BUPRENORPHINE

How Long Until It Works
• Effects on withdrawal can be immediate
• Effects on reducing opioid use disorder/dependence can take many months of treatment

If It Works
• Reduces cravings, decreases opioid consumption
• Reduces effects of opioid withdrawal
• Diminishes rewarding effects of opioid consumption

If It Doesn’t Work
• Evaluate for and address contributing factors
• Consider switching to another agent
• If patients receiving the implant feel a need for supplemental dosing, they should be evaluated and transmucosal buprenorphine should be considered

Best Augmenting Combos for Partial Response or Treatment Resistance
• Augmentation with behavioral, educational, and/or supportive therapy in groups or as an individual is probably key to successful treatment
• Buprenorphine can be prescribed in combination with naloxone (Suboxone) to decrease the potential for abuse or diversion

Tests
• Liver function tests at baseline and during treatment

SIDE EFFECTS
How Drug Causes Side Effects
• Binding at mu opioid receptors

Notable Side Effects
• Headache, constipation, nausea
• Oral hypoesthesia, glossodynia
• Orthostatic hypotension
• Implant specific: insertion site pain, pruritis, erythema

Life-Threatening or Dangerous Side Effects
• Respiratory depression
• Hepatotoxicity

How the Drug Works
• Binds with strong affinity to the mu opioid receptor, preventing exogenous opioids from binding there and thus preventing the pleasurable effects of opioid consumption
• Because buprenorphine is a partial agonist, it can cause immediate withdrawal in a patient currently taking opioids (i.e., reduces receptor stimulation in the presence of a full agonist) but can relieve withdrawal if a patient is already experiencing it (i.e., increases receptor stimulation in the absence of a full agonist)
• Buprenorphine is also an antagonist at the kappa opioid receptor
• In combination with naloxone: naloxone is a mu opioid receptor antagonist and can therefore block the effects of buprenorphine; however, because naloxone has poor sublingual bioavailability, it does not interfere with buprenorphine’s effects when used properly. Naloxone does have good parenteral bioavailability; thus, if one tries to administer the buprenorphine/naloxone formulation intravenously, naloxone will prevent any rewarding effects from buprenorphine.
• Observe patient for at least 2 hours with initial dose, then have 1–2 visits in first week
• Achieve the lowest dose that eliminates withdrawal symptoms and illicit opioid use
• Stabilization (up to 2 months) and maintenance dose is generally 8–24 mg (8 mg/2 mg up to 24 mg/6 mg for buprenorphine/naloxone)
• During stabilization patients should be seen once per week
• During maintenance patients should be seen biweekly or monthly

Dosing Tips – Sublingual
• Buprenorphine must be administered sublingually, as swallowing reduces its bioavailability
• Patients should be instructed to place the sublingual formulation under the tongue and allow it to dissolve completely; the formulation should not be divided, crushed, chewed, or swallowed
• Can be dosed less often than once daily; one should double the dose for each additional 24-hour interval
• Buprenorphine alone is often used to initiate treatment, while buprenorphine/naloxone is preferred for stabilization and maintenance treatment
• Only buprenorphine with naloxone should be used for unsupervised administration, unless the patient has a proven allergy to naloxone
• Can be distributed through clinicians’ offices by those who obtain a DEA DATA 2000 waiver
• Patients being switched between the 2 sublingual formulations (tablet and film) should be started on the same dose as the previously administered product; however, because the sublingual film has greater bioavailability than the sublingual tablet, patients must be monitored for over-medication (when switching from tablet to film) or under-medication (when switching from film to tablet); dose adjustment may be necessary

How to Dose – Implant
• Patient must have achieved and sustained prolonged clinical stability on transmucosal buprenorphine

Initiation (7 days)

