Pharmacology of Buprenorphine & Other Opioids

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PHARMACOLOGY OF BUPRENORPHINE AND OTHER OPIOIDS

Goal:
To prepare the learner to apply an understanding of the biology and pharmacology of buprenorphine when treating patients with opioid use disorder.

After completing this module participants will be able to:
• Relate the functions of opioid receptors to the clinical effects and treatment of opioid use disorder
• Compare the pharmacology of opioid agonists, partial agonists, and antagonists
• Relate pharmacological properties of buprenorphine and naloxone to physiological effects in patients
• Apply concepts relevant to addiction, including overdose, tolerance, and withdrawal, to opioid use

Professional Practice Gaps
The Substance Abuse and Mental Health Services Administration (SAMHSA), based on National Survey on the 2013 Drug Use and Health survey, found the following evidence of a continuing opioid epidemic and need for additional treatment among Americans age 12 and over\(^1\):

• Current use:
  • 289,000 or 0.1 percent current users of heroin (similar to 2008 to 2012)
  • 4.5 million or 1.7% current users of non-medical use of pain relievers (similar to 2011 and 2012).
• New use:
  • 169,000 new initiates to heroin (similar to estimates from 2007 to 2012)
  • 1.5 million new initiates to nonmedical use of pain relievers (lower than 2002 to 2012, which was 1.9 million to 2.5 million).
• Receiving treatment: Only a small fraction of users needing treatment for an opioid use disorder receive it, especially for prescription pain relievers, but the numbers increased in 2013:
  • Past year receipt of treatment for heroin users rose from 277,000 persons in 2002 to 526,000 persons in 2013
  • Past year receipt of treatment for nonmedical users of prescription pain relievers increased from 360,000 in 2002 to 746,000 in 2013.

Buprenorphine is a safe and effective treatment for opioid use disorder that offers patients a more widely available, accessible, convenient treatment option as compared to traditional opioid treatment programs (OTP)\(^2\text{-}^4\). The Drug Addiction Treatment Act (DATA) of 2000—an amendment to the Controlled Substances Act — allowed physicians who are not part of an OTP to prescribe buprenorphine with additional training and a waiver to the Controlled Substances Act. The
Comprehensive Addiction and Recovery Act of 2016 (CARA) added nurse practitioners and physician assistants to the list of providers who can train to prescribe buprenorphine and become waivered.

The law requires physicians to complete an 8-hour buprenorphine training conducted by an approved organization in order to prescribe it; the required training for nurse practitioners and physician assistants is 24 hours. While buprenorphine is relatively safe, there are risks of overdose and death due to buprenorphine and there is a risk of diversion\(^5\), which, in addition to skills needed to prescribe the medication effectively for each individual, are among the reasons for the mandatory training.

This buprenorphine training activity prepares providers to prescribe buprenorphine safely and effectively to address needs of the millions of Americans with opioid use problems. The activity has been developed to meet the DATA 2000 training guidelines as defined in Public Law 106-310-106th Congress as well as the Comprehensive Addiction and Recovery Act of 2016 (S 524, Title III, Section 303-114th Congress) and is endorsed by the American Society of Addiction Medicine, one of the approved training organizations named in DATA 2000. The activity content was initially based upon SAMHSA's 2004 publication Treatment Improvement Protocol (TIP) #40: Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction and follow the Model Policy on DATA 2000 and Treatment of Opioid Addiction in the Medical Office\(^5\). It has been edited to SAMHSA's Sublingual and Transmucosal Buprenorphine for Opioid Use Disorder - Review and Update (2016), ASAM's National Practice Guideline For the Use of Medication in the Treatment of Addiction Involving Opioid Use (2015), and the CDC's guidelines on opioid treatment\(^6\) as well as CARA 2016. The courses are regularly reviewed and updated by ASAM members who are experts in the field of addiction medicine and buprenorphine treatment.

Specific Gap in Training: Providers need to understand the pharmacology of opioids and buprenorphine so they can safely and effectively treat their patients with opioid use disorder. TIP 40\(^4\) devotes an entire chapter to the pharmacology of opioids and specifically buprenorphine, including its safety and effectiveness for the treatment of opioid use disorder, demonstrating the importance of this topic for providers planning to prescribe buprenorphine\(^7\). The FSMB Model Policy for DATA 2000 described specific requirements for prescriptions and that the provider educate the patient adequately\(^5\).

**MODULE INTRODUCTION**

Knowledge of the pharmacology of opioids is important in order to understand both opioid use disorder and buprenorphine treatment. After presenting a foundation of the relevant pharmacology, this module will discuss concepts relevant to opioid addiction and its treatment: overdose, tolerance, and withdrawal

**Case Illustrations**

The following cases will be used to illustrate how the pharmacology of opioids, including buprenorphine, is relevant to patients with opioid use disorder.

**MR. DEXTER**

Mr. Dexter was recently taken to the ER with severe drowsiness and dizziness after mixing the benzodiazepine alprazolam and buprenorphine.
How common is it to have such a severe reaction to mixing these two medications?

MR. SAMUELS

Mr. Samuels recently ran out of the oxycodone and reports flu-like symptoms.

Do you know the symptoms of opioid withdrawal well enough to distinguish them from other causes?

Source

This content was originally adapted from the Substance Abuse and Mental Health Services Administration's (SAMHSA's) Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction (TIP 40) (2004). Because it is the basis for the content, we do not cite the TIP 40 source in the text.

The content has been updated, as noted by citations, according to SAMHSA's (2016) Sublingual and Transmucosal Buprenorphine for Opioid Use Disorder - Review and Update, expert review, and other subsequent literature including The ASAM National Practice Guideline For the Use of Medication in the Treatment of Addiction Involving Opioid Use (2015).

BupPractice was created using NO pharmaceutical or other industry support.

WHAT ARE OPIOIDS?

Because buprenorphine is itself an opioid, and is used to treat addiction to opioids, this module first reviews the pharmacology of opioids

Opioids include:

1. Chemicals produced naturally by plants (morphine)
2. Synthetic or semisynthetic drugs (methadone and heroin)

In humans, opioids act as analogs for neurotransmitters, such as endorphins, enkephalins, and dynorphins, with a variety of effects:

- Pain modulation
- Regulation of gastrointestinal tract motility
- Immune function

Opioids are used clinically for:

- Analgesia
- Treating diarrhea
- Cough suppressant
**OPIOID CATEGORIES BY SOURCE**

**Sources of Opioids**
An opioid is any chemical that interacts with opioid receptors in the body. In humans, many different peptides are produced that act as endogenous ligands for opioid receptors, including neurotransmitters such as endorphins, enkephalins, and dynorphins. Some opioids, such as morphine, are produced naturally by plants, while other opioids, such as methadone and heroin, are synthetic or semisynthetic drugs.

**Naturally-Occurring Opioid Alkaloids**
These opioid alkaloids occur naturally in plants. They can be used on their own or used to create semi-synthetic opioids. These alkaloids include codeine, morphine, and thebaine.

**Semi-Synthetic Opioids**
These opioids are derivatives of the naturally-occurring opioids. They include heroin (derived from morphine) and buprenorphine (derived from thebaine).

**Synthetic Opioids**
These opioids are synthesized artificially, using no plant-based precursors. They include fentanyl and methadone.

**Endogenous Opioids**
These opioid peptides are produced by the body, and are key in the regulation of pain, immune function, and the GI tract. They include endorphins, dynorphins, enkephalins, and endomorphins.

**Clinical Applications**
These neurotransmitters are involved in a wide range of biological processes, including pain modulation, regulation of gastrointestinal tract motility and immune function. Opioids are used in the clinical setting primarily as analgesics. They can also be used to treat diarrhea or coughing, though these uses are less prevalent. Most clinically relevant opioids also have properties which make them highly reinforcing, and therefore have a high potential for abuse.

**OPIOID RECEPTORS**

**Review of Opioid Receptor Types**
Opioids exert their effect by interacting with receptors on the surface or interior of cells and altering cell function. 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 partial agonism with mu receptors and can produce mild reinforcement and dependence.

**Mu Receptors**
Physiological responses to activation of the mu receptor are varied; some important effects are:

- Analgesia
- Sleepiness
- Reduced awareness
- Respiratory depression
- Gastrointestinal depression
- Pupillary 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, that is, rewarding, analgesic, and respiratory depressant.

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

- Analgesia

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

- Dysphoria rather than euphoria
- Aversion rather than reinforcement

Kappa agonist examples include:

- Pentazocine
- Menthol
- Oxycodone

**Delta Receptors**
Delta receptors have not been studied as extensively as mu or kappa receptors. Preliminary studies suggest that they may mediate the emotional aspects of opioid addiction.

**OPIOID CLASSIFICATION: AGONISTS, PARTIAL AGONISTS, AND ANTAGONISTS**

**Classification of Opioids**

- (Full) agonists
- Partial agonists
- Antagonists
The chart below from SAMHSA (2001) shows the dose/response profiles in terms of receptor activation, for the different classifications:

**Agonists**
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 morphine.

**Partial Agonists**
1. Bind to the same receptors as agonists
   - At low doses, partial agonists also exhibit dose-dependent binding.
2. At higher doses, receptor activation does not increase proportionally with dose and a plateau effect is seen:
   - The response curve for a partial agonist flattens far more quickly than a full agonist
   - Reaches maximal activation at a much lower dose
3. Have a ceiling effect
4. Partial agonists may still bind to all available receptors

Example: buprenorphine. Note that buprenorphine is a partial agonist with respect to respiratory depression effects. Its ceiling may not apply to its analgesic properties\(^\text{11}\).

**Antagonists**
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.

- Opioids are usually referenced 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.
QUIZ: RECEPTOR TRIGGERS

Question: Activation of which type of opioid receptor triggers respiratory depression?

Choose one

1. delta
   - Feedback:
   - Incorrect. Delta opioid receptors appear to mediate the emotional aspects of opioid addiction. However, mu opioid receptors produce respiratory depression, along with analgesia, sleepiness, reduced awareness, gastrointestinal depression, pupillary constriction, and euphoria.

