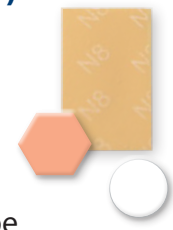
U.S. Department of Veterans Affairs
Veterans Health Administration
PBM Academic Detailing Service

Buprenorphine for Opioid Use Disorder

Quick facts about buprenorphine for treatment of opioid use disorder (OUD)



- Medications, like buprenorphine, are the gold-standard treatment for patients with OUD. Buprenorphine saves lives, reduces illicit opioid use and opioid cravings, and improves retention in treatment and well-being.[1-5]
- OUD is a chronic, relapsing disease. While the optimal treatment duration for OUD has not been defined, medications are often continued indefinitely. Discontinuation should be based on collaborative discussion and the patient's ability to maintain recovery without medication. Medication should NOT be discontinued upon return to non-prescribed opioid use.[1,6]

For questions about buprenorphine or assistance evaluating for OUD, contact your local pain and/or addiction specialists, or your Stepped Care for OUD Train the Trainer (SCOUTT) Team: **https://dvagov.sharepoint.com/sites/VHASUD/SCOUTT**

Buprenorphine formulations FDA approved for treatment of OUD[1,2,6,7;a]

Generic name (Brand name)	Buprenorphine and naloxone (Suboxone®)[8,9;b]		Buprenorphine (Subutex®)[10]	Buprenorphine (Sublocade®)[11]
Dosage form and strengths	Sublingual (SL) tablet: 2/0.5 mg, 8/2 mg	SL film: 2/0.5 mg, 4/1 mg, 8/2 mg, 12/3 mg	SL tablet: 2 mg, 8 mg	Extended release subcutaneous (SC) injection: 100 mg, 300 mg
Non-formulary consult	Not required	Required	Not required	Required
X-waiver	Required	Required	Required	Required
When to use	• Preferred for initiation and maintenance in most patients • Reduced risk of misuse and diversion versus Subutex®	Adverse effects, intolerance, absorption issues with SL tablets (e.g., swallowing or spitting out tablets)	• Not recommended first line in most cases; naloxone combination is preferred • May be used in pregnant women	• After use of SL buprenorphine 8-24 mg/day for ≥7 days • If daily dosing is difficult or risky (e.g., homeless, unstable housing, living with children), or concern for diversion, misuse, or insufficient response with SL
Frequency of use	• Daily for OUD • When used to treat OUD and pain, or off-label for a primary pain indication, consider adjusting the dosage interval to twice or three times daily to provide adequate analgesia			• Monthly (≥26 days between doses) • Administer a missed dose as soon as possible, with the following dose given no less than 26 days later • Occasional delays in dosing <2 weeks should not have significant impact

[a] Buprenorphine perioperative guidance: https://dvagov.sharepoint.com/sites/VHAPBM/Formulary/Clinical%20Guidance/Forms/AllItems.aspx. REMS (risk evaluation and mitigation strategies) for all formulations can be found at: www.accessdata.fda.gov/scripts/cder/rems/index.cfm.

[b] Bunavail® (buprenorphine/naloxone buccal film), Zubsolv® (buprenorphine/naloxone sublingual tablet), and Cassipa® (buprenorphine/naloxone sublingual film) dosing differs from Suboxone®.[16-18] All require a non-formulary consult.

Buprenorphine formulations FDA approved for treatment of OUD[1,2,6,7;a] *(continued)*

Generic name (Brand name)	Buprenorphine and naloxone (Suboxone®)[8,9;b]	Buprenorphine (Subutex®)[10]	Buprenorphine (Sublocade®)[11]

Typical dosing	**During initiation, titrate dose to treat withdrawal, cravings, and as tolerated.**
	• **DAY 1:** Initiate
	  • Suboxone® 2/0.5 mg or 4/1 mg; titrate by 2/0.5 mg or 4/1 mg every 1-2 hours to a target dose of 8/2 mg/day
	  • Subutex® 2 or 4 mg; titrate by 2 or 4 mg every 1-2 hours to a target dose 8 mg/day
	• **DAY 2:** Start with Day 1 dose, continue titrating
	  • Suboxone® in 2/0.5 mg or 4/1 mg increments to a target dose of 16/4 mg/day
	  • Subutex® in 2 or 4 mg increments to a target dose of 16mg/day
	• **Target maintenance dose:** Suboxone® 12/3 mg to 16/4 mg/day or Subutex® 12-16 mg/day in a single daily dose
			• **Initiate:** 300 mg SC injection in abdominal adipose tissue monthly for 2 months
			• **Maintenance:** 100 mg monthly; can increase to 300 mg monthly if 100 mg tolerated but unsatisfactory clinical response (e.g., opioid cravings, withdrawal, use of non-prescribed opioids)
			• A 2-month dosing interval may be appropriate in some cases (e.g., extended travel). Administer a single 300 mg dose to cover 2 months, then resume 100 mg daily.

