

Buprenorphine for the Management of Chronic Pain

National Guidance Document

March 2024

VA Pharmacy Benefits Management Services and the National Formulary Committee in Collaboration with the VHA National Office of Pain Management, Opioid Safety and PDMP (PMOP)

The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. Local adjudication should be used until updated guidance and/or CFU are developed by the National PBM. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. The drug Product Information should be consulted for detailed prescribing information.

1. Background

Pain Management, Opioid Safety, and Prescription Drug Monitoring Program (PMOP) and PBM Formulary service are providing guidance on use of buprenorphine for outpatient pain management. This field-based guidance was created to provide clarity on the use of buprenorphine for outpatient pain management with input from the PMOP Buprenorphine Subject Matter Expert (SME) Workgroup. It is recommended that the principles of LTOT prescribing for full mu agonist opioid medications are applied to prescribing buprenorphine for pain, particularly in the absence of Opioid Use Disorder (OUD).

2. Care Considerations in Use of Buprenorphine for Chronic Pain

- a. LTOT principles outlined in VA/DoD Clinical Practice Guideline for the Use of Opioids in the Management of Chronic Pain ([VADoDOpioidsCPG.pdf](#)) should be followed when prescribing buprenorphine for pain, including:
 - o LTOT should primarily focus on functional improvement in physical, social, and psychological domains consistent with the biopsychosocial model of care.
 - o Opioid analgesic medications have less evidence of benefit and higher risk of potentially serious adverse outcomes with LTOT compared to short term prescribing for pain.
 - o Buprenorphine retains many of the same risks associated with use of full agonist opioids for chronic pain management, yet demonstrates less risk of respiratory depression.
 - o Risks versus benefits should be assessed periodically throughout treatment.
 - o Tapering or discontinuing buprenorphine should be considered when risks outweigh benefits or based on patient preference.
 - o Buprenorphine for chronic pain should be used at the lowest dose and for the shortest duration necessary. While evidence supports using buprenorphine for OUD as a lifelong/lifesaving treatment, the use of buprenorphine for chronic pain treatment is not evidence-based.
- b. Pain Management Teams (PMT) should be available to provide specialty care support upon request for the initiation and stabilization of buprenorphine for pain.
 - o Opioid transitions are high-risk, and buprenorphine is no exception.
 - o Collaboration and co-management can assist with the frequent monitoring indicated, in particular during transitions to buprenorphine.
- c. Screening for and assessment of risk for Opioid Use Disorder (OUD) prior to initiation of treatment is recommended, and assessment for OUD when patterns of unhealthy medication use (misuse, higher risk behaviors concerning for OUD) emerge during LTOT. Veterans should be offered treatment for OUD if appropriate consistent with the VA/DoD Clinical Practice Guideline for the Management of Substance Use Disorders ([VADoDSUDCPG.pdf](#))
 - o Providers should discuss any concerns about increased risk for OUD, with the Veteran and carefully determine if a higher level of care is indicated
 - o When appropriate, seek consultation with an Addiction Medicine Provider and seek referral to treatments consistent with VA/DoD Clinical Practice Guideline for the Management of Substance Use Disorders

3. Buprenorphine may be appropriate.

- a. Lack of progress towards functional goals and/or inadequate analgesic benefit with full mu agonist opioid
- b. High potential for adverse effects due to medical conditions, mental health or behavioral considerations with full mu agonist LTOT
- c. Any transition to buprenorphine, regardless of formulation or frequency, should be considered only if an around-the-clock opioid therapy is appropriate.

4. Buprenorphine may NOT be appropriate. *Clinical situations include:*

- a. Infrequent use of immediate-release opioid medication for episodic pain (e.g., PRN).
- b. Veteran on opioid therapy agreeing to taper or requesting taper (i.e., traditional taper). Utilizing the existing opioid to taper is preferred and avoids complications of transitions including adverse effects or concerns for lack of effectiveness
 - o Note: transitions to buprenorphine may be reconsidered if medical/behavioral/psychological concerns emerge during taper
- c. Demonstrating functional improvement and expressing preference to remain on full agonist LTOT, in the absence of medical, mental health, or behavioral risk for adverse effects

5. Dosage Considerations

Priorities in chronic pain management, even when using buprenorphine, are managing pain to improve function and quality of life, whereas priorities in managing OUD are more focused on harm reduction. Therefore, the dosages used for treating chronic pain with buprenorphine versus treating OUD are fundamentally different. Clinicians selecting buprenorphine primarily for chronic pain management should consider the following:

- a) Veterans may stabilize on lower doses of buprenorphine for pain compared to OUD.
 - History of opioid exposure and dosages must be considered when starting buprenorphine for pain.
 - Clinicians should be responsive and Veteran-centric when making dose titrations since recommended conversions for chronic pain are conservative.
 - Due to buprenorphine's long half-life, it takes about five days to achieve steady state. Clinicians should assess the full effect of each dose adjustment when making changes
- b) Using the lowest effective dose of buprenorphine for pain that improves function and quality of life while reduces the risk of dose-dependent adverse outcomes and limits physiologic dependence
- c) Veterans displaying higher risk behaviors in the absence of diagnosed OUD, require additional considerations with transitions to buprenorphine including:
 - Prioritizing stabilization or resolution of withdrawal symptoms and discomfort
 - Titrating dose slowly toward pain control and functional improvement
 - Focusing on early recognition of pain reduction and benefits

Note: *Low dose buprenorphine is generally not sufficient or appropriate for treatment of OUD.*

6. Buprenorphine Initiation/Transition Strategies:

- a. ***FDA-approved labeling guidance*** should be followed in most cases for new starts and standard opioid transitions to buprenorphine formulations approved for pain, for example patch and buccal film (e.g., microgram/mcg). Alternatively, low dose initiation (microdosing, overlapping dosing) may be useful for some Veterans (see below).
 - o Providers should be aware that published conversion recommendations are highly conservative (i.e., reduced 50-75%) and already include a reduction for lack of tolerance or cross-tolerance
 - o Providers should avoid rapid titrations without assessing effectiveness and tolerability at steady state
- b. ***STOP-START method*** (traditional buprenorphine induction/initiation) is defined as stopping full agonist opioids for 12-24 hours and starting buprenorphine in the early stages of withdrawal. This decreases risk of precipitated withdrawal and promotes acceptance and quick adjustment to buprenorphine.

- This method is quick and generally well tolerated by most Veterans
- It allows for quick recognition of buprenorphine effectiveness to treat the Veteran's pain condition.

c. Low dose buprenorphine initiation (microdosing, overlapping dosing) allows short-term overlap of buprenorphine titration while on full agonist opioid therapy to mitigate withdrawal and discomfort with transition from full agonist opioid therapy. This strategy may be particularly helpful for Veterans concerned about experiencing withdrawal and discomfort.

