CLINICIAN GUIDE

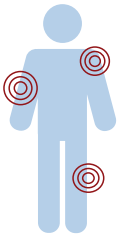
VA | U.S. Department of Veterans Affairs
Veterans Health Administration
PBM Academic Detailing Service

Buprenorphine for Chronic Pain

Quick facts about buprenorphine for treatment of chronic pain

Non-opioid medications in combination with non-pharmacologic interventions are preferred for treatment of chronic pain.[1] However, when treatment with opioids is indicated, buprenorphine may be preferred over full agonist opioids due to a **unique mechanism of action and safety profile:**[2-4]

Partial mu-opioid receptor agonist	• Potent analgesia • Dose-related ceiling effect on respiratory depression and euphoria ↓ Risk opioid overdose (risk increases when combined with alcohol, benzodiazepines, other central nervous system depressants [CNS]) ↓ Addiction, tolerance, withdrawal ↓ Constipation, immune suppression, hypogonadism ↓ Depression, suicidal ideation, dysphoria, anxiety
Kappa-opioid receptor antagonist	↓ Depression, suicidal ideation, dysphoria, anxiety, hostility ↓ Sedation, hyperalgesia, immune suppression, addiction, tolerance
Delta-opioid receptor antagonist	• Anti-opioid effects, myocardial protection ↓ Constipation, respiratory depression
Reduced affinity for orphan-like receptor 1 (ORL-1)	• Increased spinal analgesia ↓ Supraspinal analgesia, opioid rewarding effects, tolerance
Blocks monoamine reuptake	• Not associated with serotonin syndrome



Buprenorphine has **similar efficacy** compared to other opioids for treatment of chronic low back pain, osteoarthritis, neuropathic pain, cancer pain, and post-operative pain.[3,4] Consider buprenorphine for:

- ✓ Patients requiring around-the-clock treatment with chronic opioids, AND
- ✓ Patients with difficulty tapering the dose of full mu-opioid agonists OR one of the following:

High risk for traditional opioid therapy[1,3,5]

- History of drug overdose
- Concurrent use of CNS depressants
- Severe respiratory instability, sleep disordered breathing
- Acute psychiatric instability, high acute suicide risk, mental health disorders
- Prescribed long-term (>90 days) or high dose opioids (>120 mg morphine equivalent daily dose [MEDD])*
- Opioid tolerance but does not meet criteria for opioid use disorder (OUD)
- Under age 30
- Traumatic brain injury

Special populations[3,6]

- Poor or unpredictable gastrointestinal absorption
- Difficulty swallowing
- Older adults
- Severe renal impairment
- Mild-moderate hepatic impairment
- Other opioids are ineffective or not tolerated
- Immunosuppressed patients
- Patients who wish to remain sexually active

* To review conversion factors and calculate MEDD for buprenorphine, visit: https://www.belbuca.com/hcp/buprenorphine-dosing-titration/opioid-conversion#

Buprenorphine formulations FDA approved for treatment of chronic pain[a,b]

Brand	Butrans® (transdermal patch)[5,7]	Belbuca® (buccal film)[5,8]
Strengths	5, 7.5, 10, 15, and 20 mcg/hour	75, 150, 300, 450, 600, 750, and 900 mcg
PADR	Required	Required
X-waiver	Not required	Not required
REMS	Must complete an accredited continuing education program to prescribe: https://opioidanalgesicrems.com	
Initial dosing*	• **Opioid-naïve:** 5 mcg/hour patch • **<30 mg MEDD:** 5 mcg/hour when next dose is due • **30-80 mg MEDD:** taper to <30 mg MEDD[c], then 10 mcg/hour when next dose is due • **>80 mg MEDD:** may not be adequate analgesia, consider buprenorphine buccal film • Change patch and rotate site every 7 days	• **Opioid-naïve:** 75 mcg film 1x daily or q12 hr, as tolerated • **<30 mg MEDD:** 75 mcg film when next dose is due, 1x daily or q12 hr • **30-89 mg MEDD:** taper to <30 mg MEDD[c], then 150 mcg q12 hr when next dose is due • **90-160 mg MEDD:** taper to 30 mg MEDD[c], then 300 mcg q12 hr when next dose is due • **>160 mg MEDD:** may not provide adequate analgesia, consider referral to X-waivered provider for buprenorphine/naloxone • Apply film to mucosa every 12 hours
Hepatic impairment	• **Severe:** has not been studied, consider alternative • **Mild-moderate:** no adjustments needed	• **Severe (Child-Pugh C):** reduce starting dose and titration by 50% • **Mild-moderate (Child-Pugh A and B):** no adjustments needed