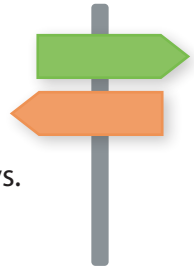
Usual max dose	24 mg/day; higher doses may be used in some cases (i.e., uncontrolled withdrawal or cravings) but should be carefully monitored, and rationale for use documented[12-15]		300 mg/4 weeks
Clinical pearls	• **Initiate when in sufficient withdrawal** (e.g., Clinical Opiate Withdrawal Scale [COWS] score ≥8) to avoid precipitated withdrawal.[c] • **SL tablet:** Place under the tongue until dissolved. For doses requiring >1 tablet, place 2 tablets under the tongue at a time until fully dissolved and repeat with remaining tablets. • **SL film:** Place 1 film under the tongue close to the base on the left or right side and allow to completely dissolve. If a second film is needed, place on the opposite side of the mouth. If a third film is needed, wait for the first two to dissolve, the place inside the right or left cheek. Do not cut or chew. • Avoid swallowing due to reduced bioavailability. • Avoid abrupt discontinuation and gradually reduce dose to taper off.		• Injection site pruritus and pain are common; apply a topical anesthetic (e.g., lidocaine 5% ointment) 10-30 minutes prior to injection; may dispense to patient to apply prior to appointment. • Peak effect occurs ~24 hours after injection, and 4-6 months needed to achieve steady-state. • After achieving steady-state, plasma levels remain detectable for ≥12 months after discontinuation and will decrease gradually over subsequent months.

[a] Buprenorphine perioperative guidance: https://dvagov.sharepoint.com/sites/VHAPBM/Formulary/Clinical%20Guidance/Forms/AllItems.aspx. REMS (risk evaluation and mitigation strategies) for all formulations can be found at: www.accessdata.fda.gov/scripts/cder/rems/index.cfm.

[b] Bunavail® (buprenorphine/naloxone buccal film), Zubsolv® (buprenorphine/naloxone sublingual tablet), and Cassipa® (buprenorphine/naloxone sublingual film) dosing differs from Suboxone®.[16-18] All require a non-formulary consult.

[c] For strategies to taper full agonist opioids prior to starting buprenorphine: https://dvagov.sharepoint.com/sites/vhaacademicdetailing/ClassicMigration/SitePages/Pain%20Management.aspx. To review conversion factors and calculate MEDD for buprenorphine, visit: https://www.belbuca.com/hcp/buprenorphine-dosing-titration/opioid-conversion#. Consider providing a medication disposal bag for disposal of any remaining full agonist opioids.

Alternative initiation approaches for sublingual buprenorphine[19-23]



For patients with concern or history of intolerable precipitated opioid withdrawal during buprenorphine initiation, consider an alternative initiation approach:

- ✓ **Continue** current full agonist opioids (including use of illicit opioids) for 4-8 days. Consider providing a medication disposal bag for disposal of any remaining full agonist opioids.
- ✓ **Gradually up-titrate** sublingual buprenorphine to the lowest effective dose for management of withdrawal and cravings, as tolerated. Doses may be further up-titrated as clinically indicated. Please note the following example requires tablet splitting.

	<80 mg MEDD		80-150 mg MEDD		>150 mg MEDD	
Day	**Full agonist opioids**	**SL Bup**	**Full agonist opioids**	**SL Bup**	**Full agonist opioids**	**SL Bup**
1	Continue	1 mg TDD	Continue	1 mg TDD	Continue	1 mg TDD
2	Continue	2 mg TDD	Continue	2 mg TDD	Continue	2 mg TDD
3	Continue	3 mg TDD	Continue	3 mg TDD	Continue	3 mg TDD
4	Continue	4 mg TDD	Continue	6 mg TDD	⬇ to 150 mg MEDD*	6 mg TDD
5 (+)	STOP	4 mg TDD	STOP	6 mg TDD	STOP	9 mg TDD