NOTE: Shared Decision-making and Veteran Preference Should Guide Treatment Approach

7. Formulation Guidance by Morphine Equivalent Daily Dose (MEDD):

Care should be individualized for each clinical situation, but if the Veteran is prescribed:

- < 50 MEDD** – Buprenorphine formulations FDA-approved for pain should be considered (mcg dosing) and either the transdermal patch or buccal films can be utilized
 - <30 MEDD – Treat as if opioid naïve and buprenorphine patch is preferred
 - 31-50 MEDD – Buprenorphine onset may be delayed up to 24 hours and not peak for 5 days. Overlapping with short-acting full agonist for the first 24 hours is acceptable
- 50-90 MEDD** – Any available buprenorphine formulation, including the transdermal patch, buccal films, or buprenorphine SL can be utilized (mcg, mg). Formulation selection will depend on multiple factors, please consider the following:
 - 1) Veterans receiving moderate doses of traditional opioids (50-90 MEDD) who are transitioning to buprenorphine but are otherwise stable are appropriate for standard outpatient transitions to buprenorphine using formulations FDA-approved for pain specifically the patch or buccal film (mcg dosing).
 - The buprenorphine buccal film is more appropriate for moderate MEDD dosing conversions and allows additional options compared to the patch where utilization is more challenging at a higher MEDD
 - Overlapping buprenorphine strategies or initiation protocols may be useful for moderate dose conversions to avoid discomfort and aid in pain control during transition to buprenorphine with both mcg and mg formulations.
 - 2) Veterans receiving moderate doses of traditional opioids (50-90 MEDD) who are not stable, and/or there is concern for potential adverse effects related to behavioral risks in the absence of diagnosed OUD are appropriate for conversion to buprenorphine SL (mg). Providers should focus on stabilization and mitigation of withdrawal symptoms and discomfort in early treatment. Upon resolution, gradually titrate to therapeutic response and re-evaluate progress toward functional goals in the Veteran's pain care plan
- >90 MEDD** – Buprenorphine SL (mg) should be considered for Veterans transitioning from high dose opioid therapy. However, Veterans on high dose LTOT often stabilize on much lower doses of buprenorphine compared to those actively using illicit fentanyl or heroin. The use of transition strategies such as STOP-START or low dose buprenorphine initiation and are likely recommended. Pain providers should focus on resolving discomfort from acute withdrawals and then transition to gradually titrating toward improved function.

TABLE 1 – Approximate dose conversion strategies from existing Long-Term Opioid Therapy		
<50 MEDD RECOMMEND: FDA approved formulations for pain (e.g. mcg dose transdermal or buccal products)	50 – 90 MEDD RECOMMEND: All buprenorphine formulations (mcg or mg) available based on patient response	>90 MEDD RECOMMEND: Buprenorphine milligram formulations should be considered
<p><30 MEDD – Treat as opioid naïve</p> <ul style="list-style-type: none"> • Patch is preferred • 5mcg recommended starting dose <p>30-50 MEDD –</p> <ul style="list-style-type: none"> • Consider 10mcg/hr patch as initial dose • Onset may be delayed 24 hours • Overlapping dosing of full agonist opioid for first 24 hours is reasonable <p>FDA conversions to buprenorphine are highly conservative –</p> <ul style="list-style-type: none"> • Manufacturer listed conversions already account for cross-tolerance • Be responsive during titration phase 	<p>Patients who are stable on existing LTOT</p> <ul style="list-style-type: none"> • Appropriate for mcg formulations as initial dose • Buccal film preferred • Overlapping strategies may be helpful <p>Patients with poor function and symptom control despite existing LTOT (or with concern for behavioral risks but without OUD)</p> <ul style="list-style-type: none"> • Appropriate for consideration of mg formulations with a focus on early stabilization of withdrawal symptoms • Gradual titration to support functional goals after initial stabilization • May stabilize on lower doses than required for OUD. 	<p>Early Emphasis on mitigating withdrawal and discomfort during the transition from full-agonist LTOT</p> <p>Veterans with pain may stabilize on lower doses that DSM-V OUD</p> <p>Veteran preference should guide method of transition</p> <ul style="list-style-type: none"> • STOP- START • Low Dose Buprenorphine initiation (LDBI) †
<p>†Example of a 5-day LDBI strategy may be found VA Academic Detailing Buprenorphine for OUD Clinician Guide or Appendix C below</p>		

8. Additional Information:

APPENDIX A: Supplemental Information which Includes: historical background, pharmacology, clinical trial summary, detailed product information, additional resource links and bibliographical reference list

APPENDIX B: Additional Examples of STOP/START or LDBI transitions

APPENDIX C: Flow Chart for reevaluation of LTOT and consideration for buprenorphine

Updated Mar 2020, May 2022, Oct 2020, Apr 2023, Mar 2024. Initially Prepared: Nov 2019

Contact: Ian W. Pace, Pharm.D. National PBM Clinical Program Manager – Formulary

Acknowledgement: The VHA National Pain Management, Opioid Safety and PDMP Program Office, Dr. Friedhelm Sandbrink (Director, PMOP), Dr. Tim Atkinson (National PMOP Program Manager), and the Buprenorphine PMOP Subject Matter Expert Working Group

APPENDIX A: BUPRENORPHINE -- SUPPLEMENTAL INFORMATION

See the **Buprenorphine for Pain Management RFU** in above sections for information on the clinical use of buprenorphine for patients with chronic pain requiring long-term opioid therapy (LTOT) as a component of their care plan.

Buprenorphine in Pain Management

Several buprenorphine formulations are FDA-approved for the management of acute or chronic moderate to severe pain; specifically, buprenorphine solution for injection 0.3mg/ml, buprenorphine transdermal system (5 to 20mcg/h 7-day patch), and buprenorphine buccal film (75 to 900 mcg/film every 12 hours). Numerous safety advantages have been identified for buprenorphine compared to pure mu agonist opioids including: a ceiling effect on respiratory depression, less euphoria, reduced tolerance, easier withdrawal, less impairment of cognitive function and psychomotor activity, lower incidence of constipation, and reduced endocrine and hyperalgesic effects. Buprenorphine has relatively few drug-drug interactions and does not accumulate in patients with renal impairment or mild/moderate hepatic impairment allowing for use in patients requiring concomitant medications, the elderly, and those with renal or hepatic impairment.^{1,2}

Buprenorphine Clinical Pharmacology in Pain Management

Pharmacologically, buprenorphine's primary effects are caused by its partial agonism of mu-opioid receptors (MORs) and antagonism at kappa-opioid receptors (KORs).³ Although it has some, but lower, ability to bind to opioid receptor ligand (ORL)-1 (also known as nociceptin) and delta-opioid receptors (DORs), the clinical effects from these are negligible.⁴⁻⁸ Its traditional categorization as a partial agonist at MORs is primarily due to its lower intrinsic activity (the biological stimulus a drug has on a receptor) compared to full MOR agonists, as shown mainly in *in vitro* binding receptor assay studies.³⁻⁸ This categorization, however, should not be confused with measures of relative clinical efficacy and potency for analgesia. Several clinical studies have shown that at low to moderate doses, buprenorphine can elicit similar analgesic effects compared to equivalent doses of full MOR agonists.⁹⁻¹⁷ Its partial agonistic activity on MORs and antagonistic activity on KORs does allow for a plateauing of the dose response curve (or ceiling effect) regarding retention of carbon dioxide (as a marker for respiratory depression), thus lowering the risk of overdose¹⁸⁻¹⁹ when used without other central nervous system (CNS) depressants. Buprenorphine also has one of the highest binding affinities toward MORs compared to all other opioids, the only exception being naltrexone.²⁰⁻²¹ This strong binding allows buprenorphine to preferentially occupy available MORs thereby disallowing full agonist opioids to bind, and while this is not a displacement per se, the net effect causes reversal of opioid activity.²²⁻²³ It also has an extremely slow dissociation rate (the measure of disengagement from the target receptor) from MORs; thus once bound, it is not easily nor quickly displaced.⁷

