Pentazocine acts as an agonist on κ receptors and is 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.
- Pentazocine produces less euphoria compared to morphine.

Nalbuphine and butorphanol

- Nalbuphine and butorphanol are mixed opioid agonist–antagonists.
- Like pentazocine, they play a limited role in the treatment of chronic pain.
- Butorphanol is available in a nasal formulation that has been used for severe headaches.
- Neither agent is available for oral use.
- Their propensity to cause psychotomimetic effects (actions mimicking the symptoms of psychosis) is less than that of pentazocine.
- Nalbuphine does not affect the heart or increase blood pressure, in contrast to pentazocine and butorphanol.

Other Analgesics

Tapentadol

- Tapentadol, a centrally acting analgesic, is an agonist at the μ opioid receptor and an inhibitor of norepinephrine reuptake.
- It has been used to manage moderate to severe pain, both chronic and acute.

Tramadol

- Tramadol is a centrally acting analgesic that binds to the μ opioid receptor.
- The drug undergoes extensive metabolism via CYP450 2D6, leading to an active metabolite with a much higher affinity for the μ receptor than the parent compound.
- It is used to manage moderate to moderately severe pain.

Opioid Antagonists

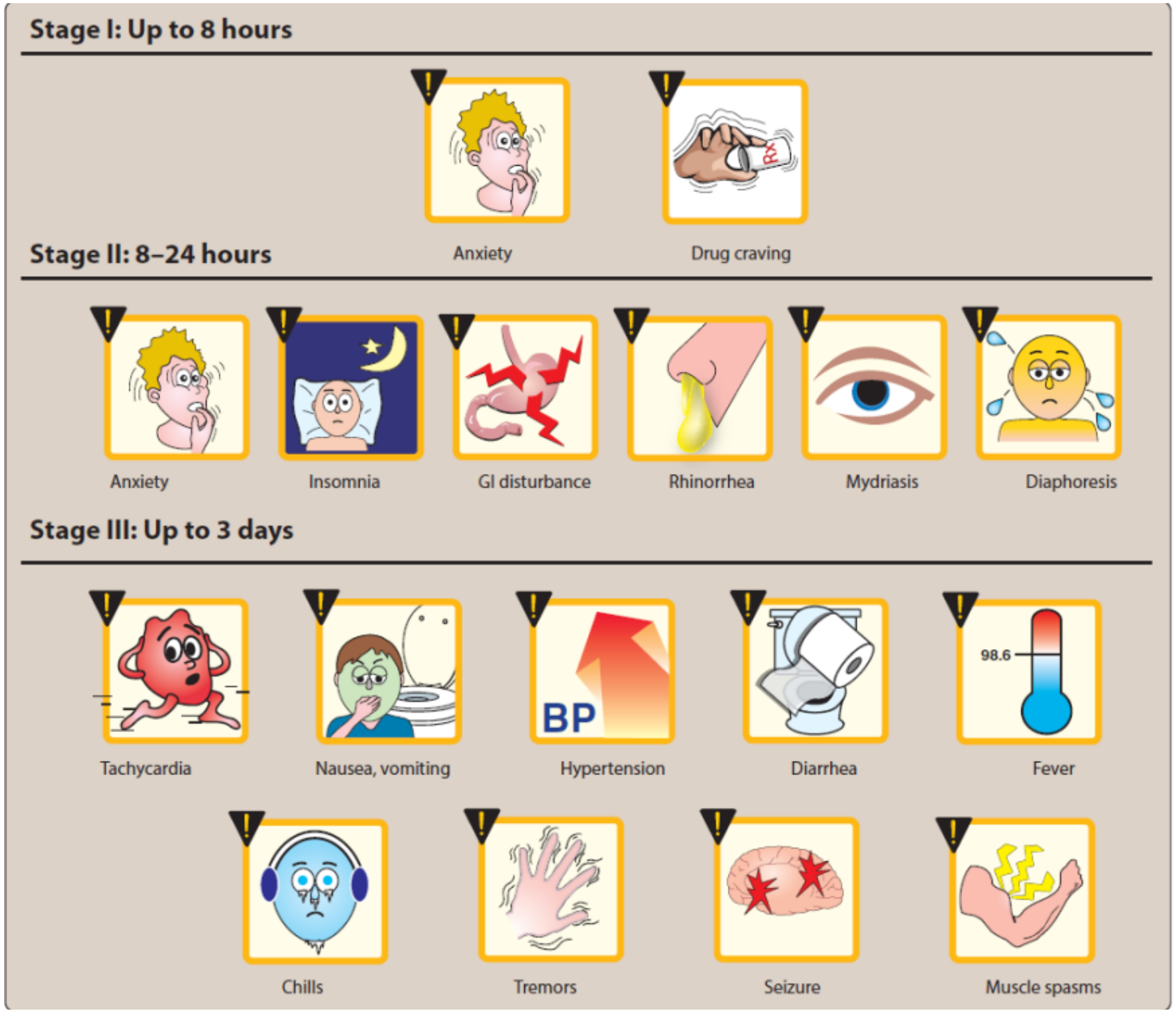
Naloxone

- Naloxone is used to reverse the coma and respiratory depression of opioid overdose within 30 seconds of IV injection.
- It rapidly displaces all receptor-bound opioid molecules and, therefore, is able to reverse the effect of a morphine overdose.

Naltrexone

- Naltrexone has actions similar to those of naloxone.
- It has a longer duration of action than naloxone, and a single oral dose of naltrexone blocks the effect of injected heroin for up to 24 hours.
- Naltrexone in combination with clonidine (and, sometimes, with buprenorphine) is used for rapid opioid detoxification.

Opiate withdrawal syndrome

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