

Opioids 2

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Codeine

Codeine is a naturally occurring opioid and a weak analgesic compared to *morphine*. It is used for mild-to-moderate pain. The analgesic actions of *codeine* are derived from its conversion to *morphine* by the CYP2D6 enzyme. CYP2D6 activity varies among patients, and ultra-rapid metabolizers may experience higher levels of *morphine*, leading to possible overdose and toxicity. Lifethreatening respiratory depression and death have been reported in children who received *codeine*, mostly following tonsillectomy and/or adenoidectomy. *Codeine* is commonly used in combination with *acetaminophen* for management of pain. The drug exhibits good antitussive activity at doses that do not cause analgesia. ***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. ***Noscapine*** is an opium alkaloid obtained from the plant *Papaver somniferum* exerts its antitussive effects through the activation of sigma opioid receptors without narcotic, analgesic, or dependence-inducing properties. *Noscapine* is registered for the treatment of a dry nonproductive cough and is available as a syrup and a tablet.

Oxycodone and oxymorphone

Oxymorphone and *oxycodone* are orally active, semisynthetic analogs of *morphine* and *codeine*, respectively. *Oxymorphone* given parenterally is approximately 10 times more potent than *morphine*, but when administered orally the potency drops to about three times that of *morphine*. *Oxymorphone* is available in both immediate-release and extended-release oral formulations. This agent has no clinically relevant drug interactions associated with the CYP450 enzyme system. *Oxycodone* is approximately two times more potent than *morphine* and is available in an immediate-release formulation, alone or in combination with *acetaminophen*, *aspirin*, or *ibuprofen*. An extended-release formulation is also available. *Oxycodone* is mainly metabolized via the CYP2D6 and CYP3A4 enzymes.

Hydromorphone and hydrocodone

Hydromorphone and *hydrocodone* are orally active, semisynthetic analogs of *morphine* and *codeine*, respectively. Oral *hydromorphone* is approximately four to seven times more potent than oral *morphine*. It is preferred over *morphine* in patients with renal dysfunction due to less accumulation of active metabolites. *Hydrocodone* is the methyl ether derivative 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. *Hydrocodone* is metabolized in the liver to several metabolites, one of which is *hydromorphone* via the actions of CYP2D6.

Fentanyl

Fentanyl is a synthetic opioid chemically related to *pethidine*. *Fentanyl* has 100-folds the analgesic potency of *morphine* and is used for anesthesia and acute pain management. The drug is highly lipophilic and has a rapid onset and short duration of action (15 to 30 minutes). It is usually administered IV, epidurally, or intrathecally.

Fentanyl is combined with local anesthetics to provide epidural analgesia for labor and postoperative pain. IV *fentanyl* is used in anesthesia for its analgesic and sedative effects. Many fast-acting transmucosal and nasal *fentanyl* products are available for cancer-related breakthrough pain in opioid-tolerant patients. The transdermal patch creates a reservoir of the drug in the skin and has a delayed onset of at least 12 hours and a prolonged offset. The patch is used for the management of chronic severe pain. It is contraindicated in opioid-naïve patients and should not be used in management of acute or postoperative pain. *Fentanyl* is metabolized to inactive metabolites by CYP 3A4 and drugs that inhibit this isoenzyme can potentiate the effect of *fentanyl*.

Sufentanil, alfentanil, remifentanil, and carfentanil

Sufentanil, alfentanil, remifentanil, and carfentanil are synthetic opioid agonists related to *fentanyl*. These agents differ in potency and metabolic disposition. *Sufentanil* and *carfentanil* are even more potent than *fentanyl*, whereas the other two are less potent and shorter acting.

Sufentanil, alfentanil, and remifentanil are mainly used for their analgesic and sedative properties during surgical procedures requiring anesthesia. *Carfentanil* is about 100 times more potent than *fentanyl*.

The drug is not used in clinical practice; however, it is of toxicological interest as it is used to lace *heroin* and has contributed to several opioid-related deaths.