Buprenorphine in Pain Management: Clinical Trials

Open-label observational studies conducted with relatively small numbers of patients have reported improved pain relief on sublingual buprenorphine after conversion from other long-acting opioids.²⁴⁻²⁸ One study of 35 patients found a mean decrease in pain score from 7.2 to 3.5, with 34 out of 35 patients reporting a pain decrease.²⁹ A Cochrane meta-analysis found buprenorphine superior to other opioids for pain relief in cancer (5 out of 11 studies), equivalent (3 out of 11 studies) or inferior to the alternative treatment (3 out of 11 studies).³⁰ The evidence for all the outcomes in the meta-analysis was considered very low quality. One systematic review which included 10 trials involving 1,190 patients reported that, while all studies demonstrated that sublingual buprenorphine showed some effectiveness as a chronic pain analgesic, the majority of studies were observational and of low quality.³¹ In another systematic review which included 25 trials involving 5 different buprenorphine formulations in patients with chronic pain, a total of 14 of the studies demonstrated clinically significant benefit.³² Only studies with acceptable methodological quality and the low risk of bias were included in this review. The studies that showed significant reduction in pain against a comparator included 1 study out of 6 sublingual and intravenous buprenorphine, the only sublingual buprenorphine/naloxone study, 2 out of 3 studies of buccal buprenorphine, and 10 out of 15 studies for transdermal buprenorphine. A retrospective chart review was conducted in 78 patients from a High-Risk Pain Clinic using SL buprenorphine/naloxone (BUP/NAL) plus a multimodal approach to help chronic pain patients with a history of Substance Use Disorder (SUD) or aberrant drug-related behavior. The overall retention of the High-Risk Pain Clinic was 41%. The mean pain score demonstrated a significant downward trend across six years of treatment observation ($p < 0.001$), while the

opposite trend was seen with buprenorphine dose ($p < 0.001$) lending support for BUP/NAL as a safe and efficacious component of comprehensive chronic pain treatment in patients with SUD or high-risk of opioid overuse or misuse.³³ Similar positive outcomes were observed in an Opioid Reassessment Clinic (ORC) in a Veterans Health Administration hospital for patients with chronic pain treated with opioid regimens deemed unsafe by their primary care providers. Nearly two-thirds (62%)³⁴ of those who engaged in the ORC rotated to buprenorphine as a modality for pain management.

Transitioning veterans presenting with buprenorphine or buprenorphine prescriptions for off-label indication for pain.^{1,35}

The Under Secretary for Health's Information Letter, Access to Medications for Transitioning Service Members, IL 10-2014-15 (July 7, 2014) and VHA Directive 2014-02, Continuation of Mental Health Medications Initiated by Department of Defense Authorized Providers (January 20, 2015) direct providers to carefully evaluate and, unless medical conditions warrant a change, existing medication therapies should be continued, including buprenorphine or buprenorphine prescriptions for off-label indication for pain.

[PBM Formulary Management - DoD-VA Continuity of Care Drug List -](#)

VA/DoD Clinical Practice Guidelines^{36,37}

The [VA/DoD Clinical Practice Guideline for Opioid Therapy for Chronic Pain](#) in general recommends against initiation of long-term opioid therapy for chronic pain and that non-opioid and non-pharmacologic alternatives for pain management be part of the treatment plan. In the most recent guideline update, the workgroup made a recommendation to consider buprenorphine over other opioids when long-term opioid therapy must be considered.

Pain is a commonly comorbid condition with substance use disorders. Opioid use disorder can similarly occur in patients treated with long-term opioid therapy for chronic pain. The rates OUD in an LTOT treated chronic pain population vary widely within published literature.³⁸ Nonetheless, if OUD is present, because of the high morbidity and mortality associated with ICD-10 Opioid dependence/DSM-5 Opioid Use Disorder and the effectiveness of Medication for OUD, providers should be prepared to provide long-term treatment with buprenorphine. There are many VA resources an initiative directed at provider education regarding the evidence based treatment of OUD including:

VA/DoD Clinical Practice Guideline [Management of Substance Use Disorder \(SUD\) 2021](#)

[Stepped Care for Opioid Use Disorder - Train the Trainer \(SCOUTT\)](#)

[VHA National Academic Detailing Service -- Opioid Use Disorder Campaign](#)

Buprenorphine – Diagnostic Coding

Prior versions of PBM buprenorphine guidance documents discussed extensively diagnostic criteria related to ICD-10 opioid dependence or DSM-V opioid use disorder (OUD). In part this was because of regulatory requirements surrounding the X-waiver which was retired as part of the Consolidated Appropriations Act passed in December 2022. As such, in this version we have redacted information pertaining to the diagnosis of OUD and reference the VA/DoD, Academic Detailing, and SCOUTT initiative resources linked above. With regarding to ICD-10 codes that may be utilized in an episode of care where buprenorphine is a part of the care plan the following options are available:

- **F11.1x (opioid abuse) and F11.2x series (opioid dependence)** – these should be utilized when the encounter is for the management of OUD as the primary diagnosis. Use of these codes has the advantage of ensuring veterans are included in population management dashboards to facilitate best practice care including medication treatment and harm reduction strategies (e.g. Psychotropic Drug Safety Initiative SUD-16 [Psychotropic Drug Safety Initiative \(PDSI\) Management System \(sharepoint.com\)](#)).
- **Z79.891: Long-term (current) use of opioid analgesic** – For patients with chronic pain and with physiologic tolerance/dependence, but without OUD, the primary diagnosis would be the painful condition. If the encounter of care is primarily for the management of the prescribed opioid, z79.891 is appropriate
- **F11.9x series** – Internal review suggests this code is being used for a significant minority of patients prescribed milligram doses of buprenorphine. The clinical scenarios in which this is being used is unknown at time of update, may represent use of the diagnostically unclear scenario of pain with a dependence or tolerance that is problematic but is without a concomitant compulsive use component. Is important to be aware that use of this series DOES NOT INCLUDE patients in the PDSI SUD 16 population management dashboards for Opioid Use Disorder

Buprenorphine Dose Equivalence to Morphine

There is wide variability in the reported buprenorphine to morphine equianalgesic ratios with estimated ratios between 1:10 and 1:100.³⁹ The Centers for Medicare and Medicaid Services (CMS) and Center for Disease Control (CDC) conversion tables^{40,41} no longer include a conversion factor for buprenorphine. Similarly, the VA OTRR, STORM and Academic Detailing reporting tools do not have a conversion or have the conversion factor calculated as zero. As such, given the wide variability in the recommended dose equivalencies between buprenorphine and morphine, we are unable to make exact recommendations for equianalgesic dosing. However, please reference this supplements' parent document in section above, for practical dosing guidance when converting from existing long-term opioid therapy.

Table 1 -- Buprenorphine Product Comparison Chart

Formulary Buprenorphine Products					
Generic Name	Brand Name	Formulation	FDA-Approved Indications	Bioavailability	Elimination Half-Life
Buprenorphine	Butrans® (VANF)	Transdermal delivery system Available in 5, 7.5, 10, 15 and 20 mcg/hr patches Max dose: 20 mcg/hr every week	Management of pain severe enough to require around-the-clock, long-term opioid treatment	~15%	~26 hours
Buprenorphine	Belbuca® (VANF)	Buccal film Available in 75, 150, 300, 450, 600, 750, 900 mcg films Max dose: 900 mcg every 12 hours	Management of pain severe enough to require around-the-clock, long-term opioid treatment	46 to 65%	11.2 to 27.6 hours
Buprenorphine and naloxone sublingual TABLETS	Suboxone® (VANF)	Sublingual tablet Available in 2-0.5 and 8-2 mg SL tabs maintenance dose for OUD is 16 – 24mg/day	Used off-label for pain management. FDA approved for the treatment of opioid dependence (a.k.a. ICD-10 F11.2x opioid dependence or DSM-5 OUD).	~30% (tab) ~36% (film)*	24 to 42 hours
Buprenorphine sublingual TABLETS	Subutex® (VANF)	Sublingual tablet Available in 2mg and 8 mg SL tablets Target maintenance dose for OUD is 16 – 24mg/day	Used off-label for pain management. FDA approved for the treatment of opioid dependence (a.k.a. ICD-10 F11.2x opioid dependence or DSM-5 OUD).	~30% (tab)	24 to 42 hours

Non-Formulary Buprenorphine Products					
Buprenorphine	Buprenex® (NF)	IM, IV Available in 0.3 mg/ml ampules Dosing: 0.3 mg every 6-8 hours as needed	Indicated for the management of pain severe enough to require an opioid analgesic and for which alternate treatments are inadequate.	100%	1.2-7.2 hours (mean 2.2 hours)
Buprenorphine and naloxone sublingual FILMS*	Suboxone Sublingual Film® (NF)	Sublingual film Available in 2-0.5 4-1, 8-2, and 12-3mg film Target maintenance dose for OUD is 16 – 24mg/day			

*The bioavailability (AUC) of buprenorphine is about 20% greater for buprenorphine with naloxone 8 mg / 2 mg sublingual film than for the corresponding tablets; but this may not be clinically important for many ⁴³

Buprenorphine Injection (BUP INJ). Intended for intramuscular (IM) or intravenous (IV) administration in the acute setting, BUP INJ was the first buprenorphine product for pain management, launched in the United States in 1985, and indicated for the management of pain severe enough to require an opioid analgesic and for which alternate treatments are inadequate.^{44, 45} It contains 0.3mg of buprenorphine per 1ml of solution. There are insufficient data to recommend single doses greater than 0.6mg and the maximum recommended adult dose is 0.6mg administered in 6-hour intervals. BUP INJ is not FDA-approved for treatment of opioid dependence/OUD.

