OPIOID MEDICATIONS
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OVERVIEW

The biology and pharmacology of opioids explains why they are effective in treating pain and also addicting. Medications like buprenorphine are effective at treating opioid addiction because they behave partially like opioids, relieving some of the addiction symptoms.

In this chapter, you will learn:

- The basic biological actions of opioids
- Common symptoms of addiction
- What buprenorphine is and how it blocks symptoms of opioid addiction
- Buprenorphine’s side effects, drug interactions, and precautions to take
- Special populations that may need to take extra care when using buprenorphine
- Other types of medication-assisted treatment and how the best one is determined for each patient case
WHAT ARE OPIOIDS?

Understanding what opioids are is important in order to understand the treatment of opioid use disorder and buprenorphine treatment.

Opioids Include:
- Chemicals produced naturally by plants (morphine)
- Synthetic or semisynthetic drugs (methadone and heroin)

In humans, opioids act as naturally occurring neurochemicals that are involved in:
- Pain modulation
- Regulation of gastrointestinal tract motility
- Immune function

Opioids Are Used Clinically For:
- Pain management (Analgesia)
- Treating diarrhea
- Cough suppressant
**OPIOID CATEGORIES**

**Opioids**
An opioid is any drug that interacts with the body's natural opioid receptors in the body. There are three types of opioids: 1) The body makes its own opioids, called “endogenous opioids.” 2) Opioids, such as morphine, are produced naturally by plants; 3) Opioids, such as methadone and heroin which are synthetic or semisynthetic drugs.

1. **Natural “Endogenous” Opioids**
Humans naturally make chemicals that bind to the opioid receptors. These chemicals are called neurotransmitters and include the endorphins, enkephalins, and dynorphins. These neurotransmitters are called endogenous opioids because they are made by our bodies, but have somewhat similar actions to the drug opioid. Endogenous opioid neurotransmitters are involved in a wide range of biological processes, including pain modulation, regulation of gastrointestinal tract motility, and immune function.

2. **Naturally Occurring Opioids From Plants**
Opiates occur naturally in some plants, such as codeine and morphine. They can be used on their own or used to create semi-synthetic opioids.

3. **Semi-Synthetic Opioids And Synthetic Opioids**
The semi-synthetic opioids are derived from the naturally-occurring opiates and include heroin (derived from morphine) and buprenorphine (derived from thebaine).

Synthetic opioids are synthesized artificially, using no plant-based precursors. They include oxycodone, hydrocodone, fentanyl, and methadone.

**Clinical Applications**
Opioids are used in the clinical setting primarily as analgesics, i.e., for pain control. They can also be used to treat diarrhea or coughing, though these uses are less prevalent. Most clinically-relevant opioids also have properties, such as euphoria (a very good mood), which make them highly reinforcing, and therefore have a high potential for abuse and addiction. They are also important in a negative way because of the risk for overdose.

**Opioid Receptors**
Opioid receptors are the places in the brain where opioids connect and cause their drug effect. Receptors are relevant to treatment of opioid use disorder because medications, such as buprenorphine, act to fight addiction by blocking these receptors.
ADVANCED REVIEW OF OPIOID RECEPTOR TYPES

Note: For patients who want a detailed understanding of opioid receptors we are including this detailed information. You may certainly skip this section if you prefer.

Opioids exert their effect by interacting with receptors on cells which activates the cell. Opioids interact with 3 types of receptors:

- mu (μ) – activation produces reinforcement and dependence.
- kappa (κ) – activation induces dysphoria and drug intake from stress
- delta (δ) – mechanisms are less well understood

Opioids may act at one or more receptor. Buprenorphine blocks kappa receptors, but also has a partial effect with mu receptors and can produce mild reinforcement and dependence.

Mu Receptors
The responses to activation of the mu receptor include:

- Analgesia
- Sleepiness
- Reduced awareness
- Respiratory depression – this is key in overdose
- Gastrointestinal depression
- Pupil constriction
- Euphoria

Mu receptor activation is also:

- Highly reinforcing psychologically
- Highly dependence inducing

Opioids used to treat pain and to treat addiction all work at the mu receptor. The clinically significant opioids have strong mu action, which means they are rewarding, analgesic, and act as respiratory depressants.

Kappa Receptors
As with the mu receptor, activation of kappa receptors produces:

- Analgesia

However, unlike the mu receptor, kappa activation is associated with:

- Dysphoria (unpleasant mood) rather than euphoria
- Aversion rather than reinforcement

Some drugs that act on Kappa receptors include pentazocine and menthol

Delta Receptors
Delta receptors have not been studied as extensively as mu or kappa receptors.

Which receptors are most relevant to overdose?
- Mu opioid receptors produce respiratory depression, which is relevant for overdose as it can be fatal. Mu receptors also produce analgesia, sleepiness, reduced awareness, gastrointestinal depression, pupil constriction, and euphoria.
• Delta opioid receptors appear to mediate the emotional aspects of opioid addiction.
• Kappa opioid receptors do not produce respiratory depression.

**Action: Agonists, Partial Agonists, and Antagonists**

“Agonists” combine with their corresponding receptors completely and produce a complete response, such as analgesia or euphoria; antagonists block agonists from this happening.