2. kappa
   - Feedback:
   - Incorrect. Kappa opioid receptors do not produce respiratory depression. However, mu opioid receptors produce respiratory depression, along with analgesia, sleepiness, reduced awareness, gastrointestinal depression, pupillary constriction, and euphoria.

3. mu
   - Feedback:
   - Correct. Mu opioid receptors do produce respiratory depression along with analgesia, sleepiness, reduced awareness, gastrointestinal depression, pupillary constriction, and euphoria.

OPIOID TOLERANCE

Repeated administration of opioid agonists and partial agonists leads to the neurological adaptation of tolerance for opioids.

TOLERANCE is a state of physiologic adaptation in which exposure to a drug induces changes that result in a diminution of one or more of the drug's effects over time. Physiologically, this means that the opioid user requires increasingly larger opioid doses to get the same drug effects.

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.

QUIZ: OPIOID TOLERANCE

Question: Which of the following is NOT a feature of opioid tolerance?

Choose all that apply

1. Must increase the dose of opioid taken to maintain level of opioid effect
   - Feedback: Correct. All of these are features of opioid tolerance except 'Intense craving for opioids.' Craving for opioids is a hallmark of addiction, which is a related but distinct
phenomenon. Both cravings and tolerance are among the criteria for the diagnosis of opioid use disorder.

2. Intense craving for opioids
   • Feedback: Incorrect. Intensive cravings are a characteristic of opioid use disorder, but not directly a feature of opioid tolerance. Cravings and tolerance are distinct phenomena. Both are common in opioid use disorder.

3. Decrease in opioid receptor sensitivity
   • Feedback: Correct. All of these are features of opioid tolerance except 'Intense craving for opioids.' Craving for opioids is a hallmark of opioid addiction, which is a related but distinct phenomenon. Both cravings and tolerance are among the criteria for the diagnosis of opioid use disorder.

4. Can be brought on by repeated use of illicit or licit opioids
   • Feedback: Correct. All of these are features of opioid tolerance except 'Intense craving for opioids.' Craving for opioids is a hallmark of opioid addiction, which is a related but distinct phenomenon. Both cravings and tolerance are among the criteria for the diagnosis of opioid use disorder.

OPIOID WITHDRAWAL

Withdrawal
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.

The first criterion for Opioid Withdrawal in the DSM 5 is that it occurs after either cessation or reduction of opioid use that was substantial and protracted OR after the administration of an opioid antagonist following a period of opioid use. The second criterion for Opioid Withdrawal in the DSM 5 requires at least three of the following symptoms:

• Dysphoric mood
• Nausea or vomiting
• Muscle aches
• Lacrimation or rhinorrhea
• Pupillary dilation, piloerection, or sweating
• Diarrhea
• Yawning
• Fever
• Insomnia
The third and fourth criteria refer to the above symptoms causing impaired functioning and not being explained by some other condition, respectively.

The duration and severity of opioid withdrawal are dependent on the individual's drug of abuse and degree of dependence.

**Buprenorphine Withdrawal**
Buprenorphine has a long therapeutic half-life. Its withdrawal syndrome is somewhat milder than heroin but is still prolonged and severe, even after a taper. Therefore, it is typically recommended that treatment 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.

**EXAMPLE PATIENT ENCOUNTER**

**Overview**
Mr. Samuels is a new patient to your clinic. He has come in complaining of flu-like symptoms, experienced over the past two days. Upon filling out the intake form, he states that he had a back injury six months ago, but no other medical issues to report.

**Patient Interview**

**Mr. Samuels:** I'm feeling really bad. I've had a fever and muscle aches for two days now. And I've been throwing up, too. Last night I couldn't sleep either, and I'm having a hard time concentrating today. Do you think I've got the flu?

**Provider:** That's a possibility. Have you been around anyone who has had the flu recently?

**Mr. Samuels:** Nobody that I know of. I started feeling bad right after I ran out of my oxycodone.

**Provider:** I see that you had a back injury six months ago. Are you taking oxycodone for that?

**Mr. Samuels:** Yes, but my prescription ran out. Then I got sick and I haven't had a chance to get a refill.

**Provider:** And you've been on it for the entire six months?

**Mr. Samuels:** Right. The pain was pretty bad for a while. It's a little bit better now, but I still have pain a couple of times a week. That's why I keep getting it refilled.
**Provider:** I think your body might be going through withdrawal from the oxycodone. Your system’s gotten accustomed to the drug being in your system, so the sudden cessation has caused you to experience very common withdrawal symptoms such as fever, vomiting, muscle aches, and insomnia.

**Mr. Samuels:** Can you do anything about it? Get me a refill or something? I'm feeling really bad.

**Provider:** I'll do some further evaluation and determine what the best course of treatment is at this time.

## TYPES OF WITHDRAWAL

The types of withdrawal associated with mu opioid agonist dependence are:

- Spontaneous Withdrawal
- Precipitated Withdrawal

Two additional clinical withdrawals are also identified:

- Protracted Withdrawal
- Medically Supervised Withdrawal

### Spontaneous Withdrawal

Spontaneous withdrawal (usually called 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 the drug being taken regularly. Examples:

#### Heroin Withdrawal

- Withdrawal from heroin has a relatively short half-life and is fairly quick:
  - Begins 6-12 hours after the last dose
  - Peaks between 36-72 hours
  - Lasts around 5 days
- Is very intense
- It 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 has a much faster onset. 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. 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.
• There has been a short time interval between the last dose of the full agonist and the first dose of buprenorphine.
• A high dose of buprenorphine is used.
• The full agonist has a long half-life, as is the case with methadone.

Protracted Withdrawal
Withdrawal symptoms or other symptoms may continue past the time expected for acute withdrawal, and sometimes last for months or years, is called protracted withdrawal. This is covered in greater detail in the module on Maintenance and Discontinuation.

Medically Supervised Withdrawal
Medically supervised withdrawal through tapering is covered in the module on Maintenance and Discontinuation.

BUPRENORPHINE PHARMACOKINETICS

Buprenorphine Is Effective In the Treatment of Opioid Use Disorder
Buprenorphine (16 mg/day of sublingual tablets or equivalent) has been shown in multiple research studies to be effective in suppressing misuse of opioids. Implant and injectable formulations for treating opioid use disorder have also been shown to be effective.

Characteristics of Buprenorphine
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. 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.
• A potent analgesic, used in low doses to avoid side effects. Formulations include intravenous or intramuscular (Buprenex) and transdermal (Butrans®).
• Mildly reinforcing, which improves treatment adherence and, therefore, clinical effectiveness compared with antagonist treatment.
• Limit on the maximum effect that can be achieved. However, the ceiling effect may not apply to the analgesic effect.

BIO-AVAILABILITY, METABOLISM, EXCRETION

Bio-availability
The bio-availability of buprenorphine varies depending on the route of administration.

Oral (Swallowed) → Very rapidly metabolized and poor bio-availability
**Sublingual (Absorbed Transmucosally)** → Skips first pass metabolism, so significantly better bioavailability

Sublingual monotherapy tablets produce peak concentrations of 62% of the solution after 7 days\(^ {23}\). In comparison, sublingual combination therapy films or tablets (using the former Suboxone® formula) produced a peak concentration of 82% of the solution after 7 days.

This suggests that naloxone increases the availability of buprenorphine in the body, which supports the use of combination buprenorphine/naloxone in office-based opioid treatment. The combination formulation is now used with nearly all patients, with few exceptions (pregnant patients and those with naloxone allergies).

Sublingual buprenorphine/naloxone serum concentrations are ~3.37 ng/mL\(^ {24,25}\).

**Implant and Injectable** → Injectable buprenorphine concentrations for the 300 mg dose was 6.54 ng/mL, and for 100 mg it was 3.21 ng/mL\(^ {26}\).

**Metabolism and Excretion**

Buprenorphine is primarily metabolized in the gastrointestinal tract and the liver, using the CYP 3A4 system\(^ {27}\). (Interactions with CYP3A4 inducers and inhibitors are described later in this module with drug interactions.)

Most buprenorphine metabolites are excreted fecally rather than through renal excretion\(^ {22}\). As a result, buprenorphine is relatively safe for patients with renal insufficiency.

**AFFINITY AND DISSOCIATION**

**Mixed Agonist-Antagonist Opioid**

Buprenorphine is a mu (μ) partial agonist and a kappa (κ) antagonist and therefore often described as a mixed agonist-antagonist opioid. The mixed nature means that it can bind to both kappa and mu opioid receptors.

**Agonist Mu-Receptor Binding**

Buprenorphine has a very high affinity for and slow dissociation from mu receptors when compared to most commonly-abused mu agonists. As a consequence, when both buprenorphine and a mu agonist are present, the buprenorphine preferentially binds to the mu receptors, effectively inhibiting the effects of the mu agonist.

In other words, buprenorphine partially or totally blocks the effects of abusable opioids, such as heroin and oxycodone\(^ {3,28}\). Buprenorphine may even precipitate withdrawal 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)\(^ {21}\)
• Relatively mild withdrawal syndrome
• Low risk of overdose

**Antagonist Kappa-Receptor Binding**
Buprenorphine also has a high affinity for kappa receptors. However, as a kappa antagonist, it causes no activity when bound to the kappa receptor.

This differing action of buprenorphine may be related to the different action at the two receptors. As the dose of buprenorphine increases, the effects increase, to a maximum, but then the effect decreases as the dose continues to increase. At high doses, the kappa antagonist effects apparently predominate, resulting in the decreasing side of the dose-response curve.

**QUIZ: BUPRENORPHINE PHARMA**
**Question:** Which of the following best describes the action of buprenorphine on opioid receptors?

Choose the best answer:

1. Partial mu antagonist, kappa agonist
   • Feedback: Incorrect. Buprenorphine is classified as a partial mu agonist, kappa antagonist, and nociceptin (kappa-type 3 opioid) receptor agonist.