Buprenorphine TDS (BUP TDS). BUP TDS is available in 5, 7.5, 10, 15, and 20 mcg/hour patches; the BUP TDS prescribing information recommends the 5mcg/hr patch as the starting dose for patients on less than 30mg oral morphine equivalents per day while the 10mcg patch is the recommended starting dose for patients on 30-80 mg of daily morphine equivalents.⁴⁶ The TDS product labeling recommends patients be tapered to 30mg oral morphine equivalent prior to initiating therapy with BUP TDS 10 mcg/hour. However, this may not be practical for all patients and the Buprenorphine in Chronic Pain guidance document provides alternate conversion strategies that can be considered. Dose adjustments should not be made until at least 72 hours of use at the same strength since it takes approximately 72 hours to achieve steady state concentrations. BUP TDS has an apparent terminal half-life of 26 hours. BUP TDS may be a viable option in those patients who cannot tolerate the oral route of administration, as well as in the geriatric population who are more susceptible to the adverse reactions related to other opioids. BUP TDS may also be a good option for use in patients where there are concerns with the prescription of oral opioids. BUP TDS may not provide adequate analgesia for patients requiring greater than 80 mg of morphine equivalents per day. BUP TDS is not FDA-approved for treatment of opioid dependence/OUD.

Buprenorphine Buccal Film (BUP BF). BUP BF is available in 75 mcg, 150 mcg, 300 mcg, 450 mcg, 600 mcg, 750 mcg, and 900 mcg dosage strengths. Opioid-naïve patients may be started at 75 mcg once daily or every 12 hours but starting doses for the opioid-experienced patient are based on the daily morphine equivalent dose when converting from other opioids to BUP BF. As with BUP TDS and per BUP BF prescribing information, patients must be tapered to 30mg oral morphine equivalent or less prior to initiating therapy with BUP BF. Two 12-week, multicenter, Phase III studies, one in opioid-naïve and one in opioid-experienced patients, were able to demonstrate statistically significant reductions in pain scores in patients with chronic low back pain with BUP BF when compared with placebo.^{47, 48} BUP BF may not provide adequate analgesia for patients requiring greater than 160 mg oral Morphine equivalent daily dose (MEDD); consider the use of an alternate analgesic.⁴⁹ BUP BF is not FDA-approved for treatment of opioid dependence/OUD.

Buprenorphine (BUP) and Buprenorphine/Naloxone (BUP/NAL). BUP/NAL was approved by the FDA in 2002 for treatment of opioid dependence (a.k.a. DSM-5 OUD)⁵⁰ but is sometimes prescribed off-label for chronic pain management.⁵¹ Possible mechanisms for pain relief by BUP/NAL include reversal of opioid induced-hyperalgesia and improvement in opioid dependence symptoms.⁵¹⁻⁵³ One randomized controlled clinical trial demonstrated the efficacy of BUP/NAL for pain management in patients being treated for opioid use disorder

(OUD).⁵⁴ Current data suggest that buprenorphine may provide pain relief in patients with chronic pain and opioid use disorder, but the data for patients without opioid use disorder is observational, retrospective only so difficult to draw conclusions from.⁵¹⁻⁵⁹ At time of document update, a prospective trial looking at use of milligram doses of buprenorphine in a high-dose opioid chronic pain population was still ongoing (personal communication, Krebbs 2024).⁶⁰ A Cochrane meta-analysis found buprenorphine superior to other opioids (5 out of 11 studies), equivalent (3 out of 11 studies) or inferior to the alternative treatment (3 out of 11 studies) for pain relief in cancer.⁵⁶ The evidence for all the outcomes in this meta-analysis was considered very low quality. One systematic review which included 10 trials involving 1,190 patients reported that, while all studies demonstrated that sublingual buprenorphine showed some effectiveness as a chronic pain analgesic, the majority of studies were observational and of low quality.⁵⁷ A retrospective cohort study in a VHA hospital Opioid Reassessment Clinic (ORC) demonstrated the feasibility of rotating patients on long-term opioid therapy for pain to BUP/NAL.⁵⁹ Further research is needed to demonstrate the efficacy of BUP/NAL for pain in patients with and without opioid dependence/OUD.

Buprenorphine for OUD During Pregnancy/Breastfeeding

Although this document is focused on the use of buprenorphine in chronic pain conditions, worth noting that the prevalence of OUD during pregnancy more than doubled between 1998 and 2011 to 4 per 1000 deliveries and is increasing.^{61, 62} Evidence-based clinical guidance on the treatment of these women and their children are needed given that women with OUD have a higher frequency of additional risk factors for adverse pregnancy outcomes than do pregnant women who do not use opioids. A literature review to support National guidance was commissioned by SAMHSA to obtain current evidence on treatment approaches for pregnant and nursing women with OUD and their infants and children.⁶¹ The report concluded that the accepted treatment for OUD during pregnancy is long-acting opioid agonist MAT that includes methadone or buprenorphine provided within the context of a comprehensive program of obstetrical care and behavioral intervention. In addition, breastfeeding among women not using other substances and maintained on methadone or buprenorphine can encourage and promote maternal-infant bonding, and likely have mitigating effects on Neonatal Abstinence Syndrome (NAS) severity. The Maternal Opioid Treatment: Human Experimental Research (MOTHER) project found that neonates of mothers treated with buprenorphine during pregnancy required significantly less morphine, had a significantly shorter hospital stay, and had a significantly shorter duration of treatment for the neonatal abstinence syndrome, as compared to neonates whose mothers were treated with methadone.⁶³ The American College of Obstetricians and Gynecologists (ACOG) recommends opioid agonist pharmacotherapy in pregnant women with an OUD as preferable to medically supervised withdrawal which is associated with higher relapse rates and worse outcomes.⁶⁴ ACOG also encourages breastfeeding in women who are stable on their opioid agonists and are not using illicit drugs or have any contraindications such as human immunodeficiency virus (HIV) infection. Because of the low levels of buprenorphine in breastmilk, its poor oral bioavailability in infants, and the low drug concentrations found in the serum and urine of breastfed infants, the NIH Drugs and Lactation Database (LactMed) database reports the use of buprenorphine as acceptable in nursing mothers.⁶⁵

Additional Considerations

QTc Monitoring. Buprenorphine mildly inhibits cardiac repolarization and has been noted to prolong the QT interval when the transdermal patch is administered at doses greater than 20mcg/hour.^{23,30} Per BUP TDS prescribing information, the effect of BUP TDS 10 mcg/hour and 2 x BUTRANS 20 mcg/hour on QTc interval was evaluated in a double-blind (BUP TDS vs. placebo),

Table 2 -- Buprenorphine for Chronic Pain Comparison Chart^{27,29,30,33,44} (See Appendix C for Buprenorphine for Pain Management Algorithm).