MEDD, morphine equivalent daily dose; SL, sublingual; Bup, buprenorphine; TDD, total daily dose.
*Additional resources for opioid tapering are available at: https://dvagov.sharepoint.com/sites/vhaacademicdetailing/ClassicMigration/SitePages/Pain%20Management.aspx

Initial assessment and monitoring[1,2,6-11]

- Evaluate the following parameters at baseline whenever possible. In some cases, baseline parameters (e.g., labs) may not be available, and risks of delaying treatment may outweigh risks of delaying labs.
- Monitor at least annually, as clinically indicated, and more frequently during treatment initiation and when unexpected results are found.
- Utilize monitoring strategies to facilitate healthy versus punitive discussions with patients.

Initial assessment and monitoring[1,2,6-11] *(continued)*

Diagnosis, assessment, treatment

- Evaluate OUD diagnosis and update the problem list (current OUD, in early remission, or in full sustained remission)
- Evaluate for opioid withdrawal and cravings using objective scales (e.g., COWS, Opioid Craving Scale)[24]
- Offer opioid overdose education and naloxone[25]

Concurrent conditions

- For patients with co-occurring pain, assess using a validated tool (e.g., PEG score)
- Assess psychological functioning, substance use, and any treatments received
- Screen for suicide risk using a validated tool (e.g., Columbia-Suicide Severity Rating Scale [C-SSRS] Screener)[26]

Databases, labs, procedures

- Review state PDMP
- Urine drug screen
- CBC, renal and hepatic function
- Infectious disease testing: tuberculosis, hepatitis B and C, HIV
- Pregnancy test (if child-bearing age)
- Electrocardiogram in patients at risk for QTc prolongation, e.g.:
  - —hypokalemia, clinically unstable cardiac disease, personal or family history of Long QT Syndrome, or taking Class Ia or Class III antiarrhythmic drugs, or drugs that prolong the QT interval*

PDMP, prescription drug monitoring program; CBC, complete blood count; HIV, human immunodeficiency virus.

*Buprenorphine mildly inhibits cardiac repolarization.[6] QTc prolongation has been observed in clinical studies with buprenorphine extended-release injection (Sublocade®).[11] Buprenorphine may be preferred over methadone in patients with QT prolongation or arrhythmia (Torsades de Pointes).[1,2]