2. Mu antagonist, kappa agonist
   • Feedback: Incorrect. Buprenorphine is classified as a partial mu agonist, kappa antagonist, and nociceptin (kappa-type 3 opioid) receptor agonist.

3. Partial mu agonist, kappa antagonist
   • Feedback: Correct! Buprenorphine is classified as a partial mu agonist, kappa antagonist, and nociceptin (kappa-type 3 opioid) receptor agonist.

4. None of the above
   • Feedback: Incorrect. Buprenorphine is classified as a partial mu agonist, kappa antagonist, and nociceptin (kappa-type 3 opioid) receptor agonist.

**BUPRENORPHINE FORMULATIONS**

**How Buprenorphine Is Supplied**
Buprenorphine is manufactured in formulations containing only buprenorphine or combined with naloxone. The following formulations are available for treating opioid addiction:

- Buprenorphine/naloxone combination for treatment of opioid use disorder
- Monotherapy buprenorphine for treatment of opioid use disorder, including long-acting subdermal implant and subcutaneous injectable forms

Other formulations of buprenorphine are available for treating pain

FSMB guidelines for buprenorphine treatment recommend that patients receive and understand the Medication Guide for the formulation of buprenorphine that they are prescribed.

SAMHSA recommends basing the selection of a buprenorphine formulation for the individual patient on what is more cost-effective and most appropriate for them.
BUPRENORPHINE/NALOXONE COMBINATION

Naloxone, an opioid antagonist, is added to reduce abuse by injection. It has little effect on the action and efficacy of buprenorphine when taken as intended\textsuperscript{22}. Injecting this buprenorphine formulation reduces effects and may precipitate acute withdrawal in dependent individuals\textsuperscript{30}. The combined buprenorphine/naloxone formulation is 4 parts buprenorphine and 1 part naloxone (a mu opioid antagonist)\textsuperscript{31}.

Buprenorphine/naloxone is available in several forms (tablet, film). Formulations taken by mouth also vary by where they are placed in the mouth (sublingual vs. buccal), dosage (small differences), time to dissolve and be absorbed through oral mucosa, and flavor.

- The buprenorphine/naloxone combination is preferred over buprenorphine monotherapy when taken via the mouth in almost all situations (except pregnancy and lactation).

The combination formulation has been the standard of care in the U.S., because, by containing naloxone it is thought to be less likely to be abused\textsuperscript{3}. However, much of this research involved IV heroin users and fewer people with prescription opioid use disorder, which is more prevalent today. The combination form is still abused.

- Available in brands sublingual Zubsolv® tablets, Suboxone® sublingual film, buccal Bunavail™, generics

COMBINATION WITH NALOXONE AS AN ABUSE DETERRENT

Decrease in Injection Misuse Potential

Both buprenorphine monotherapy and combination buprenorphine/naloxone are misused and diverted. However, the combination formulation is less often misused via injection than the monotherapy formulation\textsuperscript{32}. Naloxone has excellent bio-availability when injected and blocks the euphoric and rewarding effects of buprenorphine when injected. However, naloxone has very poor bioavailability when taken sublingually or orally, so film and tablet formulas are still abused. Furthermore, naloxone's aversive effects last only about 20 to 30 minutes, after which buprenorphine's reinforcing effects would be felt, and so the combination formulations are sometimes injected.

A survey of 543 opioid substitution clients in the New England area over an 8 year period\textsuperscript{32} found that:

- Reports of weekly or more injection of prescribed medication by combination film buprenorphine/naloxone clients were fewer than by monotherapy clients (3% vs. 11%, 95% CI).
- Injecting buprenorphine/naloxone film and tablets were reported at similar rates, but the proportion of film doses injected was lower.
- Among clients who were injection drug users, buprenorphine monotherapy injection levels were higher
Consequences of Injecting the Combination Film or Tablet

Consequences of injecting the combination film or tablet vary depending on the severity of the patient's physical dependence on opioids:

<table>
<thead>
<tr>
<th>People who are:</th>
<th>Have this reaction to injection of combination buprenorphine/naloxone:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dependent on illicit opioids or on most medically used opioid agonists</td>
<td>Very likely to go into opioid withdrawal</td>
</tr>
<tr>
<td></td>
<td>Unlikely to go into withdrawal</td>
</tr>
<tr>
<td>Maintained on buprenorphine/naloxone</td>
<td>Buprenorphine has a very high affinity for mu opioid receptors and is unlikely to be displaced by naloxone. However, the partial agonist effects of buprenorphine are attenuated by naloxone, which should decrease the desirability of injecting. Will not be affected by naloxone, although the agonist effects of buprenorphine will be attenuated. This group is the most likely to abuse buprenorphine/naloxone combination tablets (Strain et al., 2004). Presumably, this applies to the newer buprenorphine film formulation as well.</td>
</tr>
<tr>
<td>Not physically dependent on opioids</td>
<td></td>
</tr>
</tbody>
</table>

**CAUTION TIP**

Tell patients to call 911 for exposure to buprenorphine tablets or film in anyone who is opioid naive. Respiratory distress may develop later.

**Warning!**

The injectable formulation should only be injected by a qualified healthcare professional. Intravenous injection could result in serious harm\(^2\), as is discussed further under the detailed discussion of this formulation.

**COMBINATION TABLETS**

**Generic Tablets**

The 4:1 combination of buprenorphine HCl with naloxone HCl dihydrate is currently the most widely used form for opioid addiction\(^3\).

**Tablets**

The generic combination buprenorphine/naloxone tablet is dissolved sublingually, as of March 2013.

- These tablets are available in 2 mg and 8 mg strengths.
- Clinicians and patients have found that they can easily cut the tablets. With precision and care, a 2 mg tablet can yield 0.5 mg doses; the 8 mg tablet can be cut to yield 2 mg doses for precise dosing.
• Target dosing: The usual maintenance doses in the U.S. for sublingual buprenorphine average 10-16 mg, but should be individualized. Need for doses over 24 mg should be documented since this approaches the ceiling and diversion is an issue.

Other Formulations
Buprenorphine/naloxone sublingual tablet (Zubsolv®) has several differences in comparison with other formulations of combination buprenorphine/naloxone including that they dissolve more rapidly and have greater bioavailability which requires lower doses. For example, a 5.7 mg tablet of this formulation is the equivalent to an 8 mg tablet of Suboxone. Consult the product information.

Consult the Formulation comparison in External Resources on this page to see a comparison of some characteristics of different formulations of buprenorphine for opioid therapy.

If a patient is induced on buprenorphine monotherapy, a slight shift to the equivalent dose in switching to other formulations may be needed. Consult product for conversion information.

We do not advocate any specific form of buprenorphine; the clinician should use their judgment based on the specific patient.

Packaging
The packaging for some formulations of buprenorphine may not include child safety measures. Patients can transfer their medication to containers with safety cap bottles. This issue may be a consideration for some patients.

COMBINATION FILM

Sublingual film
• The current formulation of Suboxone® is a combination of buprenorphine and naloxone in the form of a thin film.
• The "Film" is dissolved under the tongue and absorbed sublingually
• The film
  • Is between the size of a nickel and a quarter
  • Comes in 2 mg, 4 mg, 8 mg, and 12 mg doses
  • The medication guide says the film should not be cut.

Possible oral side effects associated with the film include: oral hypoesthesia, glossodynia, and oral mucosal erythema.

Buccal Film
A buccal buprenorphine/naloxone combination film formulation, (Bunavail™), is approved by the FDA. It is described as providing around twice the bioavailability of other available buprenorphine combination formulations, which may allow for lower doses. For example, a 4.2 mg film is equivalent to an 8 mg tablet of Suboxone. Product descriptions include a claim that fewer patients experience the side effect of constipation.
Switching Between Tablets and Film
The sublingual film is clinically interchangeable with buprenorphine plus naloxone sublingual tablets. However, a slight adjustment in dosage may be needed by some patients. Patients being switched from a combination tablet to the film, which is also combination, do NOT have to undergo an induction to change formulations.

However, the newer sublingual tablet (Zubsolv®) and buccal film (Bunavail™) do require dosage changes. Product information should be consulted about switching to these formulations from other formulations.

Unique Diversion of Sublingual Film
Buprenorphine, in the form of film or crushed tablets, has been smuggled into prisons. For example, it has been dissolved into children's artwork, placed under postage stamps, and painted on paper including pages in Bibles. Prisoners tear out the coated paper and chew it in order to absorb the buprenorphine.

EXPLAINING BUPRENORPHINE TO PATIENTS

Example Dialogue
Provider: The buprenorphine/naloxone formulation that I am prescribing you is a thin film that you place under your tongue. It needs to be absorbed directly through the lining of your mouth, rather than your stomach, so it is important to let it slowly dissolve under your tongue and try not to swallow.

Patient: That's different. I just swallowed the opioids whole.

Provider: Yes, it is different. Buprenorphine is actually an opioid, too, but it only works partially like the opioids you are trying to quit. And because it works partially like an opioid, it will prevent you from experiencing withdrawal symptoms even though you stop taking other opioids.

Patient: I welcome that!

Provider: You will be physically dependent on buprenorphine, but you will not experience the need for increasing doses as happened with opioids. I want to make sure you understand how it works, because it will help you succeed in this treatment. What questions do you have so far?

Patient: How long do I have to take it?

Provider: You will most likely need to take it a long time, possibly even indefinitely. You will be better able to live a normal life on a stable dose while taking it, instead of the disrupted life you experienced from opioid use disorder.

PRACTICE TIP
FSMB guidelines for buprenorphine treatment recommend that patients receive and understand the Medication Guide for the formulation of buprenorphine that they are prescribed.
BUPRENORPHINE MONOTHERAPY

Monotherapy Tablets
The buprenorphine monotherapy and buprenorphine/naloxone formulations have nearly identical effects when used as directed. The naloxone component is minimally active unless injected. Recommendations for the clinical use of one are also valid for the other unless specifically noted otherwise.

Almost all patients should be prescribed the buprenorphine/naloxone combination if not being maintained on the implant.