**Classification Of Opioids And Related Medications**

- Full agonists
- Partial agonists
- Antagonists

The graph from SAMHSA (2001) shows the dose/response profiles in terms of receptor activation, for the different classifications of drugs:

**Agonist Drugs**

1. Bind to and activate receptors in a dose-dependent manner until all opioid receptors are occupied.
2. At this point, the maximum possible response has been reached, and increased doses of agonist lead to respiratory depression and overdose.
3. Most abused opioids, as well as some drugs used to treat opioid use disorder, have an agonist effect at mu receptors.

Examples: heroin, methadone, and oxycodone.

**Partial Agonist Drugs**

Bind to the same receptors as agonists but only cause partial activation.

1. At low doses, partial agonists also exhibit dose-dependent binding.
2. At higher doses, receptor activation stops increasing with increased dose and a plateau or ceiling effect is seen.
3. The plateau or leveling off of the curve happens after fewer receptors are activated and at a lower dose than a full agonist.

Buprenorphine is a partial agonist with respect to respiratory depression effects, making it safer than the full agonist opioids, such as fentanyl. The ceiling effect seen in buprenorphine applies to the euphoria and analgesia. As a result, buprenorphine also has less of these properties than a full agonist opioid.

**Antagonist Drugs**

1. Bind to the same receptors as full and partial agonists but do NOT cause activity at the receptor.
2. Antagonists block agonists and partial agonists from binding, preventing receptor activation altogether.

Examples: naloxone, naltrexone, and nalmefene.
• Naloxone is the antagonist used in combination with buprenorphine in the most common form of buprenorphine therapy. It is also widely used to reverse opioid overdoses and is now often distributed along with a prescription for chronic opioids. Naltrexone is commonly used to treat alcohol use disorder.

• Opioids are sometimes referred to by the receptors with which they interact and how they interact with those receptors. For example, heroin and many other opioids that are abused are mu agonists.

• Some opioids have different effects at different receptors—for example, buprenorphine is a mu partial agonist and a kappa antagonist. Oxycodone is a mu agonist and a selective kappa agonist.
**OPIOID TOLERANCE**

Repeated use of opioids leads to a physiological adaptation where it takes more drug to get the same effect, called **tolerance**.

Physiologically, this means that the opioid user requires increasingly larger opioid doses to get the same drug effects\(^5\).

A consequence of this neurological adaptation is that habitual use of opioids, both illicit and licit, leads to physical dependence on opioids. The adapted neurological system is unable to function "normally" if there is a drop in levels of opioids, such as might occur if the dependent individual stops taking an opioid agonist or the actions of the opioid agonist are blocked by an opioid antagonist\(^6\).

Because buprenorphine is only a partial agonist, you will not develop tolerance to buprenorphine, as you may have experienced with opioids. Patients tend to be able to stay at a stable dose of buprenorphine for a long time.
OPIOID WITHDRAWAL

Withdrawal
The symptoms of opioid withdrawal and their timing may mimic symptoms from other causes, such as the flu, overdose, and depression. Being able to distinguish them is important during buprenorphine treatment. For example, having withdrawal symptoms may signal that you need another dose. Your provider can help you learn to recognize withdrawal and distinguish it from the flu.

Dependent patients who experience a drop in opioid levels go into a dysphoric state of withdrawal. Withdrawal from opioids is uncomfortable and has been compared with having a severe case of influenza, but is not life-threatening in most cases.

1. The first criterion for opioid withdrawal in the DSM 5 is that it occurs after either stopping or reducing opioid use that was substantial for a long time OR after the administration of an opioid antagonist, such as naloxone, following a period of opioid use.

2. The second criterion for opioid withdrawal is to have at least three of the following symptoms from the DSM 5:
   - Dysphoric mood
   - Nausea or vomiting
   - Muscle aches
   - Runny eyes or nose
   - Dilated pupils, goosebumps, or sweating
   - Diarrhea
   - Yawning
   - Fever
   - Insomnia

3. The third criterion is that the above symptoms impair your ability to function

4. The fourth criterion is that the above symptoms cannot be explained by some other condition.

The duration and severity of opioid withdrawal are determined by the opioid that you are dependent on and the degree of your dependence.

Buprenorphine Therapeutic Window and Withdrawal
Buprenorphine has a long therapeutic half-life, which relates to how long it is active in your bloodstream. This means it is effective with dosing once per day.

Buprenorphine’s withdrawal syndrome is somewhat milder than heroin, but is still prolonged and severe, even after tapering to a lower dose. Therefore, it is typically recommended that treatment with buprenorphine be continued long-term.

Non-opioid Medication Approved for Short-Term Withdrawal Treatment
Lofexidine HCL: The FDA approved a non-opioid drug in May 2018 (available for patients in August 2018) for treatment of the physical symptoms of withdrawal in adults, lofexidine hydrochloride (Lucemyra). Mood symptoms of withdrawal are not impacted. Its mechanism of action is to inhibit the release of norepinephrine in the brain and elsewhere in the nervous system. Lofexidine is supplied as an oral tablet and can be used for up to
14 days. The medication can be used to reduce symptoms of withdrawal and thus help people who are stopping opioids adhere to their treatment or detoxification. One use for the medication is expected to be to help patients detoxify before starting treatment with naltrexone.
TYPES OF WITHDRAWAL

There are two types of withdrawal associated with mu opioid agonist dependence:

- Spontaneous Withdrawal
- Precipitated Withdrawal

Spontaneous Withdrawal
Spontaneous withdrawal (usually called just “withdrawal”) occurs when a physically-dependent individual suddenly stops or significantly decreases opioid usage. The time frame for withdrawal is heavily dependent on the half-life of whatever opioid is being taken regularly.