Topic	BUP TDS (BUTRANS)	BUP Buccal Film (BF) (BELBUCA)	BUP and BUP/NAL (SUBOXONE, generics)
Recommended Conditions for Use in Pain Management	<p>Indication is management of moderate to severe chronic pain requiring a continuous, around-the-clock opioid analgesic for an extended period of time</p> <p>AND</p> <p>The patient is assessed as high risk for traditional oral opioid therapy and alternate buprenorphine products are not advisable.</p> <p>OR</p> <p>Patient has documented difficulty swallowing, poor or unpredictable gastrointestinal absorption (e.g., short bowel; nausea, vomiting).</p> <p>BUP TDS 20 mcg/hour may not provide adequate analgesia for patients requiring greater than 80 mg/day oral morphine equivalents. Consider the use of an alternate analgesic or, if buprenorphine is required, consider the use of BUP BF.</p>	<p>Indication is management of moderate to severe chronic pain requiring a continuous, around-the-clock opioid analgesic for an extended period of time</p> <p>AND</p> <p>The patient is assessed as high risk for traditional oral opioid therapy and alternate buprenorphine products are not advisable.</p> <p>OR</p> <p>Patient has documented difficulty swallowing, poor or unpredictable gastrointestinal absorption (e.g., short bowel; nausea, vomiting).</p> <p>BUP BF may not provide adequate analgesia for patients requiring greater than 160 mg/day oral morphine equivalents. Consider the use of an alternate analgesic or, if buprenorphine is required, consider referral to an x-waivered provider for consideration of buprenorphine or buprenorphine/naloxone Sublingual tablet.</p>	<p>BUP and BUP/NAL SL tablets are indicated for the induction and maintenance treatment of opioid dependence (ICD-10, a.k.a. OUD).</p> <p>BUP and BUP/NAL may be used by any DEA licensed provider for pain management and comorbid opioid dependence/OD.</p>
Considerations for Use	<ul style="list-style-type: none"> Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve BUP TDS for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain. BUP TDS is not indicated as an as-needed (prn) analgesic. Instruct patients to wear BUP TDS for 7 days and to wait a minimum of 3 weeks before applying to the same site. Do not abruptly discontinue BUP TDS in a physically dependent patient. Allow 3 days on current dose to evaluate the full therapeutic effect prior to making additional dosage adjustments <p>Do not apply direct heat</p>	<ul style="list-style-type: none"> Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve BUP BF for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain. BUP BF is not indicated as an as-needed (prn) analgesic. To be prescribed only by health care providers knowledgeable in use of potent opioids for management of chronic pain. Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals <p>Individualize dosing based on the severity of pain, patient response, prior analgesic experience, and risk factors for addiction, abuse, and misuse</p>	<p>BUP sublingual tablet contains no naloxone and may be preferred during pregnancy.</p> <p>BUP/NAL sublingual tablet is preferred for most patients, but especially if there are concerns for misuse or diversion.</p> <p>If used for pain in a patient without ICD-10 opioid dependence, the encounter should indicate the pain condition diagnosis, the prescription should state "for pain management"</p>

<p>Considerations for Use (Continued)</p>	<p>extended-release opioid formulations, reserve BUP TDS for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain.</p> <ul style="list-style-type: none"> • BUP TDS is not indicated as an as-needed (prn) analgesic. • Instruct patients to wear BUP TDS for 7 days and to wait a minimum of 3 weeks before applying to the same site. • Do not abruptly discontinue BUP TDS in a physically dependent patient. • Allow 3 days on current dose to evaluate the full therapeutic effect prior to making additional dosage adjustments • Do not apply direct heat 	<p>extended-release opioid formulations, reserve BUP BF for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain.</p> <ul style="list-style-type: none"> • BUP BF is not indicated as an as-needed (prn) analgesic. • To be prescribed only by health care providers knowledgeable in use of potent opioids for management of chronic pain. • Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals • Individualize dosing based on the severity of pain, patient response, prior analgesic experience, and risk factors for addiction, abuse, and misuse 	<p>BUP sublingual tablet contains no naloxone and may be preferred during pregnancy, BUP/NAL sublingual tablet is preferred for most patients, but especially if there are concerns for misuse or diversion.</p> <ul style="list-style-type: none"> • If used for pain in a patient without ICD-10 opioid dependence, the encounter should indicate the pain condition diagnosis, the prescription should state “for pain management”.
<p>Baseline Evaluation</p>	<p>Urine drug screen (UDS) Prescription Drug Monitoring Program (PDMP) Check Liver transaminases Monitor for effectiveness of pain relief Assess patient's risk for physical or psychological dependence, drug diversion and sensitivity to adverse effects, particularly respiratory depression Assess mental status, respiratory status, and increased risk for falls.</p>	<p>Urine drug screen (UDS) Prescription Drug Monitoring Program (PDMP) Check Liver transaminases Monitor for effectiveness of pain relief or prevention of opioid withdrawal symptoms Assess patient's risk for physical or psychological dependence, drug diversion and sensitivity to adverse effects, particularly respiratory depression Assess mental status, respiratory status, and increased risk for falls.</p>	<p>Urine drug screen (UDS) Prescription Drug Monitoring Program (PDMP) Check Liver transaminases Urine beta-HCG for females Monitor for effectiveness of pain relief or prevention of opioid withdrawal symptoms Assess patient's risk for physical or psychological dependence, drug diversion and sensitivity to adverse effects, particularly respiratory depression Assess mental status, respiratory status, and increased risk for falls.</p>

<p>Dosage and Administration</p>	<p>BUP TDS doses of 7.5, 10, 15, and 20 mcg/hour are for opioid experienced patients only. For opioid-naïve patients, initiate with a 5 mcg/hour patch. Each BUP TDS patch is intended to be worn for 7 days.</p> <p>*</p> <ul style="list-style-type: none"> <u>Conversion from Other Opioids to BUP TDS</u> Discontinue all other around-the-clock opioid drugs when BUP TDS therapy is initiated. There is a potential for buprenorphine to precipitate withdrawal in patients who are already on opioids. <p><i>Prior Total Daily Dose of Opioid Less than 30 mg of Oral Morphine Equivalents per Day:</i></p> <ul style="list-style-type: none"> Initiate treatment with BUP TDS 5 mcg/hour at the next dosing interval <p><i>Prior Total Daily Dose of Opioid Between 30 mg to 80 mg of Oral Morphine Equivalents per Day:</i></p> <ul style="list-style-type: none"> Taper the patient's current around-the-clock opioids for up to 7 days or more as tolerated by the patient, to no more than 30 mg of morphine or equivalent per day before beginning treatment with BUP TDS. Then initiate treatment with BUP TDS 10 mcg/hour at the next dosing interval Patients may use short-acting analgesics as needed until analgesic efficacy with BUP TDS is attained. <p><i>Prior Total Daily Dose of Opioid Greater than 80 mg of Oral Morphine Equivalents per Day:</i></p> <ul style="list-style-type: none"> BUP TDS 20 mcg/hour may not provide adequate analgesia for patients requiring greater than 80 mg/day oral morphine equivalents. Consider the use of an alternate analgesic. <p>If the patient experiences problems with adhesion, the patch may be secured with a transparent adhesive film dressing such as Tegaderm™.</p>	<p>BUP BF is for oral buccal use only and is to be applied to the buccal mucosa every 12 hours.</p> <p>*Discontinue all other around-the-clock opioid drugs when BUP BF therapy is initiated.</p> <p><i>For the Opioid-Naïve or Opioid Non-Tolerant patient.</i></p> <ul style="list-style-type: none"> Initiate treatment in opioid-naïve and opioid-non-tolerant patients with a 75 mcg film once daily or, if tolerated, every 12 hours for at least 4 days, then increase dose to 150 mcg every 12 hours. Individual titration to a dose that provides adequate analgesia and minimizes adverse reactions should proceed in increments of 150 mcg every 12 hours, no more frequently than every 4 days. Doses up to 450 mcg every 12 hours were studied in opioid-naïve patients in the clinical trials; use of higher starting doses in patients who are not opioid tolerant may cause fatal respiratory depression. <p>*</p> <p><i>Conversion from other Opioids to BUP BF</i></p> <ul style="list-style-type: none"> There is a potential for buprenorphine to precipitate withdrawal in patients who are already on opioids. To reduce the risk of opioid withdrawal, taper patients to no more than 30 mg oral MEDD daily before beginning BUP BF Initial BUP BF dose based on prior opioid expressed as oral MEDD <ul style="list-style-type: none"> Less than 30 mg oral MEDD ; BUP BF 75 mcg qd or q 12 hours 30 to 89 mg oral MEDD ; BUP BF 150 mcg q 12 hours 90 to 160 mg oral MEDD ; BUP BF 300 mcg q 12 hours > than 160 mg oral MEDD ; consider alternate analgesic. 	<p><u>For patients on BUP/NAL for ICD-10 opioid dependence/ OUD.</u> The current 24-hour dose of BUP/NAL can be split and divided for BID or TID dosing for pain management.</p> <p>*</p> <p><u>When initiating BUP/NAL for patients who do not meet ICD-10 definition of opioid dependence but who are not appropriate for BUP TDS or BUP BF</u></p> <p>Opioids should be discontinued the day prior, and the patient should be in mild withdrawal prior to initiation of BUP or BUP/NAL</p> <p>The most common dose prescribed in VHA is 16mg/day. Primarily for OUD. Doses of BUP or BUP/NAL necessary for long-term opioid therapy as part of a chronic pain are not well known. In general a starting dose of 2mg to 4mg may be adequate with dose adjustment initially</p> <p>Alternatively, patients with moderate to severe withdrawal symptoms (COWS* score >8) may require buprenorphine induction with stabilization at the lowest effective dose that controls withdrawal symptoms and minimizes side effects.</p> <p>The need for higher doses is determined by the function and clinical status of the patient, optimally following a shared decision-making model.</p> <p>*COWS = Clinical Opioid</p>
----------------------------------	---	--	--