Use of the monotherapy tablets has been discouraged due to concerns about abuse and diversion, however, combination tablets are also diverted. Combination tablets should NOT be prescribed to patients who:

- Are pregnant
- Have had an allergic reaction to naloxone (rare)
- Are being treated in supervised inpatient settings

Patients who meet one of these requirements may be prescribed monotherapy tablets if:

- They have demonstrated that they can remain substance free
- Have no evidence of buprenorphine diversion
- And are stable psychosocially
- Or if they are willing to take buprenorphine only under direct supervision

If these conditions cannot be met, consider whether observed dosing 3 times per week would be sufficient. Otherwise, an alternative therapy, such as methadone maintenance, may be more appropriate.

Monotherapy, buprenorphine without naloxone is "a reasonable and recommended alternative to methadone a for pregnant women." Evidence for the use of combination buprenorphine/naloxone in pregnancy was considered "insufficient." Although there is not much research available, monotherapy is also sometimes used during lactation.

Note that the implant formulation which is for stable patients in the maintenance phase of treatment who are on moderate dose, is monotherapy.

Abuse and Diversion of Generic Buprenorphine Without Naloxone vs. Decreased Cost
Although generic buprenorphine monotherapy may be less expensive than combination therapy, it appears to have a higher rate of abuse and diversion. Injecting buprenorphine monotherapy does not cause withdrawal in users dependent on illicit opioids, because there is no naloxone. A study looking at untreated injection users' abuse of buprenorphine alone in comparison to buprenorphine in combination with naloxone found that injection users had a strong preference for the monotherapy version (without naloxone). A large majority of these users indicated that injecting buprenorphine in combination with naloxone caused a "bad" experience.
Additionally, RADARS® found that buprenorphine alone is abused at a much higher rate than the buprenorphine/naloxone combination products and fetches a higher street price.\(^{38}\)

Weigh the risks vs benefits when deciding which formulation to prescribe to each patient.

**ADVANTAGES AND DISADVANTAGES OF EXTENDED RELEASE IMPLANTS AND INJECTABLES**

Advantages of extended release buprenorphine of implants and injectables include:\(^{20,31,40}\):

- Ensures long-term compliance with taking medication.
- Provides steady-state levels of medication in the blood.
- Ensures a consistent dose, whereas absorption through oral mucosa is somewhat dependent on patient technique.
- Decreases loss of medication, theft, and diversion.
- Advantageous for patients who might have difficulty obtaining their buprenorphine, such as those who are incarcerated or travel extensively.
- Advantageous for patients who cannot use transmucosal buprenorphine, for example, due to an oral mucosal condition or lack of dexterity.

Disadvantage:

- These formulations cost more than transmucosal buprenorphine, especially the generic formulation. Some pharma companies have offered various help to defray costs initially.
- Specific side effects for each formulation are discussed below.

**BUPRENORPHINE IMPLANTS**

**Implants**

A subdermal buprenorphine implant, Probuphine®, was approved by the FDA in May, 2016.\(^{36}\) It releases a constant, low dose of buprenorphine into the bloodstream "for maintenance treatment of opioid dependence."

**Implants: Basic Clinical Information**\(^{36}\):

- The implant only is appropriate for selected patients and in the maintenance phase only: Stable patients requiring 8 mg per day or less. Clinical trials were in patients with \(\geq 3\) months of stability.\(^{40}\)
- The implants consist of small, inch long, solid rods made of a combination of ethylene-vinyl acetate and buprenorphine.
- Typically 4 implant rods are placed subdermally in a simple procedure by a physician, usually on the inside of the upper arm.
- Placed surgically only by a healthcare provider who has completed the Probuphine Risk Evaluation and Mitigation Strategy (REMS) live training and certification, which includes specific training to learn how to insert and remove the implant.
Monitoring includes the first week after implantation and no less than once monthly.
Each implant placement is effective for 6 months and then must be replaced.
For use as "part of a complete treatment program that includes counseling and psychosocial support"\(^{36}\)

**Implants: Efficacy and Safety Evidence for Implants**

Efficacy and safety of implants have been demonstrated in several clinical trials including a 24-week, placebo controlled study with 163 patients reported in JAMA\(^{31}\). In a double-blind, double-dummy study, the implant met the primary endpoint of non-inferiority to sublingual buprenorphine; the responder rate was 96.4% vs. 87.6% (\(p=0.034\)), remaining free from illicit use of opioids was also superior (85.7% vs. 71.9\%)\(^{40}\)

One study of patients who were stable on an appropriately low dose of sublingual buprenorphine found that a group switched to the implant had a lower relapse rate than the randomized control group that continued on sublingual buprenorphine\(^{41}\). Over 6 months 85.7% in the active implant/sublingual placebo group and 71.9% in the control, active sublingual buprenorphine/placebo implant group maintained opioid abstinence (hazard ratio, 13.8; 95% CI, 0.018-0.258; \(P = .03\)).

Concerns regarding buprenorphine implants include:
- Some patients end up needing to supplement their dose from the implant with sublingual buprenorphine.

**BUPRENORPHINE INJECTABLE EXTENDED RELEASE**

A subcutaneous injectable form of buprenorphine (Sublocade™) was approved by the FDA in late 2017 and became available for use in 2018. It is administered subcutaneously by a health care provider as a once-monthly injection in patients who have been stabilized at an effective dose for at least one week on trans-mucosal buprenorphine\(^{28}\). The injected medication forms a depot subcutaneously from which the medication is slowly released over time. Injection by patients is not approved and is, in fact, dangerous because of the risk of intravenous injection.

Advantages of injectable over implants:
- They are available in higher doses than is available via implants.
- They do not require a surgical procedure.

Disadvantage of injectable over implant:
- Require monthly appointments

**Patient Status Requirements**
- Stabilized dose of a transmucosal buprenorphine for at least 7 days.\(^{42}\)

**Dose**
- 300 mg is injected one per month for the first 2 months
- 100 mg are injected each month thereafter for maintenance; this may be increased to 300 mg for some patients not having enough therapeutic benefit from the lower dose.
- Everyone gets the same dose, whether they had been on 8 or 16 mg.
- Obtaining the dose: You may either prescribe it for the individual patient from a certified pharmacy or become REMS certified yourself and order a supply.
• Storage: store at 2-8 degrees Celsius (35.6-46.4 degrees Fahrenheit). May be stored in original package up to 7 days at room temperature prior to administration.
• Missed doses: Administer as soon as possible with the following dose no less than 26 days later.

Injectable Side Effects
• Some patients have reported withdrawal in week 2 or 3 of a monthly injection.
• Some patients have reported feeling like they are on too much medication.
• A visible lump is present under the skin of the abdomen and it is larger earlier in the month. It has been compared to the size of a silver dollar.

Injectable Risk:
Aside from the risks for any buprenorphine formulations:
• There is risk of an occlusion from an intravenous injection and therefore it should only be injected subcutaneously and by a qualified health professional.
• If there are adverse reactions requiring the medication be stopped before the end of the month, the depot must be surgically removed.
• Avoid use in patients with QT syndrome.

BUPRENORPHINE FORMULATIONS COMPARISON

<table>
<thead>
<tr>
<th>Product</th>
<th>How Supplied (Buprenorphine / Naloxone mg)</th>
<th>Induction Dosage</th>
<th>Increments (until opioid withdrawal signs and symptoms are suppressed)</th>
<th>Recommended Target Dose for Maintenance</th>
<th>Instructions for Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suboxone®</td>
<td>2 mg bup./0.5 mg nal.</td>
<td></td>
<td>Increments/ decrements of 2 mg bup./0.5 mg nal. or 4 mg bup./1 mg nal. up to 8 mg bup./2 mg nal. day 1 (in divided doses at around 2 hour intervals)</td>
<td>Target Dose: 16 mg bup./4 mg nal. single daily dose (Range: 4 mg bup./1 mg nal. to 24 mg bup./6 mg nal. per day)</td>
<td>Place film under the tongue, close to the base on the left or right side. Must be kept under tongue until completely dissolved.</td>
</tr>
<tr>
<td>Sublingual Film</td>
<td>4 mg bup./1 mg nal.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reckitt Benckiser</td>
<td>8 mg bup./2 mg nal. 12 mg bup./3 mg nal.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Product</td>
<td>How Supplied (Buprenorphine / Naloxone mg)</td>
<td>Induction Dosage Increments (until opioid withdrawal signs and symptoms are suppressed)</td>
<td>Recommended Target Dose for Maintenance</td>
<td>Instructions for Use</td>
<td></td>
</tr>
<tr>
<td>-----------------------------</td>
<td>-------------------------------------------</td>
<td>-------------------------------------------------------------------------------------</td>
<td>---------------------------------------</td>
<td>---------------------</td>
<td></td>
</tr>
<tr>
<td><strong>Zubsolv®</strong></td>
<td>1.4 mg bup./0.36 mg nal. 5.7 mg bup./1.4 mg nal. Dissolves more rapidly, menthol flavor, and smaller tablet.</td>
<td>Day 2, administer up to 16 mg bup./4 mg nal. of sublingual film single daily dose.</td>
<td>Target Dose: 11.4 mg bup./2.8 mg nal. single daily dose</td>
<td>Wet the inside of the cheek. Hold the film with the text (BN2, BN4, or BN6) facing up and place that side with the text.</td>
<td></td>
</tr>
<tr>
<td>Sublingual Tablet</td>
<td>Increment/decrements of 1.4 mg bup./0.36 mg nal. or 2.8 mg bup./0.72 mg nal.</td>
<td>(Range: 2.8 mg bup./0.72 mg nal. to 17.1 mg bup./4.2 mg nal. per day)</td>
<td>Conversion Information: One ZUBSOLV 5.7 mg bup./1.4 mg nal. sublingual tablet equivalent to one SUBOXONE 8 mg bup./2 mg nal. sublingual tablet</td>
<td>Tablet should be placed under the tongue until dissolved. Do not cut, chew, or swallow tablets.</td>
<td></td>
</tr>
<tr>
<td>Orexo</td>
<td><strong>Bunavail™</strong> 2.1 mg bup./ 0.3 mg nal. 4.2 mg bup./ 0.7 mg nal. 6.3 mg bup./ 1 mg nal.</td>
<td>Increments/decrements of 2.1 mg bup./0.3 mg nal.</td>
<td>Target Dose: 8.4 mg bup./1.4 mg nal. per day single daily dose</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Buprenorphine Training Activity v5.0 For Physicians