Heroin Withdrawal
Withdrawal from heroin has a relatively short half-life, and so it comes on fairly quickly after stopping the drug.

- Begins 6-12 hours after the last dose
- Peaks between 36-72 hours
- Lasts around 5 days
- Is very intense
- May be several months before the patient feels completely “normal” again

Withdrawal From Drugs With Longer Half-lives (e.g., Methadone, Buprenorphine)

- Has a later onset
- Lasts longer

Precipitated Withdrawal
Precipitated withdrawal is similar to regular withdrawal, but is more intense and starts more rapidly. Precipitated withdrawal occurs when a full agonist, such as heroin, is displaced from opioid receptors by an antagonist, such as naloxone. The naloxone in buprenorphine/naloxone sublingual medication is not significantly bio-available sublingually or orally, so it is basically inactive UNLESS it is injected\textsuperscript{11}. The naloxone is there as a deterrent to injecting it.

A partial agonist such as buprenorphine can precipitate withdrawal in someone who is dependent on a full agonist. Buprenorphine is more likely to precipitate withdrawal if:

- The patient has a high level of physical dependence on the full agonist opioid they misuse.
- There has been a short time interval between the last dose of the full agonist and the first dose of buprenorphine. For this reason, your provider will recommend that you stop taking your last opioid a while (around 12-24 hours) before starting buprenorphine.
- A high dose of buprenorphine is used. For this reason, when you start buprenorphine, it is typically at a lower dose than you will eventually take.
- The full agonist has a long half-life, as is the case with methadone. For this reason, when you take an opioid that is long-acting, you typically stop taking it even earlier before starting buprenorphine, as much as 36 hours.

Protracted Withdrawal
Withdrawal or other symptoms from stopping opioid use often continue past the time expected for acute withdrawal, sometimes lasting months or even years, which has been called protracted withdrawal\textsuperscript{12}. These
symptoms are often improved with buprenorphine treatment. Thus, protracted withdrawal is a reason for long-term maintenance therapy with buprenorphine.

The following symptoms may be experienced weeks to months following acute withdrawal from opioids if you stop taking buprenorphine:

• Anxiety
• Depression
• Sleep disturbances
• Fatigue
• Dysphoria
• Irritability
Opioid Medications

BUPRENORPHINE

Buprenorphine is an opioid, but it only works partially like the opioid you are trying to quit. So, it will prevent you from experiencing withdrawal symptoms even though you stop taking other opioids. It doesn't have most of the adverse effects of being addicted to opioids. For example, you would not need increasing doses over time to experience the same effect. As with the opioid you have been taking, you would experience withdrawal if you stopped taking buprenorphine - Not as severe as with oxycodone, but significant.

The drug Buprenorphine is a partial opioid agonist used in the treatment of opioid use disorder from prescription opioids or heroin. Although it has less potential for abuse than Schedule I and II drugs, it may lead to moderate or low physical dependence or high psychological dependence if abused. 

Indications for Buprenorphine and Efficacy

Buprenorphine is used for withdrawal and maintenance treatment for opioid use disorder. Buprenorphine is primarily prescribed to patients who currently meet the DSM 5 criteria for opioid use disorder, but may be used for patients who are at risk of relapsing to opioid use disorder.

Contraindications

Buprenorphine should NOT be prescribed to:
- Patients who have suffered a head injury or have intracranial lesions
- Patients with a history of hypersensitivity to buprenorphine
- Patients with elevated liver function testing 3-5 times greater than normal
- Patients with moderate to severe hepatic impairment
- Patients who indicate benzodiazepine abuse
- Patients with at-risk alcohol use or alcohol use disorder

Buprenorphine with naloxone should NOT be prescribed to:
- Pregnant women (monotherapy tablets may be used)
- Patients who have had hypersensitivity/allergic reaction to naloxone (monotherapy tablets may be used)
- Patients with hypersensitivity/allergic reaction to buprenorphine

CAUTION TIP

- Buprenorphine can cause fatal respiratory depression in children accidentally exposed to it. Be sure to keep buprenorphine-containing medications out of reach of children.
- Buprenorphine may impair mental or physical abilities required to operate a motor vehicle or machinery, especially during the induction, and dose adjustment stages. Use caution when operating such equipment during treatment.
Adverse Events

Severe Adverse Events
When taken as directed, severe adverse events from buprenorphine are exceedingly rare. An evaluation of waiver programs found that only 0.4% inducted onto buprenorphine ever experienced severe adverse reactions\(^{19}\). The specific reactions reported were\(^{19}\):

- Withdrawal (n=103)
- Allergic reactions (12)
- Respiratory depression (9)
- Drug interactions (9)
- Liver problems (2)
- Renal insufficiency or aggravation of it (2)
- Unspecified (80)

Allergic Reaction
Rarely, patients may develop allergic reactions to either buprenorphine or other components in the tablets, resulting in itchy hives and/or a rash\(^ {15}\). Severe itching of the skin can be a side effect of opioid use instead of a sign of an allergic reaction.