***Recommendation to taper to <30mg MEDD (BUP TDS and BUP BF) or interrupting opioid therapy until withdrawal symptoms occur (BUP or BUP NAL) may not be required or realistic in all patients. See Appendix B for alternate initiation and dose conversion strategies**

See individual product prescribing information for Contraindications, Warnings/Precautions, Dosing in Special Populations, Major and Common Adverse Effects, Drug Interactions, and monitoring.

<p>Discontinuation and tapering guidance</p>	<p>A decision to discontinue BUP TDS after a period of therapy should be part of a comprehensive treatment plan. There is insufficient data to determine the best method of dose taper at the end of treatment. For BUP TDS, it is reasonable to consider reducing the dose by 5mcg/hour every 2 to 4 weeks until the 7.5mcg/hour dose is reached; BUP TDS may be discontinued thereafter</p>	<p>A decision to discontinue BUP BF after a period of therapy should be part of a comprehensive treatment plan. There is insufficient data to determine the best method of dose taper at the end of treatment. For BUP BF, as with other full mu agonists, it is reasonable to consider reducing the dose by 5 to 20% every 4 weeks for a slow taper, or 5 to 20% every week for a faster taper. See the Academic Detailing Opioid Taper Decision Tool for more guidance</p>	<p>A decision to discontinue SL BUP or BUP/NAL after a period of therapy should be part of a comprehensive treatment plan. There is insufficient data to determine the best method of dose taper</p>
<p>Patient Education</p>	<p>See BUP TDS Prescribing Information for full patient counselling guidance. Advise patients of the addiction, abuse and misuse potential of BUP TDS, the risks for life threatening respiratory depression, accidental exposure (especially in children), interaction with alcohol and other CNS depressants, risk for Neonatal Opioid Withdrawal Syndrome, side effects such as constipation, and caution with driving or operating heavy machinery. Advise patients on the proper administration and application of the patch, application site rotation, disposal, and to not apply direct heat. BUP TDS should be stored and kept out of sight and reach of children.</p>	<p>See BUP BF Prescribing Information for full patient counselling guidance. Advise patients of the addiction, abuse and misuse potential of BUP TDS, the risks for life threatening respiratory depression, accidental exposure (especially in children), interaction with alcohol and other CNS depressants, risk for Neonatal Opioid Withdrawal Syndrome, side effects such as constipation, and caution with driving or operating heavy machinery. Instruct patients how to properly use BUP BF, including the following:</p> <ul style="list-style-type: none"> • To carefully follow instructions for the application of BUP BF and to avoid eating or drinking until it dissolves. • Advise patients that, after BUP BF has completely dissolved in the oral mucosa, to take a sip of water, swish it gently around their teeth and gums, and swallow. Advise patients to wait for at least one hour after taking BUP BF before brushing teeth. Instruct patients to inform their dentist that they have started therapy on BUP BF. • To apply BUP BF once daily, or every twelve (12) hours at the same time or times each day. • To avoid applying BUP BF to areas of the mouth with any open sores or lesions. • To not use BUP BF if the pouch seal is broken or the buccal film is cut or damaged 	<p>See BUP and BUP/NAL Prescribing Information for full patient counselling guidance. Discuss methods to enhance medication adherence. Negotiate patient's commitment to monitored ingestion. The pill is taken once a day under the tongue, allow dissolving, do NOT chew or swallow. Store in secure place out of the reach of children. Adverse effects, if any, are usually mild and go away after the medication has been taken for a while. If you have side effects you should NOT abruptly stop taking your medication, instead, talk to your doctor about it.</p> <ul style="list-style-type: none"> • Advise patients that, after BUP or BUP/NAL has completely dissolved in the oral mucosa, to take a sip of water, swish it gently around their teeth and gums, and swallow. Advise patients to wait for at least one hour after taking BUP/NAL before brushing teeth. <p>Instruct patients to inform their dentist that they have started therapy on BUP/NAL</p>