<table>
<thead>
<tr>
<th>Product</th>
<th>How Supplied (Buprenorphine / Naloxone mg)</th>
<th>Induction Dosage Increments (until opioid withdrawal signs and symptoms are suppressed)</th>
<th>Recommended Target Dose for Maintenance</th>
<th>Instructions for Use</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Generic Buprenorphine HCl &amp; Naloxone HCl Dihydrate</strong></td>
<td>2 mg bup./0.5 mg nal.</td>
<td>Increments/decrements of 2 mg bup./0.5 mg nal. or 4 mg bup./1 mg nal.</td>
<td>12.6 mg bup./2.1 mg nal. per day</td>
<td>Half a normal dose can achieve same result as other products, due to twice the bioavailability.</td>
</tr>
<tr>
<td>Sublingual Tablets</td>
<td>8 mg bup./2 mg nal.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Actavis Elizabeth LLC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Buprenorphine (Without Naloxone)</strong></td>
<td>2 mg bup.</td>
<td>Increment/decrements of 2 mg or 4 mg bup.</td>
<td>16 mg bup. single daily dose</td>
<td>Tablet should be placed under the tongue until it is dissolved.</td>
</tr>
<tr>
<td>HCl</td>
<td>8 mg bup.</td>
<td>Up to 8 mg bup. on Day 1 and 16 mg bup. on Day 2.</td>
<td>(Range: 4 mg bup./1 mg nal. to 24 mg bup./6 mg nal. per day).</td>
<td></td>
</tr>
<tr>
<td>Sublingual Tablet</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Roxane Laboratories, Inc</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Conversion information: BUNAVAIL 4.2 mg bup./0.7 mg nal. buccal film equivalent to a SUBOXONE 8 mg bup./2 mg nal. sublingual tablet.*

*Target Dose: 16 mg bup./4 mg nal. single daily dose (Range: 4 mg bup./1 mg nal. to 24 mg bup./6 mg nal. per day).*

*Instructions for Use:*
- Press and hold the film in place for 5 seconds.
- Against the inside of the cheek.
- Put the tablet(s) under your tongue. Let them dissolve completely. While the tablets are dissolving, do not chew or swallow the tablet. Talking while the tablet is dissolving can also affect
**Product** | **How Supplied (Buprenorphine / Naloxone mg)** | **Induction Dosage Increments (until opioid withdrawal signs and symptoms are suppressed)** | **Recommended Target Dose for Maintenance** | **Instructions for Use**
--- | --- | --- | --- | ---
Probuphine® | One inch long rods containing buprenorphine | For use in patients already stable on a low to moderate dose of 8 mg buprenorphine or less per day. Placed surgically. Replaced at 6 months. | Target dose is 8 mg or less per day | Implant is typically placed inside the upper arm, under the skin, for 6 months. Requires specific REMS training and certification for the physician to insert and remove. Once monthly subcutaneous injection by a qualified health care provider after dose stabilized at least one week on submucosal buprenorphine. Forms visible depot under the skin from which medication is slowly released over time.

Sublocade™ | Comes pre-filled syringes with a 19 gauge 5/8-inch needle. In 100mg and 300 mg doses. | Not used for induction. For use after patient is stabilized for at least one week on transmucosal buprenorphine. | Target Dose: 300 mg monthly for two months, then 100 mg monthly but may be increased up to 300 mg if needed. See product information for details. | 

** QUIZ: BUP FORMULATIONS **

Match the drug or drug formulation on the left with a correct corresponding characteristic on the right.
**Response:**

<table>
<thead>
<tr>
<th>MATCH</th>
<th>SUGGESTED ANSWER</th>
<th>FEEDBACK</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buprenorphine/naloxone</td>
<td>Preferred formulation for most patients</td>
<td>Buprenorphine/naloxone combination is the formulation preferred for most patients to treat opioid use disorder.</td>
</tr>
<tr>
<td>combination</td>
<td></td>
<td>In none of the current formulations is the tablet or film swallowed. Instead, it is allowed to dissolve slowly in the mouth and absorbed through the oral mucosa.</td>
</tr>
<tr>
<td>Buprenorphine tablet (swallowed)</td>
<td>Formulation not available</td>
<td>Naloxone is combined with buprenorphine as an abuse deterrent.</td>
</tr>
<tr>
<td>Naloxone</td>
<td>Abuse deterrent</td>
<td>In pregnancy, buprenorphine monotherapy without naloxone is recommended.</td>
</tr>
<tr>
<td>Buprenorphine monotherapy</td>
<td>Formulation used in pregnancy</td>
<td>The buccal film has greater bioavailability than the original formula and some of the other current formulations, so typically, a lower dose may be needed. Dosages vary by formula and so product information needs to be consulted.</td>
</tr>
<tr>
<td>Buccal film</td>
<td>Greater bioavailability than original buprenorphine formulas</td>
<td>The buccal film has greater bioavailability than the original formula and some of the other current formulations, so typically, a lower dose may be needed. Dosages vary by formula and so product information needs to be consulted.</td>
</tr>
<tr>
<td>Buprenorphine implant</td>
<td>Reduces diversion and accidental exposure</td>
<td>The buprenorphine implant is diversion resistant and reduces risk of accidental exposure.</td>
</tr>
<tr>
<td>Injectable buprenorphine</td>
<td>Not used for induction</td>
<td>Patients should be stabilized on submucosal buprenorphine for 7 days prior to being transferred to long-acting injectable buprenorphine.</td>
</tr>
</tbody>
</table>

**BUPRENORPHINE FOR PAIN**

The transdermal patch (Butrans®), injection (Buprenex®), and a newer buccal film (BELBUCA™) are the buprenorphine formulations that are FDA-approved for chronic pain control, but NOT opioid use disorder. A sublingual formula for pain is available in some other countries.

These formulations of buprenorphine are used to manage moderate to severe pain. They are used for round-the-clock, long-term pain management rather than as-needed. They are used when alternative pain management options, such as non-opioid analgesics or immediate-release opioids, are inadequate.

Conversely, use of buprenorphine formulations for treating opioid use disorder to treat pain is considered off-label use. The formulation specifically for treating pain should be used to treat pain.

Like the formulations for treating opioid addiction, the formulations of buprenorphine for treating pain have the potential for physical dependence, drug interactions, abuse, and diversion. See the specific product information of each formulation for details.
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 of Suboxone® include:

- Headaches
- Withdrawal syndrome (Consider whether withdrawal may have been precipitated)
- Pain
- Nausea and vomiting
- Constipation
- Insomnia
- Sweating
- Numb mouth and painful tongue

Less Common Side Effects of Opioids
Other less common side effects seen in opioids are also seen with buprenorphine. For example, sleep disordered breathing. A study found that, even at routine therapeutic doses, buprenorphine may induce notable breathing alterations during sleep. The FDA also included buprenorphine in several safety warnings for all opioids, including warning of risk for serotonin syndrome, adrenal insufficiency, and decreased sex hormone levels with chronic use. These side effects tend to be less common with buprenorphine compared to other full agonist opioids.

OTHER SIDE EFFECTS

Other Possible Side Effects
Independent clinical trials of buprenorphine have reported many of these same side effects and others:

- 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 what is obtained in a patient taking the buprenorphine formulation that is specifically for pain.
TREATING SIDE EFFECTS

Side effects that cause discomfort to the patient should be treated symptomatically in the short-term. In long-term cases, side effects are treated by the following:

- Lowering the dose of buprenorphine
- Giving the patient time to become slightly tolerant to the medication
- Making lifestyle changes
- Constipation can be treated with dietary adjustments, increased fiber consumption, stool softeners, and increased fluids

CAUTION TIP

Sedating Effects

Patients should be warned of 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.

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. The specific reactions reported were:

- 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. Note that pruritus can be a side effect of opioid use instead of a sign of an allergic reaction.

HEPATIC CONCERNS

Hepatotoxicity

Elevated liver enzymes were reported in the early years of buprenorphine treatment, particularly with a history of hepatitis or high dose or injected buprenorphine.
Only a small percentage of patients (2.1%) had elevation of transaminases sufficient to require medical attention, in a 24 week prospective study of patients with high risk for liver disease and taking a median dose 24 mg buprenorphine\textsuperscript{55}. Patients who had extreme elevations of transaminases were more likely to have seroconverted to hepatitis during the study and use illicit drugs in the first 8 weeks of treatment. These results suggest other factors might be involved in their hepatotoxicity.

Research on the relationship between sublingual buprenorphine use and acute hepatitis in patients with chronic HCV led to the conclusion that buprenorphine-induced hepatitis is uncommon. However, it may still occur in patients who are not misusing the drug\textsuperscript{56}.

Guidelines for Hepatic Safety
- Liver function tests including transaminases, bilirubin, prothrombin time/INR, and albumin should be run at baseline and periodically during treatment for all patients. Tests should be run semi-annually or more often with other risk factors.\textsuperscript{55}
- Hepatitis B and C panels should be obtained at baseline in patients with unknown serostatus and risk.\textsuperscript{55}
- Describe signs and symptoms of hepatotoxicity for patients and have them contact their provider immediately if they develop (e.g., fever, malaise, nausea, vomiting, abdominal distress, dark urine, clay-colored stools, or icterus).\textsuperscript{55}
- With clinical or laboratory evidence of hepatotoxicity\textsuperscript{55},
  - Evaluate all possible causes of liver injury.
  - Consider gastroenterology or hepatology consult.
  - Consider lowering or discontinuing buprenorphine.
  - Follow these patients clinically and with laboratory testing serially until evidence of hepatotoxicity is resolved.