Characteristics
Buprenorphine is a derivative of thebaine, an alkaloid found in opium poppies (Papaver somniferum). Buprenorphine also has the following characteristics:

- Classified as a partial mu agonist, kappa antagonist, nociceptin agonist\(^ {20}\). As a partial agonist, its effects increase only to a certain point with increased dose, and level off at moderate doses, thus contributing to its being abused less than full agonists\(^ {21}\).
- A potent analgesic, used in low doses to avoid side effects\(^ {20}\). Formulations include intravenous or intramuscular (Buprenex) and transdermal (Butrans®).
- Mildly reinforcing, which improves treatment adherence and, therefore, clinical effectiveness compared with antagonist treatment\(^ {20}\).
- Limit on the maximum effect that can be achieved\(^ {20}\). However, the ceiling effect may not apply to the analgesic effect\(^ {4}\).

Metabolism and Excretion
Buprenorphine is primarily metabolized in the gastrointestinal tract and the liver, using the CYP 3A4 system\(^ {22}\). (Interactions with CYP3A4 inducers and inhibitors are described in the related section on drug interactions.) Most buprenorphine metabolites are excreted fecally rather than through renal excretion\(^ {23}\). As a result, buprenorphine is relatively safe for patients with renal insufficiency.
PRECAUTIONS

Abuse Potential
Buprenorphine is somewhat less prone to abuse than most mu agonists – including opioid replacement drugs such as methadone. However, it is abused. Factors that help decrease abuse include that when taken sublingually:

- It does not cause the rush sought by many opioid misusers
- Abuse potential is reduced by the slow speed it reaches the brain

Nevertheless, buprenorphine can be misused, especially if injected; intravenous buprenorphine can cause a rush. Reports from the National Drug Intelligence Center indicate that Suboxone® is used intranasally with success by abusers.

Factors that contribute to buprenorphine's abuse potential include:

- Taken intravenously or intranasally, it does have addiction potential
- Quickly crosses the blood-brain barrier, increasing the possibility for abuse
- Withdrawal from buprenorphine is mild, making it desirable as a drug of abuse

Because buprenorphine is a partial agonist, it potentially can precipitate withdrawal in individuals highly dependent on a full agonist opioid with lower affinity. These individuals are consequently less likely to abuse buprenorphine.

In contrast, individuals who are relatively inexperienced with opioids will experience a more powerful agonist effect from buprenorphine. Opioid-naive individuals who try buprenorphine for the euphoria are therefore more likely to continue to abuse it.

Overdose Risk
Buprenorphine has a ceiling effect, meaning that its effect and respiratory depression increases with increased dose, but this increase levels out at moderate doses. Due to its ceiling effect and poor bioavailability, the risk of overdose from buprenorphine, either accidentally or intentionally, is relatively low.

However, the opioid agonist effect of buprenorphine renders overdose and abuse possible.

Drug Combinations That Enhance Overdose Risk
The risk of overdose is particularly high when combining buprenorphine with sedative-hypnotics, especially benzodiazepines. Taking buprenorphine in conjunction with other drugs, including other opioids, benzodiazepines, alcohol, sedatives, and the drugs described in this module that interact with buprenorphine increases the risk of overdose.

Overdose: Treatment
Buprenorphine overdose is treated with an opioid antagonist, such as naloxone, to displace the buprenorphine. Naloxone kits are often prescribed when chronic opioid therapy is prescribed for use in the event of an overdose. This includes buprenorpine.
### Special Precautions

- Your provider may need to change the dose of your buprenorphine or other drugs you take if they are metabolized using the same pathway (e.g., CYP 3A4).

- Liver disease slows down removal from the body of buprenorphine and the drug it is usually paired with, naloxone. If you have problems with your liver’s function, your provider may need to adjust your dose and monitor you for toxicity or overdose.

- It is best to abstain from alcohol while taking buprenorphine because it depresses your central nervous system which can increase your risk for overdose of any opioid, including buprenorphine.

- Taking buprenorphine and benzodiazepines together is dangerous due to central nervous system depression which increases your risk for overdose. Your providers are likely to avoid prescribing these medications together and will monitor you carefully and introduce other precautions if you do take both. Be sure to let all your providers know about other medications you are taking, especially when you are being prescribed a new one.

- For benzodiazepines and all sedating medications (sedative hypnotics, benzodiazepines, alcohol) taken simultaneously with buprenorphine, your provider may monitor you carefully, until the effect on you is understood.

- If you already have compromised respiratory function from lung disease, such as chronic obstructive pulmonary disease (COPD), respiratory depression from an overdose could be more dangerous. As a result, providers prescribing buprenorphine would prescribe buprenorphine.

- If you take seizure medication, your provider may need to adjust the dosage and monitor your plasma levels of buprenorphine to make sure they are at therapeutic levels.
BUPRENORPHINE ACTIONS AT THE CELLULAR LEVELS

Mixed Agonist-Antagonist Opioid
Buprenorphine is a mu (μ) partial agonist and a kappa (κ) antagonist which means that it binds to mu receptors, activating them and binds to kappa opioid receptors, blocking them.