REFERENCES

1. American Society of Addiction Medicine. The ASAM national practice guideline for the treatment of opioid use disorder: 2020 focused update. Rockville, MD: American Society of Addiction Medicine;2020. **2.** Substance Abuse and Mental Health Services Administration. Medications for opioid use disorder. Treatment Improvement Protocol (TIP) Series 63, Full Document. Rockville, MD: Substance Abuse and Mental Health Services Administration;2020. **3.** Kakko J, Svanborg KD, Kreek MJ, Heilig M. 1-year retention and social function after buprenorphine-assisted relapse prevention treatment for heroin dependence in Sweden: a randomised, placebo-controlled trial. *Lancet.* 2003;361(9358):662-668. **4.** Evans EA, Zhu Y, Yoo C, Huang D, Hser YI. Criminal justice outcomes over 5 years after randomization to buprenorphine-naloxone or methadone treatment for opioid use disorder. *Addiction.* 2019;114(8):1396-1404. **5.** Schackman BR, Leff JA, Botsko M, et al. The cost of integrated HIV care and buprenorphine/naloxone treatment: results of a cross-site evaluation. *J Acquir Immune Defic Syndr.* 2011;56 Suppl 1(Suppl 1):S76-S82. **6.** Buprenorphine Formulations for Chronic Pain Management in Patients with Opioid Use Disorder or on Long-Term Opioid Therapy with Physiologic Tolerance: Buprenorphine Inj, Buprenorphine TDS, Buprenorphine SL Film, Buprenorphine/Naloxone SL tabs Recommendations for Use. March 2020. VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives; National Mental Health Office – Substance Use Disorders; National Pain Management Strategic Coordinating Committee. Accessed Jan 4, 2021. **7.** The Management of Substance Abuse Disorders Work Group. VA/DOD Clinical practice guideline for the management of substance use disorders. VA/DoD. 2015;Version 3.0(December 2015):1-169. **8.** Reckitt Benckiser Pharmaceuticals, Inc. Buprenorphine and naloxone (Suboxone) [package insert]. U.S. Food and Drug Administration Website. https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020733s007s008lbl.pdf. Issued December 2011. Accessed February 2, 2021. **9.** Indivior, Inc. Buprenorphine and naloxone (Suboxone) [package insert]. U.S. Food and Drug Administration Website. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/022410s042lbl.pdf. Revised October 2019. Accessed August 30, 2020. **10.** Indivior, Inc. Buprenorphine (Subutex) [package insert]. U.S. Food and Drug Administration Website. https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020732s006s007lbl.pdf. Revised Oct 2019. Accessed August 30, 2020. **11.** Indivior, Inc. Buprenorphine (Sublocade) [package insert]. U.S. Food and Drug Administration Website. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/209819s012lbl.pdf. Revised February 2020. Accessed August 30, 2020. **12.** Danilewitz M, McLean M. High-dose buprenorphine for treatment of high potency opioid use disorder. *Drug Alcohol Rev.* 2020;39(2):135-137. **13.** Ahmadi J, Sarani EM, Jahromi MS. Rapid effect of a single-dose buprenorphine on reduction of opioid craving and suicidal ideation: A randomized, double blind, placebo-controlled study. *Ci Ji Yi Xue Za Zhi.* 2019;32(1):58-64. **14.** Ahmadi J, Jahromi MS, Ghahremani D, London ED. Single high-dose buprenorphine for opioid craving during withdrawal. *Trials.* 2018;19(1):675. **15.** Ahmadi J, Jahromi MS, Ehsaei Z. The effectiveness of different singly administered high doses of buprenorphine in reducing suicidal ideation in acutely depressed people with co-morbid opiate dependence: a randomized, double-blind, clinical trial. *Trials.* 2018;19(1):462. **16.** BioDelivery Sciences International, Inc. Buprenorphine and naloxone (Bunavail) [package insert]. U.S. Food and Drug Administration Website. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/205637s020lbl.pdf. Revised Oct 2019. Accessed August 30, 2020. **17.** Orexo US, Inc. Buprenorphine and naloxone (Zubsolv) [package insert]. U.S. Food and Drug Administration Website. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/204242s017lbl.pdf. Revised October 2019. Accessed August 30, 2020. **18.** TEVA Pharmaceuticals USA, Inc. Buprenorphine and naloxone (Cassipa) [package insert]. U.S. Food and Drug Administration Website. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/208042s000lbl.pdf. Issued September 2018. Accessed January 28, 2021. **19.** Becker WC, Frank JW, Edens EL. Switching From High-Dose, Long-Term Opioids to Buprenorphine: A Case Series. *Ann Intern Med.* 2020;173(1):70-71. **20.** Edens EL, Abelleira A, Declan B, Becker WC. You say Pain. I say addiction. Let's call the whole thing off. *Psychiatric Times.* 2020 Nov 9;37(11):47-51. **21.** Randhawa PA, Brar R, Nolan S. Buprenorphine-naloxone "microdosing": an alternative induction approach for the treatment of opioid use disorder in the wake of North America's increasingly potent illicit drug market. *CMAJ.* 2020;192(3):E73. **22.** Hämmig R, Kemter A, Strasser J, et al. Use of microdoses for induction of buprenorphine treatment with overlapping full opioid agonist use: the Bernese method. *Subst Abuse Rehabil.* 2016;7:99-105. **23.** Brar R, Fairbairn N, Sutherland C, Nolan S. Use of a novel prescribing approach for the treatment of opioid use disorder: Buprenorphine/naloxone micro-dosing – a case series. *Drug Alcohol Rev.* 2020;39(5):588-594. **24.** Northrup TF, Stotts AL, Green C, et al. Opioid withdrawal, craving, and use during and after outpatient buprenorphine stabilization and taper: a discrete survival and growth mixture model. *Addict Behav.* 2015;41:20-28. **25.** Naloxone Rescue: Recommendations for Issuing. Naloxone Rescue [Naloxone HCl nasal spray (Narcan®) and Intramuscular Naloxone Kit] for the VA Opioid Overdose Education and Naloxone Distribution (OEND) Program. Nov 2020. VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives in collaboration with the VA OEND National Support and Development Work Group. Accessed Jan 4, 2021. **26.** The Assessment and Management of Suicide Risk Work Group. VA/DoD Clinical Practice Guideline for the Assessment and Management of Patients at Risk for Suicide. VA/DoD. 2019;Version 2.0:1-142.