Patients with elevated liver function test 3-5 times greater than normal should not be put on buprenorphine treatment\textsuperscript{57}. One buprenorphine/naloxone formulation package insert also states that buprenorphine is not appropriate for patients with severe hepatic impairment and may not be appropriate with moderate impairment\textsuperscript{35}. Buprenorphine and naloxone pharmacokinetic parameters differed significantly in this group of patients relative to healthy subjects. However, they did not find a need for dosing adjustment due to Hepatitis C infection without hepatic impairment.

Patients who have a history of IV drug use should be encouraged to receive immunization for hepatitis A and B\textsuperscript{57}.

Hepatic monitoring of patients who have other risk factors for liver problems is recommended\textsuperscript{56}.

PRACTICE TIP
Buprenorphine should be used cautiously in patients with hepatic insufficiency\textsuperscript{54}, however, mildly elevated liver enzymes do not contraindicate buprenorphine treatment\textsuperscript{57}.

QUIZ: DIAGNOSING SYMPTOMS
Mrs. Thomas has come to your office complaining of nausea and sweating. She has recently started buprenorphine treatment after ceasing use of opioids. Mrs.
Thomas reports that the symptoms have come on within the past two days and she is having a hard
time sleeping at night as well.

**Question:** Based on her symptoms, what is Mrs. Thomas experiencing?

**Choose one**

1. Opioid withdrawal
   - Feedback: These are symptoms of opioid withdrawal, but they are also present as a
   result of buprenorphine side effects.

2. Side effects from buprenorphine
   - Feedback: These are side effects of buprenorphine, but they are also present as a
   result of opioid withdrawal.

3. Unable to determine based on symptoms
   - Feedback: Correct. These symptoms are present both during opioid withdrawal and as
   a result of buprenorphine side effects.

**DRUG INTERACTIONS**

**General**
The following section describes the most significant drug interactions with buprenorphine and the
combination of buprenorphine/naloxone. Consult drug information for the most recent and complete
description. Consider also, that drug interactions not documented are possible. Also consider that
studies often focus on the interaction between two drugs, but many patients are on multiple drugs.

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 CNS depression:

- Patients who indicate benzodiazepine abuse are likely not good candidates for office-based
  opioid treatment.
- Patients with a history of benzodiazepine addiction or abuse are at high risk to abuse while on
  buprenorphine and should be closely monitored.
- Similar problems occur with sedative hypnotics, e.g., phenobarbital and clonazepam.
- When a potentially serious drug interaction is likely, such as CNS depressants, CYP3A4
  inhibitors, atazanavir) patients should be monitored daily.
- Timing of when symptoms develop varies and depends on a number of factors.
- Dose adjustments needed vary with the patient.
BENZODIAZEPINES

Benzodiazepines and Opioids

The interaction between buprenorphine and benzodiazepines can be particularly serious.

Overdosing on both benzodiazepines and opioids, including buprenorphine, at the same time may cause fatal respiratory depression.

The ceiling effect that results in buprenorphine having less risk of respiratory depression when taken by itself than full mu agonists, is reduced by benzodiazepines.

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.

- In 81% of the 123,000 emergency room Xanax® (alprazolam) related cases, patients used the drug with another prescription drug. Of these cases, more than one-third used alprazolam with a prescription painkiller, such as oxycodone.
- Coma and death are possible when these two drugs are combined, particularly if buprenorphine is injected.

The most commonly misused benzodiazepines among lifetime misusers are: diazepam (Valium®), alprazolam (Xanax®), lorazepam (Ativan®), and clonazepam (Klonopin®).

Symptoms of Concurrent Use of Benzodiazepines and Opioids

Among 250 opioid dependent subjects with previous buprenorphine prescriptions, Nielsen (2007) reported the following symptoms when also taking benzodiazepines:

- Extreme drowsiness 24%
- Unconsciousness 3%
- Overdose 1%

Clinical Guidelines For Use of Benzodiazepines with Buprenorphine

Be wary of simultaneously prescribing both buprenorphine and benzodiazepines, using a high level of caution. Closely monitor your patients who are taking both.

Consider a dose reduction of prescribed benzodiazepine, buprenorphine, or both.

Counsel patients about the danger of abusing benzodiazepines when taking buprenorphine.

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

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. Monitor closely and try to decrease benzodiazepine use over time if possible.

CASE: DRUG INTERACTION

Provider: I see that you recently had a visit to the ER after taking a Xanax®.

Mr. Dexter: Yes, I thought I was having a stroke or something. I was dizzy and drowsy. They said it was from mixing Xanax with buprenorphine.

Provider: You didn't tell us that you take Xanax. It is one of the drugs we discussed being important to me to know about. Did someone prescribe that for you recently?

Mr. Dexter: Well, it's my wife's actually. And I don't take it regularly, just when I need it. That's why I didn't mention it.

Provider: You should not take Xanax or other benzodiazepines while taking buprenorphine because it can cause serious, potentially fatal effects. It's very important that I know any drugs or medications that you take, even if you do so only occasionally. I want to be sure there won't be any more dangerous interactions with buprenorphine.

ALCOHOL AND SEDATING MEDICATIONS

Alcohol

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

It is important to screen for alcohol use during the evaluation before starting buprenorphine. If a positive screen occurs, assess further to determine if there is at-risk drinking (Recommended limits per day for women 3 drinks, for men 4 drinks):
Determine the level of intervention needed, from brief intervention, brief treatment with pharmacotherapy, or detoxification and more intense treatment.

Prescribing office-based treatment with active at-risk alcohol use or alcohol use disorder is not recommended, 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 together with buprenorphine only with caution and monitoring, because they increase the risk of respiratory depression, over-sedation, hypotension, coma, and death.\(^7\)

Mildly Sedating Medications
Other medications having milder sedating effects that might be additive, should be used with caution, especially at first, until you understand how the medication affects the patient. For example, SSRI antidepressants may increase drowsiness in interaction with buprenorphine, especially initially.\(^6\)

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

CAUTION TIPS
- Use caution when prescribing buprenorphine to patients who take (or abuse) other CNS depressants, including alcohol. Patients with active alcohol use disorder rarely make good candidates for office-based opioid treatment.\(^5\)

KEY POINTS
- Buprenorphine and some sedative-hypnotics have an additive effect when taken together, which may potentially be fatal.
- Buprenorphine's interaction with benzodiazepines is particularly dangerous.

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, adding buprenorphine to their system may precipitate withdrawal.

Check the resources page information about clinically significant drug-drug interactions.
Cocaine and Marijuana
According to ASAM practice guidelines, "use of marijuana, stimulants, or other addictive drugs should not be a reason to discontinue buprenorphine treatment"\(^{37}\). Rates of marijuana and cocaine use were higher in individuals taking buprenorphine than in the general population\(^{67,68}\). However, further research is needed on drug interactions between buprenorphine and these two drugs\(^{69}\).

- **Marijuana**: According to expert opinion at a 2015 update on buprenorphine, there was no evidence that marijuana use affects buprenorphine treatment outcome and so they concluded its use by itself does not justify discharge from treatment\(^{70}\).

- **Cocaine**: Used with buprenorphine, cocaine may increase metabolism and diminish buprenorphine plasma concentrations\(^{7}\). Experts have noted that patients who are actively addicted to cocaine tend to be high risk for office-based treatment\(^{70}\).

Gabapentin
Cases of gabapentin being used while on buprenorphine in order to enhance its effects potentially resulting in psychotic-like symptoms has been described in a personal communication\(^{52}\). Like any CNS depressant in combination with buprenorphine, the potential for serious side effects should be considered.

Anticholinergics
Anticholinergics, including inhaler medications (e.g., ipratropium bromide, oxtropium bromide, tiotropium) and certain medications for gastrointestinal and urinary tract disorders increase the risk of urinary retention and/or severe constipation and potentially, paralytic ileus\(^{7}\).

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\(^{27}\).

- **Medications that inhibit** CYP 3A4 may increase 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\(^{7}\)

- **Medications that induce** CYP 3A4 activity can decrease buprenorphine's plasma concentration and potentially require a higher daily dose of buprenorphine\(^{4}\).
  - Includes: phenobarbital, carbamazepine, phenytoin, rifampicin\(^{7}\)

Buprenorphine can, in turn, also affect plasma concentration and dose of other medications metabolized via CYP 3A4.
CAUTION TIP
Be cautious when prescribing buprenorphine with any other CYP 3A4 medication, inducers, or inhibitors. Monitor the patient carefully for over or underdosing, especially at the start or end of these medications and be prepared to adjust medication dosage if necessary.

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.

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.

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 prescribing these medications in combination.

Antiretrovirals may alter buprenorphine levels, but most antiretrovirals that have been tested do not cause buprenorphine withdrawal or toxicity.

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. Atazanavir/ritonavir produced an even larger increase in concentrations.

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, which would increase buprenorphine plasma levels
  - NNRTIs (neviraphine, delavirdine, and efavirenz) have also shown interactions with opioid treatment, both methadone and buprenorphine.

Specific Potential Interactions

- Protease Inhibitors (PI)
• Atazanavir – Buprenorphine concentration increased. Cognitive impairment or oversedation in some patients. Use slow titration and/or dose reduction as needed.
• Darunavir-ritonavir – Some pharmacokinetic effect, need for dose adjustment unlikely, but monitor
• Ritonavir and Tipranavir – Some pharmacokinetic effect, no dose adjustment
• Nonnucleoside reverse transcriptase inhibitors (NNRTI)⁷
  • Delavirdine – Non-significant increase in buprenorphine concentration, need for dose adjustment unlikely, but monitor
  • Efavirenz – Some pharmacokinetic effect, need for dose adjustment unlikely
  • Nevirapine – Some pharmacokinetic effect, no dose adjustment
• Integrase inhibitor – Some pharmacokinetic effect, no dose adjustment⁷

QUIZ: DRUG INTERACTIONS

Question: Which of the following drugs that interact with buprenorphine is most likely to have a relatively severe interaction with buprenorphine?