Agonist Mu-Receptor Binding
Buprenorphine has a very high affinity for mu receptors which means that they bind well to these receptors. It also means the drug dissociates from mu receptors slowly. As a result, when both buprenorphine and a mu agonist are present (for example, heroin) the buprenorphine competes with the agonist and binds more readily to the mu receptors, effectively inhibiting the effects of the mu agonist (blocks the heroin).

In other words, buprenorphine partially or totally blocks the effects of abusable opioids, such as heroin and oxycodone\cite{14,30}. Buprenorphine may even precipitate withdrawal symptoms if the individual has also taken a mu agonist, such as heroin.

High affinity and low dissociation also contribute to buprenorphine's:
- Relatively long therapeutic half-life (37 hr average, 20-73 hr range)\cite{20}
- Relatively mild withdrawal syndrome
- Relatively low risk of overdose\cite{27}

Antagonist Kappa-Receptor Binding
Buprenorphine also has a high affinity for kappa receptors. However, as a kappa antagonist, it does not activate the kappa receptor\cite{14}.

Effectiveness for Opioid Use Disorder
Buprenorphine is the most commonly prescribed drug for treatment of opioid use disorder. It is as effective as methadone treatment for reducing opioid use disorder in addicted individuals\cite{31} and effective at markedly reducing relapse rate when taken long-term.

Physicians reported that 68 to 81% of patients were “very satisfied” with buprenorphine treatment\cite{32}.

Buprenorphine (16 mg/day sublingual) has been shown in multiple research studies to be effective in suppressing misuse of opioids\cite{21} and effective when used in a qualified practitioner's office\cite{33-35}

Implant and injectable formulations for treating opioid use disorder have also been shown to be effective\cite{36,37}. 

BUPRENORPHINE SIDE EFFECTS

Commonly Reported Side Effects
Buprenorphine is a safe medication when used as indicated. Side effects are rare, usually minor, and similar to side effects of other opioids. Some of the most commonly reported side effects include:

- Headaches
- Withdrawal syndrome (often precipitated by taking an opioid agonist simultaneously)
- Pain
- Nausea and vomiting
- Constipation
- Insomnia
- Sweating
- Numb mouth and painful tongue

Less Common Side Effects
Other less common side effects of buprenorphine include:

- Breathing problems during sleep
- Risk for serotonin syndrome, adrenal insufficiency, and decreased sex hormone levels with chronic use
- Taste perversion (to tablet or film)
- Anxiety (more common in patients transferring from methadone)
- Drowsiness
- Mood disturbances

Buprenorphine Analgesia
Buprenorphine may cause some analgesia in patients being treated for opioid use disorder. However, the analgesia is less profound and shorter in duration than the buprenorphine formulation that is specifically for pain.

Treating Side Effects
Short term side effects are treated symptomatically. Your provider may address long-term side effects by:

- Lowering the dose of buprenorphine
- Giving time for tolerance to develop to the medication
- Advise you to make lifestyle changes
- Treating constipation with dietary adjustments, increased fiber consumption, stool softeners, and increased fluids or other medication

CAUTION TIP
Sedating Effects
Buprenorphine has the potential for sedation or impairment of psychomotor function during early stages of therapy (induction and titration).
Patients should be advised to avoid other sedating medication, both over the counter and prescribed, as well as alcohol. The addition of benzodiazepines has been associated with overdose death\(^{41}\).

**Buprenorphine Physical Dependence**

Buprenorphine treatment maintains physical dependence. Even though you no longer take the opioid you used previously, your body will still be physically dependent, except now it will be on the less addicting drug, buprenorphine.

Tolerance and physical dependence develop more slowly to buprenorphine than to mu agonists. Individuals who are physically dependent on buprenorphine can be abstinent for longer than individuals dependent on full agonists before withdrawal sets in, but they do still experience withdrawal.

Withdrawal from buprenorphine is:

- Somewhat less severe than withdrawal from a full agonist, such as oxycodone or fentanyl\(^{25}\). However, withdrawal from buprenorphine still can be severe and prolonged even with a taper.
- Withdrawal from buprenorphine may be more tolerable than from full agonists\(^{24}\). However, relapse rates after tapering from buprenorphine are very high\(^{42-44}\).

Drug Interactions of Buprenorphine

**General**

Being familiar with drug interactions of buprenorphine is important, as some are potentially fatal. The following section describes the most significant drug interactions with buprenorphine and the combination of buprenorphine/naloxone. Drug information should be consulted for the most recent and complete description.

Known interactions with buprenorphine or buprenorphine/naloxone combination include the following drug classes:

- Benzodiazepines
- CNS Depressants CYP3A4 inducers and inhibitors
- Nonbenzodiazepine muscle relaxants
- Anticholinergics
- Psychostimulants

**CAUTION TIP**

Due to an increased risk for central nervous system (CNS) depression:

- Individuals misusing benzodiazepine are likely not good candidates for office-based opioid treatment
- Individuals with a history of benzodiazepine addiction or abuse are at high risk to abuse while on buprenorphine and should be monitored closely\(^{16}\).
- Similar problems occur with sedative-hypnotics, e.g., phenobarbital and clonazepam
- When a potentially serious drug interaction is likely (such as taking buprenorphine with CNS depressants and certain HIV medications) patients should be monitored daily\(^{21}\)
- Dose adjustments due to drug interactions vary with the patient\(^{21}\)
Benzodiazepines
The most commonly misused benzodiazepines among lifetime misusers are:

- diazepam (Valium®)
- alprazolam (Xanax®)
- clonazepam (Klonopin®)

Benzodiazepines And Opioids
The interaction between buprenorphine and benzodiazepines can be particularly serious if both medications are considered essential, providers may consider a dose reduction of prescribed benzodiazepine, buprenorphine, or both.