Methadone

Methadone is a synthetic, orally effective opioid that has variable equianalgesic potency compared to that of *morphine*, and the conversion between the two products is not linear. *Methadone* is a μ agonist, an antagonist of the N-methyl-D-aspartate (NMDA) receptor, and a norepinephrine and serotonin reuptake inhibitor. Therefore, it is useful in the treatment of both nociceptive and neuropathic pain. *Methadone* may also be used for opioid withdrawal and maintenance therapy in the setting of prescription opioid and *heroin* abuse. The withdrawal syndrome with *methadone* is milder but more protracted (days to weeks) than that with other opioids. *Methadone* induces less euphoria and has a longer duration of action than *morphine*. Unlike *morphine*, *methadone* is well absorbed after oral administration. *Methadone* is also constipating, but less so than *morphine*. *Methadone* can produce physical dependence like that of *morphine*, but it has less neurotoxicity than *morphine* due to lack of active metabolites. *Methadone* can prolong the QTc interval and cause torsades de pointes, possibly by interacting with cardiac potassium channels. Baseline and routine ECG monitoring is recommended

Pethidine (meperidine)

Pethidine 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. *Pethidine* is very lipophilic and has anticholinergic effects, resulting in an increased incidence of delirium compared with other opioids. *Pethidine* has an active minor metabolite (norpethidine) which is potentially neurotoxic whereas the major metabolite is meperidinic acid along with glucuronide conjugation metabolites which are excreted via kidney. As they are renally excreted, they can cause accumulation in patients with renal insufficiency. It can cause delirium, hyper-reflexia, myoclonus, and seizures in any patient following overdose, long-term use, especially in patients with renal insufficiency. Due to the short duration of action and the potential for toxicity, *pethidine* should only be used for short-term (≤ 48 hours) management of pain. *Pethidine* should not be used in elderly patients or in those with renal insufficiency, hepatic insufficiency, pre-existing respiratory compromise, or concomitant or recent administration of MAOIs. Serotonin syndrome has been reported in patients receiving both *pethidine* and selective serotonin reuptake inhibitors (SSRIs). *Pethidine* is primarily used as an analgesic and in preanesthetic medication. It can also be used to control shivering during the postsurgical recovery period. Transdermal *pethidine* is used for the management of cancer pain. On the transdermal route, the onset of pain is delayed up to 12 hours; however, on subsequent administration, the analgesic effect is sustained for prolonged periods in patients.

Tramadol

Tramadol is a centrally acting analgesic that binds to the μ opioid receptor. It undergoes extensive metabolism via CYP2D6, leading to an active metabolite which has a much higher affinity for the μ receptor than the parent compound. In addition, it weakly inhibits reuptake of norepinephrine and serotonin. It is used to manage moderate-to-severe pain. Of note, *tramadol* has less respiratory-depressant activity compared to *morphine*. Administration of *naloxone* can only partially reverse *tramadol* toxicity and has been associated with an increased risk of seizures. Anaphylactoid reactions have been reported. Overdose or drug–drug interactions with SSRIs, MAOIs, and tricyclic antidepressants can lead to toxicity manifested by CNS excitation and seizures. *Tramadol* should be used with caution in patients with a history of seizures. As with other agents that bind the μ opioid receptor, *tramadol* has been associated with misuse and abuse.

Diphenoxylate and loperamide

Diphenoxylate and *loperamide* are used for the treatment of diarrhea.

At a much higher dose, *diphenoxylate* shows opioid activity including euphoria. Therefore, *diphenoxylate* is combined with *atropine* to reduce the chance of abusing liability. *Definoxin* is a metabolite of *diphenoxylate* which is also being marketed along with *atropine* as a fixed-dose combination. *Loperamide* shows action similar to that of *diphenoxylate*. It exerts its action by interacting with the opioid receptors in the intestine. Abdominal cramps and constipation are the common side effects observed with these agents.