Choose one

1. Antiretroviral agents
   • Feedback: Incorrect. Many antiretroviral agents have interactions with opioid treatment but they are not as likely to be life-threatening as interactions with benzodiazepines or alcohol.

2. Cocaine
   • Feedback: Incorrect. Drug interactions between buprenorphine and cocaine are not clear; severe interactions have not been reported commonly. The interaction between buprenorphine and benzodiazepines can be particularly serious. Overdosing on both of these drugs at the same time may cause fatal respiratory depression. Alcohol and other CNS depressants also can cause overdose, respiratory depression, and death when taken with buprenorphine.

3. Benzodiazepines
   • Feedback: Correct! The interaction between buprenorphine and benzodiazepines can be particularly serious. Overdosing on both of these drugs at the same time may cause fatal respiratory depression. Alcohol and other CNS depressants also can cause overdose, respiratory depression, and death when taken with buprenorphine.

4. SSRI antidepressants
   • Feedback: Partially correct. May increase drowsiness a little in combination with buprenorphine especially initially. Depressants, such as benzodiazepines, alcohol, sedatives, hypnotics, general anesthetics, tranquilizers, and other opioids, are more dangerous in combination with buprenorphine.
BUPRENORPHINE OVERDOSE

Buprenorphine Overdose Risk

Studies of safety and efficacy have shown that buprenorphine can be used safely and effectively in the primary care setting\(^74,75\).

Buprenorphine has a ceiling effect, meaning that its effect and respiratory depression increases with increased dose, but this increase levels out at moderate doses\(^76\). Due to its ceiling effect and poor bioavailability, the risk of overdose from buprenorphine, either accidentally or intentionally, is relatively low\(^29,30\). Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS) data shows that the risk of severe intoxication is lower for buprenorphine than for other opioids\(^77\).

However, the opioid agonist effect of buprenorphine renders overdose and abuse possible. As a result, SAMHSA’s update for buprenorphine therapy recommends\(^7\):

- Patient education about the possibility of buprenorphine overdose and opioid overdose if they return to opioid use
- Consider prescribing naloxone for patients on buprenorphine to use in the event of an overdose

The risk of overdose is higher in patients who inject buprenorphine or take it in conjunction with other drugs, including other opioids, benzodiazepines, alcohol, sedatives, or certain medications that interact with buprenorphine\(^7\). Misusing buprenorphine and sedative-hypnotics, particularly benzodiazepines, greatly increases the risk of overdose.

Risk of overdose is also higher in opioid naive persons.

Prevalence of Overdose and Abuse

- In 2011, an estimated 21,483 emergency room visits for misuse and 3,625 cases of toxic buprenorphine exposure were reported\(^78\).
- SAMHSA reported 30,135 hospital emergency department visits linked to buprenorphine in 2010, with 52% involving misuse. Of the misuse-related visits:
  - 41% involved just the use of buprenorphine
  - 59% involved the use of other substances, including benzodiazepines, narcotic pain relievers, marijuana, heroin and cocaine\(^79\).

\(\) Source: SAMHSA, 2013
Accidental and non-accidental ingestion of buprenorphine in children is also increasing in proportion to an increase in availability and clinical use: There were 2,380 overdoses in young children in 2009\textsuperscript{80}. In a review of 4879 buprenorphine exposures in identified in children under age 6, around a third had a serious medical outcome and only one fatal outcome was reported\textsuperscript{77}. Deaths have been reported, however, with low doses of buprenorphine in the form of sublingual tablets for analgesia in opioid naive individuals, as low as 2 mg\textsuperscript{81}, which underscores the importance of safe, preferably locked storage.

**REMS**
To counteract the risk of buprenorphine diversion and abuse, the FDA requires a Risk Evaluation and Mitigation Strategy from the manufacturers of certain buprenorphine products. The strategy includes provider education and medication guides for patients\textsuperscript{64}.

**THINK AHEAD**
What do you think is the effect of adding naloxone to buprenorphine?

**OVERDOSE RECOGNITION & PREVENTION**

**Signs and symptoms of buprenorphine overdose:**
- Cold, clammy skin
- Weakness
- Constricted pupils (Note: After brain damage occurs, pupils may dilate.)
- Hypotension
- Loss of consciousness/unresponsiveness
- Respiratory depression

Of these, respiratory depression may be fatal if untreated\textsuperscript{4}.

**Preventing Overdose**
- Advise your patients of the consequences of buprenorphine overdose.\textsuperscript{4}
- Warn against mixing buprenorphine and alcohol.\textsuperscript{4}
- Warn against mixing buprenorphine and benzodiazepines.\textsuperscript{4}
- Use caution when prescribing both buprenorphine and benzodiazepines or other sedating medications.\textsuperscript{4}
- Warn your patients not to inject buprenorphine. Unless contraindicated, prescribe buprenorphine/naloxone combination tablets or film, which are less\textsuperscript{4}
- Unless contraindicated, prescribe buprenorphine/naloxone combination tablets or film, which are less likely to be injected than medication containing only buprenorphine.\textsuperscript{4}

**OVERDOSE SPECIAL CONSIDERATIONS**

**Special Considerations for Benzodiazepines**
If the patient must remain on benzodiazepines\textsuperscript{82}:
- Start at a low dose of buprenorphine (1-2 mg) and slowly increase dosage
- Use shorter acting versions (e.g., Lorazepam or Oxazepam)
• Avoid long-term use of benzodiazepines

**Other Special Considerations**
Additional patient populations that may need a lower starting dose and slower increase:

• Patients <20 years old
• Patients >60 years old
  • Particularly those who are frail, have HIV, hepatitis C, cancer, or are taking other sedatives (e.g., lithium)
• Patients taking multiple drugs

**OVERDOSE: TREATMENT**
Buprenorphine overdose is treated with supportive care and an opioid antagonist, such as naloxone, to displace the buprenorphine. Recommendations for treating opioid overdose, for adults, are as follows:

1. Start with 0.4 mg to 2 mg naloxone (NARCAN) intravenously (or intramuscular or subcutaneous if intravenous is not available). If respiratory function has not improved sufficiently, repeat at 2 to 3-minute intervals up to a total dose of 10 mg. Buprenorphine's affinity for opioid receptors is strong enough that a relatively higher dose of naloxone may be needed to reverse respiratory depression; reversal effects are gradual with buprenorphine. [Note that naloxone injection solution USP is supplied in 1mg/mL concentration.]

2. If there has been no response, re-evaluate the diagnosis of opioid toxicity or partial opioid toxicity. Respirations should be mechanically assisted and other measures for resuscitation used if clinically indicated.

3. Because the duration of naloxone is relatively short, continue to monitor the patient. Additional doses may be needed when the naloxone effect wears off. This varies with the amount of opioid taken and whether it was long-acting/extended release.

4. If respiratory depression is prolonged and continued boluses of naloxone are needed, continuous IV infusion of naloxone should be considered.

**Considerations:**

• **Withdrawal symptoms.** Note that patients who are physically dependent on opioids are likely to experience withdrawal symptoms with abrupt reversal of opioid effects by naloxone.

• **Caution for cardiac disease.** Use caution in patients with cardiac disease or who are on medications with potential adverse cardiovascular effects such as hypotension, ventricular tachycardia or fibrillation and pulmonary edema.

• **Is there also a benzodiazepine overdose?** Consider whether there is a mixed overdose with benzodiazepines that is contributing. Treatment for the benzodiazepine part of the overdose is usually supportive including maintaining airway, respiration, and hemodynamic support until there is natural recovery.

**PRACTICE TIP**
Warn your patients to keep supplies away from where children can find them.
FYI
Naloxone taken intravenously has good bioavailability. When buprenorphine/naloxone combination is injected by someone who is dependent on opioids, the naloxone can cause precipitated opioid withdrawal.\textsuperscript{86}

NALOXONE FOR OVERDOSE

Naloxone Overdose Reversal Kit
Naloxone kits are used for the reversal of a narcotic overdose, induced by opioids. Although rare, buprenorphine overdose can occur. The kits can be used to counteract a buprenorphine overdose, however, as described on the previous page, naloxone does not work as well for buprenorphine as it does for other abused opioids. SAMHSA recommends considering prescribing naloxone for patients on buprenorphine.\textsuperscript{87}

The following kits are currently available:

- Single-dose hand-held, auto-injector systems (FDA approved in 2014)
- Muscle syringes. One syringe per 1 ml of naloxone (FDA approved)
- Intranasal spray (Narcan®)
- Injectable dosages for intravenous, intramuscular and subcutaneous administration include 1 mg/ml and 10 ml (multi-dose)

Candidates for naloxone kits may include patients who are:

- Taking high doses of opioid medication for the prolonged management of chronic pain/illness
- At risk for incomplete cross-tolerance
- Taking extended-release opioid preparations that may pose a risk for overdose
- At risk for overdose due to medically prescribed analgesia, combined with a suspected or confirmed history of substance abuse, or dependence

The FDA approved a user-friendly intranasal formulation of naloxone in November 2015. The amount of medication gets into the body and how rapidly it is effective is comparable to the injectable version.\textsuperscript{88}

PRACTICE TIP
Naloxone kits can be distributed to family members, friends, peers, employers, non-medical staff and volunteers in addition to the at-risk patient.

QUIZ: NALOXONE

Question: With respect to treating overdose, how does naloxone treatment of buprenorphine (a partial opioid agonist) overdose compare to naloxone treatment of full agonist opioid overdose:

Choose one
1. Faster
   • Feedback: Incorrect. As compared to other opioid antagonists, the effects of utilizing naloxone for buprenorphine overdose is slower.

2. About the same
   • Feedback: Incorrect. As compared to other opioid antagonists, the effects of utilizing naloxone for buprenorphine overdose is slower.

3. Slower
   • Feedback: Correct. As compared to other opioid antagonists, the effects of utilizing naloxone for buprenorphine overdose is slower.