Overdosing on both benzodiazepines and opioids, including buprenorphine, at the same time may cause fatal respiratory depression. The risk is even greater if the buprenorphine is injected.

Symptoms are extreme drowsiness, followed by unconsciousness, and then death.

Opioid prescription-related deaths have increased in recent history, and often, more than one type of drug is involved. Benzodiazepines are the most frequently reported other medication in these deaths. The increase in opioid-related deaths corresponds in time to an increase in the co-prescribing of benzodiazepines with opioids.

- A combination often seen in patients brought into the emergency room is alprazolam (Xanax) with a prescription painkiller, such as oxycodone.
- Coma and death are more likely in sedating drug interactions if buprenorphine is injected.

"The use of benzodiazepines and other sedative-hypnotics [outside of medical supervision, such as Xanax] may be a reason to suspend agonist treatment because of safety concerns related to respiratory depression."

Providers should consider whether a patient with anxiety might be better managed with alternative medications. For example, SSRIs can be very effective for reducing anxiety. Prazosin, which reduces nightmares, improves total and REM sleep, PTSD, and lowers blood pressure, has been described as an alternative. Note: Doxazosin has similar abilities to prazocin and may be preferred due to longer half-life.

Patients who have been historically and consistently maintained on low dose benzodiazepines (e.g., 1 mg of Ativan, 2-3 times a day) can safely start buprenorphine induction. Providers should monitor closely and try to decrease benzodiazepine use over time, if possible.

Alcohol and Sedating Medications
Alcohol
Alcohol is a depressant and, when taken with buprenorphine, it can increase the risk for overdose, respiratory depression, and death. Deaths have been reported in association with the use of buprenorphine together with alcohol. Patients should limit and ideally abstain from alcohol use while taking buprenorphine because of the combined depressant effects. Because of the risk from mixing alcohol with buprenorphine, patients having alcohol use disorder may be considered for referral to an opioid treatment program rather than office-based treatment or approached with a high level of caution.

Your provider will likely screen for alcohol use during the evaluation before starting buprenorphine. It is important to be open and honest about your alcohol use so that a plan can be developed to meet your needs.
positive screen occurs, providers often assess further to determine if there is at-risk drinking (Recommended limits per day for women 3 drinks, for men 4 drinks\(^5\)). Providers will determine the level of intervention needed, from brief intervention, brief treatment with pharmacotherapy, or detoxification and more intense treatment.

Office-based treatment is not recommended for individuals having active at-risk alcohol use or alcohol use disorder, due to known interactions.

**Other CNS Depressants**

Buprenorphine and some sedative-hypnotics have an additive effect when taken together, which is potentially fatal. CNS depressants, including sedatives, hypnotics, general anesthetics, tranquilizers, and other opioids should be used at the same time as buprenorphine only with caution and monitoring because they increase the risk of respiratory depression, over-sedation, hypotension, coma, and death\(^2\).

**Mildly Sedating Medications**

Other medications having milder sedating effects that might be additive, should be used with caution, especially at first, until providers understand how the medication affects the patient. For example, SSRI antidepressants may increase drowsiness in interaction with buprenorphine, especially initially\(^5\).

**Muscle Relaxants**

Nonbenzodiazepine muscle relaxants, such as carisoprodol and cyclobenzaprine, also may increase respiratory depression when taken with buprenorphine\(^7\).

**Interactions With Other Drugs**

**Other Opioids**

Buprenorphine should be used carefully, if at all, in conjunction with other drugs that act on mu opioid receptors. Such drugs include the following:

- Opioid agonists, such as many analgesics used for pain management (e.g., hydrocodone, oxycodone), as well as drugs of abuse (e.g., heroin)
- Opioid antagonists, such as the anti-abuse drug naltrexone

Because of buprenorphine’s high affinity for and slow dissociation from opioid receptors, the medication may block the effects of other opioids. In patients who are physically dependent on opioid agonists, taking buprenorphine may precipitate withdrawal.

**Cocaine And Marijuana**

Further research is needed on drug interactions between buprenorphine and these two drugs\(^5\).

- *Marijuana*: According to expert opinion at a 2015 update on buprenorphine, there was no evidence that marijuana use affects buprenorphine treatment outcome\(^3\).
- *Cocaine*: If used with buprenorphine, cocaine may increase metabolism and diminish buprenorphine plasma concentrations\(^2\). Patients who are actively addicted to cocaine tend to be high-risk for office-based buprenorphine treatment\(^3\).