Titration	• Titrate dose no sooner than every 72 hours based on analgesic response and adverse effects
	• May apply two 5, 7.5, or 10 mcg/hr patches at one time for dose individualization
	• Short-term, short acting analgesia may be used for break-through pain as dose is titrated
		• Titrate no sooner than every 4 days based on response and adverse effects:
		  • If dose 75 mcg q12 hr, titrate to 150 mcg q12hr
		  • If dose 150 mcg q12hr or higher, titrate in 150 mcg increments q12hr
		• Short-term, short acting analgesia may be used for break-through pain as needed as dose is titrated

Max dose*	• 20 mcg/hour	• 900 mcg every 12 hours
Administration	• Apply to clean, dry, hairless/nearly hairless skin on upper chest, upper back, side of chest, upper outer arm • Change patch and rotate application site every 3 weeks • Do not cut patch; may secure edges with first aid tape or cover with transparent adhesive film dressing	• Lick inside of cheek or rinse with water if mouth is dry to moisten the area • Hold buccal film with clean dry fingers with yellow side facing up • Place yellow side of buccal film on the middle inside of cheek inside of mouth, hold for 5 seconds, leave in place until dissolved (approximately 30 minutes)
Clinical pearls	• Clean application site with lukewarm water and air dry • Avoid soaps, alcohol, oils, lotions, or abrasives on site • Avoid shaving site or applying to hairy/sweaty areas • Avoid exposing site to heat, direct sunlight, or hot water to prevent increase in drug delivery, overdose, and death • Can cause rash and erythema but is not a reason for discontinuation; treat with hydrocortisone cream • Avoid abrupt discontinuation; gradually taper if indicated	• Avoid eating, drinking acidic beverages, and using toothpaste or mouthwash 30 minutes before, during, or 30 minutes after application • Avoid application on open sores, lesions, too high or far back in cheek • Avoid touching/moving the film until dissolved; if film is not fully dissolved after 30 minutes, remove residue and rinse with water; avoid chewing or swallowing buccal film • Avoid abrupt discontinuation and gradually reduce dose to taper off • Patients with dexterity issues may have challenges with application
Disposal	• Fold adhesive side to itself and flush down the toilet	• Remove from foil packaging and flush down the toilet

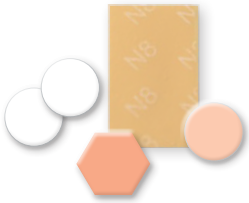
*FDA-approved. PADR, prior authorization drug request; REMS, risk evaluation and mitigation strategy.

[a] Buprenorphine perioperative guidance: https://dvagov.sharepoint.com/sites/VHAPBM/Formulary/Clinical%20Guidance/Forms/AllItems.aspx.

[b] Buprenex® (buprenorphine hydrochloride injection solution) is intended for use in acute treatment settings via deep intramuscular or slow intravenous injection over at least 2 minutes.[8] The starting dose is typically 0.3 mg, a second dose of 0.3 mg may be given 30-60 minutes later, and subsequent doses are given every 6-8 hours based on patient response.[9]

[c] For strategies to taper full agonist opioids prior to starting buprenorphine: https://dvagov.sharepoint.com/sites/vhaacademicdetailing/ClassicMigration/SitePages/Pain%20Management.aspx. Consider providing a medication disposal bag for disposal of any remaining full agonist opioids.