PRECAUTIONS & CONTRAINDICATIONS

Special Precautions
- Because buprenorphine is metabolized using the CYP 3A4 pathway, use caution when prescribing medications metabolized similarly.
- Because hepatic impairment reduces buprenorphine clearance and even more so, naloxone clearance, the following adjustments should be made in patients with existing hepatic insufficiency along with careful monitoring:
  • Mild impairment (Child-Pugh score of 5-6) - dose adjustment not needed\(^8^9\)
  • Moderate impairment (Child-Pugh score of 7-9) - Combination buprenorphine/naloxone is not recommended for induction, because it could precipitate withdrawal\(^8^9\). The combination formula may be used for maintenance after induction on buprenorphine monotherapy in these patients\(^8^7\). Monitor for toxicity or overdose.
  • Severe impairment (Child-Pugh score of 10-15) - Combination buprenorphine/naloxone should not be used\(^2^4,8^9\). Half doses of monotherapy can be titrated carefully with monitoring for toxicity and overdose\(^9^0\).

Also consider that the additional naloxone may interfere with the efficacy of buprenorphine\(^8^7\).

- Advise patients to abstain from alcohol while taking buprenorphine
- Monitor patients who are simultaneously prescribed buprenorphine and benzodiazepines closely. Also, counsel them regarding the danger of abusing benzodiazepines while taking buprenorphine.
- Monitor patients taking sedating medications simultaneously, until the effect on the patient is understood.
- For patients with compromised respiratory function (COPD, decreased respiratory reserve, hypoxia, hypercapnia, preexisting respiratory depression) prescribe with caution and monitor closely\(^7\). Warn about risks of using benzodiazepines and other depressants along with buprenorphine.
- Use buprenorphine with caution in patients being treated for seizures for several reasons\(^4,7,5^4\):
  • The metabolism of both buprenorphine and antiseizure medications may be altered by their combination, so therapeutic plasma levels may need to be monitored.
  • Buprenorphine can interact with sedative-hypnotics.
Contraindications

Buprenorphine should \textbf{NOT} be prescribed to:

\begin{itemize}
\item Patients who have suffered a head injury or have intracranial lesions.
\item Patients with a history of hypersensitivity to buprenorphine.
\item Patients with elevated liver function testing 3-5 times greater than normal.
\item Patients with moderate to severe hepatic impairment.
\item Patients who indicate benzodiazepine abuse.
\item Patients with at risk alcohol use or alcohol use disorder.
\end{itemize}

Buprenorphine with naloxone should \textbf{NOT} be prescribed to:\textsuperscript{3,35,52,54,57}

\begin{itemize}
\item Pregnant women (monotherapy tablets may be used)
\item Patients who have had hypersensitivity/allergic reaction to naloxone (monotherapy tablets may be used). Patients with hypersensitivity/allergic reaction to buprenorphine.
\end{itemize}

\textbf{CAUTION TIP}

\begin{itemize}
\item Buprenorphine can cause fatal respiratory depression in children accidentally exposed to it. Be sure to keep buprenorphine-containing medications out of reach of children
\item 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.
\end{itemize}

\textbf{BUPRENORPHINE PHYSICAL DEPENDENCE}

Many patients do not understand the fact that buprenorphine treatment maintains physical dependence, so this needs to be explained. Sometimes they think that because buprenorphine 'blocks' opioids of abuse, that they no longer are physically dependent.

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 maintenance is:

\begin{itemize}
\item Somewhat less severe than withdrawal from a full agonist\textsuperscript{91}, however, withdrawal from buprenorphine still can be severe and prolonged even with a taper.
\item Withdrawal from buprenorphine may be more tolerable than from full agonists\textsuperscript{92}, however relapse rates after tapering from buprenorphine are very high\textsuperscript{93–95}.
\end{itemize}

\textbf{BUPRENORPHINE ABUSE POTENTIAL}

Buprenorphine is somewhat less prone to abuse than most mu agonists – including opioid replacement drugs such as methadone\textsuperscript{92}, however, it is abused. Factors that help decrease abuse include that when taken sublingually:

\begin{itemize}
\item It does not cause the rush sought by many opioid misusers\textsuperscript{91}
\end{itemize}
• 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
  • It is highly lipophilic and 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.
The buprenorphine implant and the injectable formulations reduce risk of accidental exposure. It may also help reduce diversion of the medication for recreational purposes by reducing the supply of single doses available for theft.

**QUIZ: BUPRENORPHINE/NALOXONE**

**Question:** Which of the following is true of buprenorphine/naloxone combination tablet or film?

**Choose one**

1. Tolerance to combination buprenorphine/naloxone tablets or film develops as quickly as tolerance to full mu agonists.
   - Feedback: Incorrect. Tolerance to buprenorphine is generally milder than for full mu agonists.
2. Withdrawal from combination buprenorphine/naloxone tablets or film is as intense as withdrawal from full mu agonists.
   - Feedback: Incorrect. Withdrawal from combination buprenorphine/naloxone tablet or film is generally milder than for full mu agonists.
3. Using combination buprenorphine/naloxone tablets or film does not cause a big "rush."
   - Feedback: Correct! Unlike heroin or methadone, combination buprenorphine/naloxone tablets or film does not cause a big rush; it is believed that this should reduce buprenorphine's abuse liability.
4. Injecting or inhaling the tablet or film will not cause a high.
   - Feedback: Incorrect. Users can get high (albeit mildly) by injecting or inhaling the combination tablet or film. The correct answer is that combination buprenorphine/naloxone tablets or film do not cause a big rush, unlike heroin or methadone. It is believed that this should reduce buprenorphine's abuse liability.
SUMMARY AND KEY POINTS

Opioid Classification
- Pharmacology: 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 drug of abuse and 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 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
- Formulations: Buprenorphine/naloxone tablets or film are the formulations that have been the most widely used to treat opioid use disorder. A buprenorphine subcutaneous implant is available for moderate to low dose maintenance (8 mg or lower). A monthly injectable form is available for patients having been stabilized for at least 7 days on submucosal buprenorphine. Monotherapy, buprenorphine without naloxone is "a reasonable and recommended alternative to methadone for pregnant women". Evidence for the use of combination buprenorphine naloxone in pregnancy was considered "insufficient."
- 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 minimizes potential for abuse
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.
Implants and injectable formulations may result in less diversion.

RESOURCES AVAILABLE THROUGH THIS MODULE:

- **Buprenorphine Product Formulations Comparison**
  Describes the different formulations of buprenorphine for treatment of opioid use disorder. Includes Brand Names, How Supplied, Dosage, Maintenance Target Dose, and Instructions for Use.

- **Common Side Effects of Buprenorphine**
  Patient Handout

- **Drug Interactions: Cytochrome P450 Drug Interaction Table**
  This table is designed as a hypothesis testing, teaching and reference tool for physicians and researchers interested in drug interactions that are the result of competition for, or effects on the human cytochrome P450 system. Clinicians and health care providers may find an abbreviated clinical table designed for practical use during prescribing more useful. The table contains lists of drugs metabolized at least in part via specific cytochrome P450 isoforms. It may not necessarily have large effects on the pharmacokinetics of the drug.

- **Drug Interactions Between Methadone or Buprenorphine and other Medications**
  Table of drug interactions between methadone or buprenorphine and other medications from a review by McCance-Katz, Sullivan, and Nallani (2010).

- **Drug Interactions Checker**
  This website provides a "Drug Interactions Checker" that explains drug interactions. Furthermore, the significance level of the drug interaction is classified as major, moderate, or minor drug interactions. You can also check for food/lifestyle and disease interactions.
- **DSM 5 Criteria for Opioid Withdrawal**
  Lists the clinical criteria for opioid withdrawal.
- **FDA approves first buprenorphine implant for treatment of opioid dependence**
  News release regarding buprenorphine implant for treatment of opioid use disorder.
- **FDA approves first once-monthly buprenorphine injection, a medication-assisted treatment option for opioid use disorder**
- **FDA news release announcing approval of once-monthly injection treatment for opioid use disorder, Sublocade.**
- **FDA approves the first non-opioid treatment for management of opioid withdrawal symptoms in adults**
- **FDA Drug Safety Information for Providers and Patients: Buprenorphine tablets**
  Buprenorphine tablets are approved for the treatment of opiate dependence. Buprenorphine treats opiate addiction by preventing symptoms of withdrawal from heroin and other opiates.
- **Medication Guide: Suboxone Sublingual Film (CIII)**
  Patient information sheet on buprenorphine plus naloxone sublingual film
- **Medication Guide: Sublocade Injection for subcutaneous use.**
- **Medication Guide: Probuphine implant.**
- **Medication Guide: Zubsolv**
- **Medication Guide: Bunavail**
- **Medication Guides: Other Formulations**
- **Monitoring of liver function tests and hepatitis in patients receiving buprenorphine/ naloxone**
  This web page provides brief recommendations for monitoring patients undergoing buprenorphine treatment using liver function tests, and the proper actions to take if a patient develops hepatitis.
- **Opioid Overdose Prevention Toolkit**
  Includes several resources: Facts for Community Members; Essentials for First Responders; Safety Advice for Patients; Information for Prescribers; and Resources for Overdose Survivors and Family Members
- **PCSS-MAT Guidance: Clinically Relevant Drug Interactions of Buprenorphine or Methadone with Other Frequently Prescribed Drugs**
  Guideline document discussing interactions between buprenorphine and HIV medication.
- **PCSS-MAT Guidance: Management of Psychiatric Medications in Patients Receiving Buprenorphine/ Naloxone**
  This document describes how to manage medications for co-occurring psychiatric disorders in a patient receiving buprenorphine.
- **Side Effect Management**
  A table describing the management of side effects.
- **Sublocade: Highlights of Prescribing Information**
- **Suboxone Prescribing Information**
  This provides prescribing information for Suboxone sublingual film and includes information on indications, dosing, contraindications, adverse reactions, drug interactions and use in specific populations.
- **Suboxone Prescription Guide**
  Medication guide for Suboxone
REFERENCES USED IN THIS MODULE:


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