**Gabapentin**

Gabapentin being used while on buprenorphine may result in psychotic-like symptoms and have sedating effects like any CNS depressant\(^1\).
Anticholinergics
Anticholinergics, including inhaler medications (e.g., ipratropium bromide, oxtropium bromide, tiotropium) and certain medications for gastrointestinal and urinary tract disorders, together with buprenorphine, increase the risk of urinary retention and/or severe constipation and potentially, paralytic ileus².
MEDICATIONS AFFECTING CYP 3A4 SYSTEM

How Buprenorphine Is Affected By Drugs That Affect The CYP 3A4 System
Buprenorphine is metabolized in the liver via the cytochrome P450 3A4 (CYP 3A4) pathway.\(^2\)

- Medications that inhibit CYP 3A4 may increase the plasma concentration of buprenorphine and potentially call for a lower daily dose of buprenorphine
  
  *Includes*: azole antifungals, e.g., ketoconazole; macrolide antibiotics, e.g., erythromycin; HIV protease inhibitors, e.g., Saquinavir, Ritonavir, and Indinavir; antidepressants, e.g., fluoxetine, fluvoxamine, and amitriptyline\(^1\)

- Medications that induce CYP 3A4 activity can decrease buprenorphine's plasma concentration and potentially require a higher daily dose of buprenorphine\(^1\)
  
  *Includes*: phenobarbital, carbamazepine, phenytoin, rifampicin\(^2\)

Buprenorphine can, in turn, also affect plasma concentration and dose of other medications metabolized via CYP 3A4.

CAUTION TIP
Taking buprenorphine with any other CYP 3A4 medication, inducers, or inhibitors can result in over or underdosing, especially at the start or end of these medications. Your provider may monitor this carefully and adjust medication dosage if necessary.
PATIENTS WITH HIV/AIDS

Buprenorphine is metabolized in the liver via the CYP 3A4 pathway. As a result, there may be interactions with drugs affecting that pathway, such as protease inhibitors used in antiretroviral therapy for AIDS (ART)\(^{19}\). Generally speaking, clinically significant drug interactions between combined ART and buprenorphine are rare. Methadone, however, does have clinically significant ART interactions that require methadone dosage adjustment.

Patients On Retroviral Medications

Buprenorphine treatment can be effective among patients with HIV/AIDS already taking combined antiretroviral therapy (ART).

• It is convenient and preferred by many patients to receive both HIV and buprenorphine treatment from the same provider. This is not possible with methadone maintenance treatment.

• Patients need monitoring for adverse reactions, such as opioid intoxication and withdrawal, because the use of certain ART medications may affect buprenorphine concentration in the bloodstream.

Patients Not On Retrovirals, But On Buprenorphine

HIV/AIDS patients who are maintained on buprenorphine and need to begin antiretroviral therapy (ART):

• Can typically be kept on their current dose of buprenorphine when starting ART

• Should learn the signs of opioid intoxication and withdrawal and report any adverse events

• Be seen more frequently during this transition period

Antiretroviral Agents

Importance Of Opioid Addiction Treatment For Adherence To HIV Treatment

When a patient has both opioid use disorder and HIV infection, treatment of the opioid addiction is necessary for successful HIV treatment. Without treatment for the opioid addiction, patient adherence to complex antiretroviral therapies greatly diminishes\(^{36}\).

Drug Interactions Between Buprenorphine And Antiretroviral Drugs

Antiretroviral medications have drug interactions with opioid addiction medications that should be considered in the treatment of both the addiction and HIV. Buprenorphine appears to have fewer interactions with antiretrovirals than methadone\(^{37}\).

Single agents are better studied than the more common combination medications. Details on specific antiretroviral interactions with buprenorphine are complex, and research is ongoing. The latest drug information should be reviewed when these medications are prescribed in combination.

Antiretrovirals may alter buprenorphine levels, but most antiretrovirals that have been tested do not cause buprenorphine withdrawal or toxicity\(^{37}\).

Although most antiretrovirals do not alter buprenorphine levels enough to produce withdrawal or toxicity, atazanavir/ritonavir is an exception. It has produced significant increases in buprenorphine levels as well as some cases of sedation and mental status changes. Buprenorphine metabolite plasma concentrations were significantly increased after a five-day administration of atazanavir with buprenorphine\(^{58}\). Atazanavir/ritonavir increase in concentrations even more.

The effects of two of the main classes of antiretrovirals, protease inhibitors, and nonnucleoside reverse transcriptase inhibitors, is as follows:
• Protease inhibitors and nonnucleoside reverse transcriptase inhibitors (NNRTIs) are metabolized by CYP450 enzymes, especially CYP3A4, which may impact buprenorphine plasma levels
• Some protease inhibitors (Indinavir, nelfinavir, ritonavir, and saquinavir) are inhibitors of CYP450 3A enzyme activity in vitro\textsuperscript{56,58}, which would increase buprenorphine plasma levels
• NNRTIs (nevirapine, delavirdine, and efavirenz) have also shown interactions with opioid treatment, including both methadone and buprenorphine\textsuperscript{56,58}

**Specific Potential Interactions**

**Protease Inhibitors (PI)\textsuperscript{2}**

• *Atazanavir* – Buprenorphine concentration increased. Cognitive impairment or oversedation in some patients. Providers should use slow titration and/or dose reduction as needed.
• *Darunavir-ritonavir* – Some pharmacokinetic effect, need for dose adjustment unlikely, but providers should monitor
• *Ritonavir and Tipranavir* – Some pharmacokinetic effect, no dose adjustment

**Nonnucleoside reverse transcriptase inhibitors (NNRTI)\textsuperscript{2}**

• *Delavirdine* – Non-significant increase in buprenorphine concentration, need for dose adjustment unlikely, but providers should monitor
• *Efavirenz* – Some pharmacokinetic effect, need for dose adjustment unlikely
• *Nevirapine* – Some pharmacokinetic effect, no dose adjustment
• *Integrase inhibitor* – Some pharmacokinetic effect, no dose adjustment\textsuperscript{2}
HEPATIC CONCERNS

Hepatotoxicity
Some liver problems have been reported in patients taking buprenorphine, however researchers concluded that liver problems caused by buprenorphine are uncommon. To protect your liver, your provider will do blood tests to make sure you do not already have some liver disease.