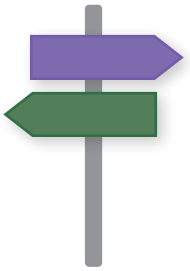
Alternative buprenorphine formulations



Buprenorphine/naloxone sublingual tablets and film (Suboxone®) and buprenorphine sublingual tablets (Subutex®) are FDA-approved for treatment of OUD. When prescribed for *both* pain and OUD, these formulations must be prescribed by a DEA-X waivered clinician and will count towards that clinician's buprenorphine panel limit. Off-label treatment of pain in patients who do not meet criteria for OUD is restricted to DEA-X waivered providers within the Veterans Health Administration. Clinical encounters should indicate the pain diagnosis, and prescription instructions should state "for pain management".[5]

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**

Alternative initiation approaches for buprenorphine buccal film



Consider an alternative initiation approach for patients unable to taper to 30 mg MEDD or with concern for/history of intolerable opioid withdrawal during buprenorphine initiation. Either convert directly to an equivalent dose, or cross-titrate for a short period of time. Provide a medication disposal bag for any remaining full agonist opioids.

1. For patients taking ≥80 mg MEDD, convert directly to an equivalent dose of buprenorphine buccal film:[10]
   - ✓ **80-160 mg MEDD:** initiate 300 mcg 8-12 hours after last dose of full agonist opioids, q12 hr
   - ✓ **161-220 mg MEDD:** initiate 450 mcg 8-12 hours after last dose of full agonist opioids, q12 hr
2. Alternatively, continue current full agonist opioids for 4-8 days and gradually up-titrate buprenorphine buccal film to the lowest effective dose.[11-16] For patients who stabilize (no withdrawal, tolerable pain) before reaching the proposed end dose, it is not necessary to proceed with further buprenorphine dose escalations. For example:

	30-59 mg MEDD		60-89 mg MEDD		90-120 mg MEDD		121-160 mg MEDD	
Day	**Full agonist opioids**	**Buccal Bup**	**Full agonist opioids**	**Buccal Bup**	**Full agonist opioids**	**Buccal Bup**	**Full agonist opioids**	**Buccal Bup**
1	Continue	150 mcg BID (300 mcg TDD)	Continue	150 mcg BID (300 mcg TDD)	Continue	300 mcg BID (600 mcg TDD)	Continue	300 mcg BID (600 mcg TDD)
2	Continue	300 mcg BID (600 mcg TDD)	Continue	300 mcg BID (600 mcg TDD)	Continue	300 mcg QAM + 600 mcg QPM (900 mcg TDD)	Continue	300 mcg QAM + 600 mcg QPM (900 mcg TDD)
3	Continue	450 mcg BID (900 mcg TDD)	Continue	450 mcg BID (900 mcg TDD)	Continue	600 mcg BID (1200 mcg TDD)	Continue	600 mcg BID (1200 mcg TDD)
4	Continue	450 mcg BID (900 mcg TDD)	Continue	600 mcg BID (1200 mcg TDD)	Continue	600 mcg QAM + 900 mcg QPM (1500 mcg TDD)	Continue	600 mcg QAM + 900 mcg QPM (1500 mcg TDD)
5 (+)	STOP	450 mcg BID (900 mcg TDD)	STOP	600 mcg BID (1200 mcg TDD)	STOP	600 mcg QAM + 900 mcg QPM (1500 mcg TDD)	STOP	900 mcg BID (1800 mcg TDD)

MEDD, morphine equivalent daily dose; Bup, buprenorphine; BID, twice daily; TDD, total daily dose; QAM, every morning; QPM, every evening.

Initial assessment and monitoring[1,5,7,8,17]

Baseline labs, patient assessments, and safety monitoring for buprenorphine are like other opioids. Whenever possible, evaluate the following at baseline. 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.

☑ Diagnosis, assessment, treatment

- Assess pain using a validated tool (e.g., PEG score)
- Evaluate for OUD if risks are present (e.g., prescribed opioids >90 days, high dose opioids >120 mg MEDD, or history of OUD or SUD)[1]
- Offer opioid overdose education and naloxone[18]

☑ Concurrent conditions

- 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)[19]

☑ Databases, labs, procedures

- Review state PDMP
- Urine drug screen
- Renal and hepatic function
- 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[a]

SUD, substance use disorder; PDMP, prescription drug monitoring program. [a]Buprenorphine mildly inhibits cardiac repolarization.[5] QTc prolongation has been observed in clinical studies for dosages of transdermal buprenorphine two 20 mcg/hr patches and buprenorphine buccal film up to 900 mcg every 12 hours. Dosages of transdermal buprenorphine >20 mcg/hr and buccal film >900 mcg every 12 hours should be avoided.[7,8]

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