References

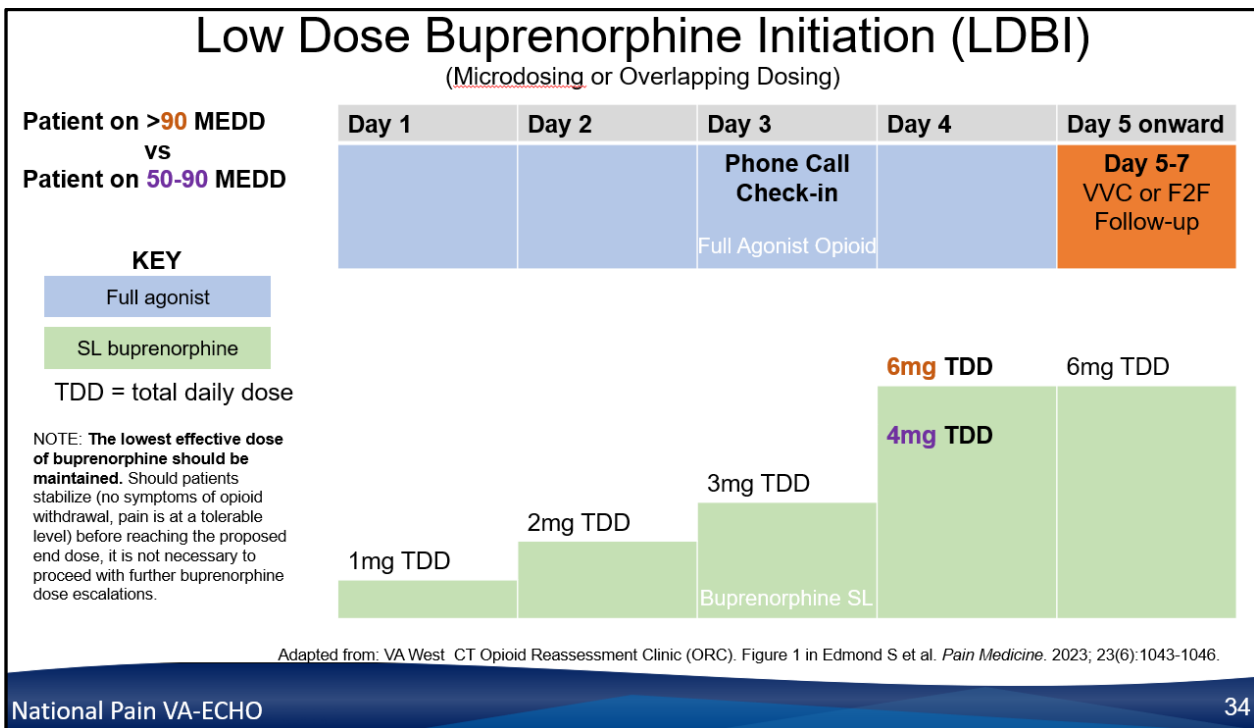
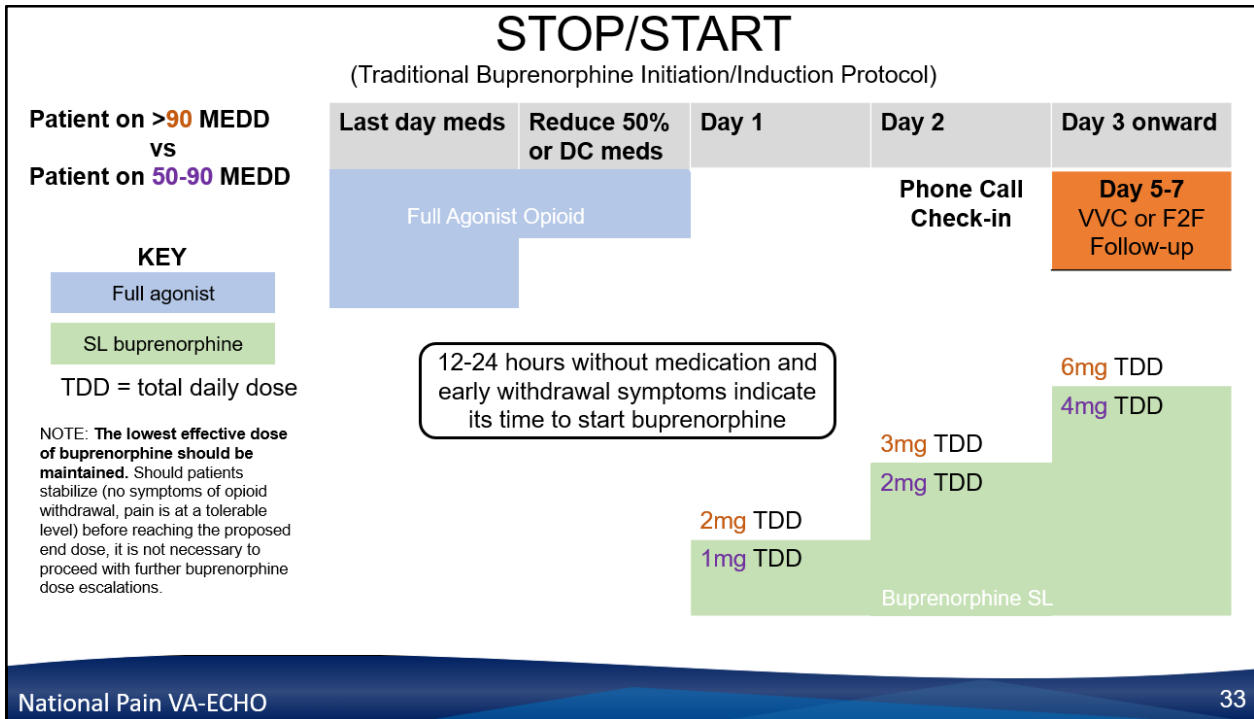
1. Under Secretary for Health's Information Letter, *Access to Medications for Transitioning Service Members*, IL 10-2014-15 (July 7, 2014)
2. Gudín J, Fudin J. A narrative pharmacological review of buprenorphine: a unique opioid for the treatment of chronic pain. *Pain Ther* 2020; 9: 41-54.
3. Chapter 18: Opioids, Analgesia, and Pain Management. In: Hilal-Dandan R, Brunton LL, editors. *Goodman and Gillman Manual of Pharmacology and Therapeutics*. 2nd ED. McGraw Hill. New York, 201
4. Brown SM, Holtzman M, Kim T, Kharasch ED. Buprenorphine metabolites, buprenorphine-3-glucuronide and norbuprenorphine-3-glucuronide, are biologically active. *Anesthesiology*. 2011;115(6):1251-6
5. Raffa RB, Haidery M, Huang HM, et al. The clinical analgesic efficacy of buprenorphine. *J Clin Pharm Ther*. 2014;39(6):577-83
6. Huang P, Kehner GB, Cowan A, Liu-Chen LY. Comparison of pharmacological activities of buprenorphine and norbuprenorphine: norbuprenorphine is a potent opioid agonist. *J Pharmacol Exp Ther*. 2001;297:688-69
7. Boas RA, Villiger JW. Clinical actions of fentanyl and buprenorphine. The significance of receptor binding. *Br J Anaesth*. 1985;57(2):192-6
8. Sadee W, Rosenbaum JS, Herz A. Buprenorphine: differential interaction with opiate receptor subtypes in vivo. *J Pharmacol Exp Ther*. 1982;223(1):157-62
9. Macintyre PE, Russell RA, Usher KA, Gaughwin M, Huxtable CA. Pain relief and opioid requirements in the first 24 hours after surgery in patients taking buprenorphine and methadone opioid substitution therapy. *Anaesth Intensive Care*. 2013;41(2):222-23
10. Tigerstedt I, Tammisto T. Double-blind, multiple-dose comparison of buprenorphine and morphine in postoperative pain. *Acta Anaesthesiol Scand*, 1980;24:462-46
11. Hovell BC, Ward AE. Pain relief in the post-operative period: a comparative trial of morphine and a new analgesic buprenorphine. *J Int Med Res*, 1977;5: 417-421.
12. Cuschieri RJ, Morran CG, McArdle CS. Comparison of morphine and sublingual buprenorphine following abdominal surgery. *Br J Anaesth*, 1984;56:855-859.
13. Gaitini L, Moskovitz B, Katz E, Vaisberg A, Vaida S, Nativ O. Sublingual buprenorphine compared to morphine delivered by a patient-controlled analgesia system as postoperative analgesia after prostatectomy. *Urol Int*, 1996;57:227-229.
14. Edge WG, Cooper GM, Morgan M. Analgesic effects of sublingual buprenorphine. *Anaesthesia*, 1979;34:463-467.
15. Bradley JP. A comparison of morphine and buprenorphine for analgesia after abdominal surgery. *Anaesth Intensive Care*, 1984;12:303-310
16. Oifa S, Sydoruk T, White I et al. Effects of intravenous patient-controlled analgesia with buprenorphine and morphine alone and in combination during the first 12 postoperative hours: a randomized, double-blind, four-arm trial in adults undergoing abdominal surgery. *Clin Ther*, 2009;31:527-541.
17. Lehmann KA, Grond S, Freier J, Zech D. Postoperative pain management and respiratory depression after thoracotomy: a comparison of intramuscular piritramide and intravenous patient-controlled analgesia using fentanyl or buprenorphine. *J Clin Anesth*, 1991;3:194-20
18. Dahan A, Yassen A, Bijl H, et al. Comparison of the respiratory effects of intravenous buprenorphine and fentanyl in humans and rats. *Br J Anaesth*. 2005;94(6):825-834.
19. Dahan A, Yassen A, Romberg R, et al. Buprenorphine induces ceiling in respiratory depression but not in analgesia. *Br J Anaesth*. 2006;96(5):627-63
20. Volpe DA, McMahon Tobin GA, Mellon RD, et al. Uniform assessment and ranking of opioid mu receptor binding constants for selected opioid drugs. *Regul Toxicol Pharmacol*. 2011;59(3):385-390.
21. Eissenberg T, Greenwald MK, Johnson RE, et al. Buprenorphine's physical dependence potential: antagonist-precipitated withdrawal in humans. *J Pharmacol Exp Ther*. 1996;276:449-45
22. Bickel WK, Stitzer ML, Bigelow GE, Liebson IA, Jasinski DR, Johnson RE. Buprenorphine: dose-related blockade of opioid challenge effects in opioid dependent humans. *J Pharmacol Exp Ther*. 1988;247(1):47-53.
23. Strain EC, Walsh SL, Bigelow GE. Blockade of hydromorphone effects by buprenorphine/naloxone and buprenorphine. *Psychopharmacology (Berl)*. 2002;159(2):161-16
24. Khanna IK and Pillarsetti S. Buprenorphine – an attractive opioid with underutilized potential in treatment of chronic pain. *J Pain Research* 2015; 8: 859-70
25. Daitch J, Frey M, Silver D et al. Conversion of Chronic Pain Patients from Full-Opioid Agonists to Sublingual Buprenorphine. *Pain Phys* 2012; 15: ES59-66
26. Baron MJ, McDonald PW. Significant Pain Reduction in Chronic Pain Patients after Detoxification from High-dose Opioids. *J Opioid Manag* 2006;2(5):277-82
27. Mailinoff HL, Barkin RL, Wilson G. Sublingual Buprenorphine is Effective in the Treatment of Chronic Pain Syndrome. *Am J Ther* 2005; 12: 379-84
28. Berland DW, Malinoff HL, Weiner MA et al. When Opioids Fail in Chronic Pain Management: The Role for Buprenorphine and Hospitalization. *Am J Ther* 2013; 20: 316-21
29. Daitch D, Daitch J, Novinson D et al. Conversion from High-Dose Full-Opioid Agonists to Sublingual Buprenorphine Reduces Pain Scores and Improves Quality of Life for Chronic Pain Patients. *Pain Med* 2014; 15: 2087-94