- Liver function tests including transaminases, bilirubin, prothrombin time/INR, and albumin are typically run at the start of your treatment and periodically during treatment. You will be tested more often if you start treatment with elevated test values. Mildly elevated liver enzymes do not contraindicate buprenorphine treatment.
- If your provider doesn't know whether you have had hepatitis B and C, you may have a blood test for them at the start of your treatment. Your provider may test your liver function more often if you have positive tests.
- Your provider may describe the signs and symptoms of liver problems so that you can contact them immediately if they develop (e.g., fever, malaise, nausea, vomiting, abdominal pain, dark urine, clay-colored stools, or yellow in the white part of the eye).
- If you develop liver problems, your provider may conduct further tests and may make a referral and consider lowering your dose of buprenorphine.

If your liver function tests are severe enough, your provider may recommend that you not take buprenorphine. Having Hepatitis C does not necessarily mean you cannot take buprenorphine. Your provider may recommend immunization for hepatitis A and B as part of your treatment and continued monitoring of your liver's health if you have risk factors for liver disease, such as a history of intravenous drug use.

Note that injecting buprenorphine can lead to severe liver damage.

Patients With Hepatitis
Buprenorphine may elevate one of the liver enzymes in people with HCV. As a result, providers may maintain these patients on the lowest effective dose of buprenorphine and monitor them closely for liver-related problems. No significant interactions have been identified between buprenorphine and most HCV medications.

Modifications To Buprenorphine Treatment By Severity Of Hepatic Impairment
Your provider may need to change the dose of your buprenorphine or other drugs you take if they are metabolized using the same pathway (CYP 3A4) if you have liver disease, because liver disease affects how your body metabolizes and removes buprenorphine and naloxone from your body. Patients whose livers don't function well may also need careful monitoring for toxicity or overdose.
KEY POINTS

Opioid Classification
• Opioids are neurotransmitter analogs and have analgesic and addictive qualities, among other effects.
• Opioids that affect mu receptors are the most important in addiction.

The Neurology of Tolerance, Withdrawal, and Physical Dependence
• Tolerance is a neurological adaptation in which sensitivity of opioid receptors decreases, requiring increasingly larger doses for the same drug effects.
• Opioid withdrawal is a severe flu-like state, with duration and severity depending on the opioid being abused and the individual's degree of physical dependence.
• Dependent individuals who stop or decrease opioid use may go into spontaneous withdrawal.
• Dependent individuals who take an opioid antagonist may go into precipitated withdrawal.

Pharmacology of Buprenorphine
• Buprenorphine is a partial opioid agonist. It can be used in the treatment of opioid addiction.
• As a Schedule III drug, buprenorphine has the potential for abuse, so a thorough understanding of how to prescribe it effectively and safely is essential.

Buprenorphine Properties:
• Partial mu agonist and a kappa antagonist
• Mildly reinforcing, which contributes to effectiveness
• Long therapeutic half-life

Buprenorphine Pharmacokinetics:
• Rapidly absorbed through oral mucosa
• No first-pass metabolism; metabolized primarily in the gastrointestinal tract and liver
• Partially or totally blocks the effects of abusable opioids, e.g., heroin and oxycodone
• May precipitate withdrawal if given to a person with mu agonist (e.g., heroin) in his or her system

Side Effects:
• Generally uncommon when taken as directed
• Mild and can be managed by lowering the dose or waiting for tolerance to develop
• Constipation is common; managed with diet changes and medication
• Implants and subcutaneous injections may be irritated after placement and are palpable and visible and.

Special Precautions, Contraindications, Interactions, Adverse Events
• Low risk of overdose due to poor bioavailability and ceiling effect; risk increased by injection
• Combination with CNS depressants, including alcohol, increases overdose risk
• Drug interactions with benzodiazepines, sedative hypnotics, cytochrome P450 3A4 drugs, antiretroviral agents, antiseizure medications, and other opioids - interactions include increased risk of overdose and need for dose adjustment in either direction. Consult current prescribing information
• Special precautions are also indicated with hepatic impairment, compromised respiratory function.

• Contraindications include head injury or intracranial lesions, hypersensitivity, elevated liver enzymes 3-5X/severe hepatic impairment, benzodiazepine abuse, alcohol use disorder or high risk, pregnancy (no combined formulation)

• Tolerance and dependence develop more slowly to buprenorphine than to full mu agonists. Buprenorphine's withdrawal syndrome is also less severe.

Abuse Potential

• Risk for misuse, even in combination with naloxone.

• Risk of abuse is less than full mu agonists.

• Still abusable, especially by injection. Combination with naloxone reduces the potential for this route of misuse.

• As a partial agonist, buprenorphine can precipitate withdrawal in individuals with a highly physical dependence on opioids or when buprenorphine is mixed with opioid agonists; reducing the risk of buprenorphine abuse somewhat.
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