Propoxyphene

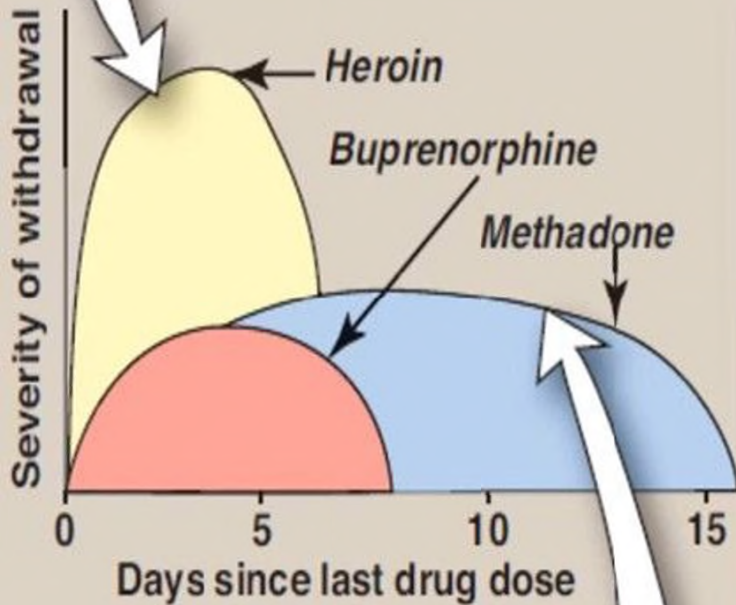
Propoxyphene is a congener of *methadone*. However, it has the analgesic activity and side effects similar to those of *codeine* but less antitussive action. It can be combined with NSAIDs such as *paracetamol* and *aspirin*. Its dextro form is found to be analgesic; therefore, it is used as dextropropoxyphene. The levo form is found to have antitussive activity.

PARTIAL AGONISTS AND MIXED AGONIST–ANTAGONISTS

Partial agonists bind to the opioid receptor, but they have less intrinsic activity than full agonists. There is a ceiling to the pharmacologic effects of these agents. Drugs that stimulate one receptor but block another are termed mixed agonist–antagonists. The effects of these drugs depend on previous exposure to opioids. In individuals who are opioid-naïve, mixed agonist–antagonists show agonist activity and are used to relieve pain. In the presence of a full agonist, the agonist–antagonist drugs may precipitate opioid withdrawal symptoms.

Pentazocine, Nalbuphine and butorphanol

Buprenorphine is used in opiate detoxification because it has a less severe and shorter duration of withdrawal symptoms compared to **methadone**.



Symptoms last longest with **methadone**, but are less severe than those of **heroin** withdrawal.

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

Stage I: Up to 8 hours



Anxiety



Drug craving

Stage II: 8–24 hours



Anxiety



Insomnia



GI disturbance



Rhinorrhea



Mydriasis



Diaphoresis

Stage III: Up to 3 days



Tachycardia



Nausea, vomiting



Hypertension



Diarrhea



Fever



Chills



Tremors



Seizure



Muscle spasms

Naloxone

Naloxone is a competitive antagonist at μ , κ , and δ receptors, with a 10-fold higher affinity for μ than for κ receptors. It rapidly displaces all receptor-bound opioid molecules and, therefore, can reverse the effects of *morphine* overdose, such as respiratory depression and coma within 1 to 2 minutes of IV administration. It is also used to diagnose opioid dependence. *Naloxone* can also be administered intramuscularly, subcutaneously, and intranasally, with a slightly longer onset of 2 to 5 minutes; however, little to no clinical effect is seen with oral *naloxone* due to extensive first-pass metabolism. Since *naloxone* has a half-life of 30 to 81 minutes, a patient who has been treated for an overdose and recovered may lapse back into respiratory depression, depending on the opioid ingested and dosage form of that opioid. Therefore, multiple doses should be administered. [Note: Much higher doses and continuous administration of *naloxone* are needed to reverse the effects of *buprenorphine* due to its high affinity for the μ receptor.] The duration of action of *naloxone* lasts for up to 48 hours; it is used to decrease the craving for alcohol.

Naltrexone

Naltrexone has actions similar to those of *naloxone*, but it has a longer duration of action and can be given orally. For example, a single oral dose of *naltrexone* blocks the effect of injected *heroin* for up to 24 hours, and the intramuscular formulation blocks the effect for 30 days. *Naltrexone* in combination with *clonidine* (and, sometimes, with *buprenorphine*) is used for rapid opioid detoxification. *Naltrexone* has been reported to cause hepatotoxicity, and monitoring of hepatic function is recommended.