<table>
<thead>
<tr>
<th>Buprenorphine</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Days 3–7</th>
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<tbody>
<tr>
<td>8 mg</td>
<td>8 mg</td>
<td>12 or 16 mg</td>
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<tr>
<td>Increase in increments of 4 mg; maximum 32 mg</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Buprenorphine/ naloxone</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Days 3–7</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 mg/2 mg</td>
<td>8 mg/2 mg</td>
<td>12 mg/3 mg or 16 mg/4 mg</td>
<td></td>
</tr>
<tr>
<td>Increase in increments of 4 mg/1 mg; maximum 32 mg/8 mg</td>
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</tbody>
</table>
**Dosing Tips – Implant**
- Implants must be inserted and removed by trained healthcare providers who are certified in the Probuphine REMS program; information is available at http://www.probuphinerems.com or 1-844-859-6341
- Patients must currently be on a maintenance dose of 8 mg/day or less of transmucosal buprenorphine and should not be transitioned to a lower dose for the sole purpose of transitioning to the implant
- Patients should be on a stable transmucosal buprenorphine dose (8 mg/day or less) for 3 months or longer without any need for supplemental dosing or adjustments
- Examine the insertion site 1 week after implant insertion for signs of infection or other problems
- Patients should not receive prescriptions for transmucosal buprenorphine for as-needed use; patients who feel a need for supplemental dosing should be evaluated and alternative treatment should be considered
- For continued treatment, new implants may be inserted subdermally in an area of the inner side of either upper arm that has not been previously used at the time of removal
- If new implants are not inserted on the same day as removal, then patients should be maintained on their previous dosage of transmucosal buprenorphine
- After one insertion in each arm, most patients should be transitioned back to transmucosal buprenorphine if continued treatment is desired, as there is no experience with re-insertion into previously used administration sites or insertion into sites other than the upper arm

**Overdose**
- Can be fatal (less common than with methadone); respiratory depression, sedation, constricted pupils, bradycardia, hypotension, coma

**Long-Term Use**
- Maintenance treatment may be required; typical maintenance period is up to 2 years but may need to be indefinite

**Habit Forming**
- Buprenorphine is a Schedule III drug
- Can cause physical dependence

**How to Stop**
- Patients may experience a mild withdrawal syndrome if buprenorphine is stopped abruptly
- Taper to avoid withdrawal effects

**Pharmacokinetics**
- Metabolized by CYP450 3A4
- Elimination half-life of sublingual buprenorphine is 24–42 hours
- Elimination half-life of naloxone is 2–12 hours
- Implant: Tmax is 12 hours; time to steady state is 4 weeks

**Drug Interactions**
- Increased depressive effects, particularly respiratory depression, have occurred when taken with other CNS depressants; consider dose reduction of either or both when taken concomitantly
- Plasma concentrations of buprenorphine may be increased by drugs that inhibit CYP450 3A4, so buprenorphine dose may need to be reduced if coadministered
- Patients taking a CYP450 3A4 inhibitor who transfer to the implant should be monitored to ensure that plasma buprenorphine levels are adequate
- If a CYP450 3A4 inhibitor is initiated in a patient with the implant, the patient should be monitored for signs of over-medication
- If a CYP450 3A4 inhibitor is discontinued in a patient with the implant, the patient should be monitored for signs of withdrawal
- Plasma concentrations of buprenorphine may be reduced by drugs that induce CYP450 3A4, so buprenorphine dose may need to be increased if coadministered
- Patients taking a CYP450 3A4 inducer who transfer to the implant should be monitored to ensure that plasma buprenorphine levels are not excessive
• If a CYP450 3A4 inducer is initiated in a patient with the implant, patients should be monitored for signs of withdrawal
• If a CYP450 3A4 inducer is discontinued in a patient with the implant, patients should be monitored for signs of over-medication

**Other Warnings/Precautions**

• Although the risk is lower, buprenorphine can be abused in a manner similar to other opioids
• Parenteral misuse of buprenorphine/naloxone may result in marked opioid withdrawal syndrome
• To prevent withdrawal in patients dependent on opioids, patients must be in a mild withdrawal state prior to initiating treatment
• Attempts by patients to overcome blockade of opioid receptors by taking large amounts of exogenous opioids could lead to opioid intoxication or even fatal overdose
• Use with caution in patients with compromised respiratory function
• Risk of respiratory depression is increased with concomitant use of CNS depressants, particularly with parenteral administration
• Can cause severe, possibly fatal respiratory depression in children who are accidentally exposed to it
• Withdrawal symptoms can occur when switching from methadone to buprenorphine
• Buprenorphine may elevate cerebrospinal fluid pressure and should be used with caution in patients with head injury, intracranial lesions, and other circumstances when cerebrospinal pressure may be increased
• Buprenorphine may increase intracholedochal pressure and should be administered with caution to patients with dysfunction of the biliary tract
• Use with caution in debilitated patients and those with myxedema or hypothyroidism, adrenal cortical insufficiency (e.g., Addison’s disease); CNS depression or coma; toxic psychoses; prostatic hypertrophy or urethral stricture; acute alcoholism; delirium tremens; or kyphoscoliosis
• Use the implant with caution in patients with a history of keloid formation, connective tissue disease, or history of recurrent methicillin-resistant *Staphylococcus aureus* (MRSA) infections
• Rare nerve damage and migration resulting in embolism and death may occur due to improper insertion of the implant in the upper arm; local migration, protrusion, and expulsion can also occur as a result of improper or incomplete insertion; protrusion and expulsion may occur as a result of infection
• In the event that an implant is expelled, the patient should store it in a plastic bag out of reach of children and bring it to their healthcare provider to ensure that the entire implant was expelled
• The prescribing healthcare provider will need to monitor the patient until the implant is replaced

**Do Not Use**

• As an analgesic
• If the patient is naive to opioid use
• If there is a proven allergy to buprenorphine
• If patient has severe hepatic impairment (buprenorphine/naloxone combinations only)
• If there is a proven allergy to naloxone (buprenorphine/naloxone combinations only)

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**SPECIAL POPULATIONS**

**Renal Impairment**

• Dose adjustment not necessary

**Hepatic Impairment**

• In patients with moderate to severe impairment, plasma levels of buprenorphine can be higher and half-life can be longer; thus, these patients should be monitored for signs and symptoms of toxicity or overdose
• For severe impairment, the dose should be reduced
• Because dose adjustment is not possible with the implant, it is not recommended for use in patients with moderate to severe hepatic impairment
• Hepatic impairment results in reduced clearance of naloxone, so patients with severe impairment should not take buprenorphine/naloxone combinations; caution is warranted for patients with moderate impairment
**Cardiac Impairment**
- Use with caution

**Elderly**
- Use with caution
- Some patients may tolerate lower doses better

**Children and Adolescents**
- Safety and efficacy have not been established

**Pregnancy**
- Effective June 30, 2015, the US FDA requires changes to the content and format of pregnancy and lactation information in prescription drug labels, including the elimination of the pregnancy letter categories; the Pregnancy and Lactation Labeling Rule (PLLR or final rule) applies only to prescription drugs and will be phased in gradually for drugs approved on or after June 30, 2001
- Controlled studies have not been conducted in pregnant women
- Buprenorphine may be preferable to methadone in pregnant women
- Neonatal withdrawal has been reported following use of buprenorphine during pregnancy

**Breast Feeding**
- Some drug is found in mother’s breast milk
  - Recommended either to discontinue drug or bottle feed

**THE ART OF PSYCHOPHARMACOLOGY**

**Potential Advantages**
- Patients with mild to moderate physical dependence

**Potential Disadvantages**
- Patients unable to tolerate mild withdrawal symptoms

**Primary Target Symptoms**
- Opioid dependence

**Pearls**
- Considered a “take home” medication that generally has less stigma and better adherence than methadone
- Relatively convenient to administer, with flexible dosing and ease of discontinuation

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**Suggested Reading**