30. Schmidt-Hansen M, Bromham N, Taubert M et al. Buprenorphine for Treating Cancer Pain (Review). *Cochrane Database Syst Rev* 2015 Mar 31;(3): CD009596
31. Cote J, Montgomery L. Sublingual Buprenorphine as an Analgesic in Chronic Pain: a Systematic Review. *Pain Med* 2014; 15: 1171-8
32. Aiyer R, Gulati A, Gungor S, Bhatia A, et al. Treatment of chronic pain with various buprenorphine formulation: a systematic review of clinical studies. *Anesth Analg* 2018; 127: 529-38.
33. Kaski S, Marshalek P, Herschler J, Wen S, et al. Sublingual buprenorphine/naloxone and multi-modal management for high-risk chronic pain patients. *J Clin Med* 2021; 10: 973-84.
34. Oldfield BJ, Edens EL, Agnoli A, Bone CW, et al. Multimodal treatment option, including rotating to buprenorphine, within a multidisciplinary pain clinic for patients on risky opioid regimens: a quality improvement study. *Pain Med* 2018; 19: S38-S45.
35. VHA Directive 2014-02. *Continuation of Mental Health Medications Initiated by Department of Defense Authorized Providers* (January 20, 2015)
36. VA/DoD Clinical Practice Guideline [The Use of Opioids in the Management of Chronic Pain 2022](#) Accessed Jan 2024
37. VA/DoD Clinical Practice Guideline [Management of Substance Use Disorder \(SUD\) 2021](#) Accessed Jan 2024
38. Hasin DS, et al. Diagnosing Prescription Opioid Use Disorder in Patients Using Prescribed Opioids for Chronic Pain. *Am J Psychiatry*. 2022 Oct;179(10):715-725.
39. Davis MP, Pasternick G, Behm B. Treating chronic pain: an overview of clinical studies centered on the buprenorphine option. *Drugs* 2018; 78: 1211-1228.
40. ML McPherson. *Demystifying Opioid Conversion Calculations*, 2nd Ed. ASHP, Bethesda, MA, 2018.
41. [Center for Medicare Services Opioid Morphine EQ Conversion Factors \(hhs.gov\)](#) Accessed Jan 2024
42. Dowell D, Ragan KR, Jones CM, Baldwin GT, Chou R. CDC Clinical Practice Guideline for Prescribing Opioids for Pain — United States, 2022. *MMWR Recomm Rep* 2022;71(No. RR-3):1–95. [CDC Clinical Practice Guideline for Prescribing Opioids for Pain — United States, 2022 | MMWR](#) Accessed Jan 2024
43. Suboxone™ [package insert]. Reckitt Benckiser Pharmaceuticals, Inc. Richmond, VA, 2011.
44. Campbell ND, Lovell AM. The history of the development of buprenorphine as an addiction therapeutic. *Ann NY Acad Sci* 2012; 1248: 124-139.
45. Buprenex™ [package insert] Indivior Inc., North Chesterfield, VA, January 2018.
46. Butrans™ [package insert]. Purdue Pharma L.P., Stamford, CT, 2014.
47. Gimbel J, Spierings EL, Katz N, Xiang Q, et al. Efficacy and tolerability of buccal buprenorphine in opioid-experienced patients with moderate to severe chronic low back pain: results of a phase 3, enriched enrollment, randomized withdrawal study. *Pain* 2016; 157: 2517-2526.
48. Rauck RL, Potts J, Xiang Q, Tzanis E, et al. Efficacy and tolerability of buccal buprenorphine in opioid-naïve patients with moderate to severe chronic low back pain. *Postgrad Med* 2016; 128: 1-11
49. Belbuca™ [package insert]. Endo Pharmaceuticals Inc., Malvern, PA, December, 2015.
50. Suboxone™ [package insert]. Reckitt Benckiser Pharmaceuticals, Inc. Richmond, VA, 2011.
51. Chen KY, Chen L, Mao J. Buprenorphine-naloxone therapy in pain management. *Anesthesiology* 2014; 120: 1262-74.
52. Davis MP, Pasternick G, Behm B. Treating chronic pain: an overview of clinical studies centered on the buprenorphine option. *Drugs* 2018; 78: 1211-1228
53. Daitch D, Daitch J, Novinson D, Frey M, et al. Conversion from high-dose full-opioid agonist to sublingual buprenorphine reduces pain scores and improves quality of life for chronic pain patients. *Pain Medicine* 2014; 15: 2087-94.
54. Neumann AM, Blondel RD, Jaanimagi U, Giambone AK, et al. A preliminary study comparing methadone and buprenorphine in patients with chronic pain and co-existent opioid addiction. *J addict Dis* 2013; 32: 68-78
55. TIP 54: Managing Chronic Pain in Adults With or in Recovery From Substance Use Disorders [Managing Chronic Pain in Adults With or in Recovery From Substance Use Disorders \(samhsa.gov\)](#) Accessed February 24, 2023
56. Schmidt-Hansen M, Bromham N, Taubert M et al. Buprenorphine for Treating Cancer Pain (Review). *Cochrane Database Syst Rev* 2015 Mar 31;(3): CD009596
57. Cote J, Montgomery L. Sublingual buprenorphine as an analgesic in chronic pain: a systematic review. *Pain Medicine* 2014; 15: 1171-8.
58. Berland DW, Malinoff HL, Weiner MA, Przybylski R. When opioids fail in chronic pain management: the role of buprenorphine and hospitalization. *Am J Therap* 2013; 20: 316-21.
59. Oldfield BJ, Edens EL, Agnoli A, Bone CW, et al. Multimodal treatment options, including rotating to buprenorphine, within a multidisciplinary pain clinic for patients on risky opioid regimens: a quality improvement study. *Pain Medicine* 2018; 19: S38-S45.
60. Krebs, EE, et al., Design, methods, and recruitment outcomes of the Veterans' Pain-Care Organizational Improvement Comparative Effectiveness (VOICE) study. *Contemporary Clin Trials* 2023 Jan; 124
61. Klamon SL, Isaacs K, Leopold A, et al. Treating women who are pregnant and parenting for opioid use

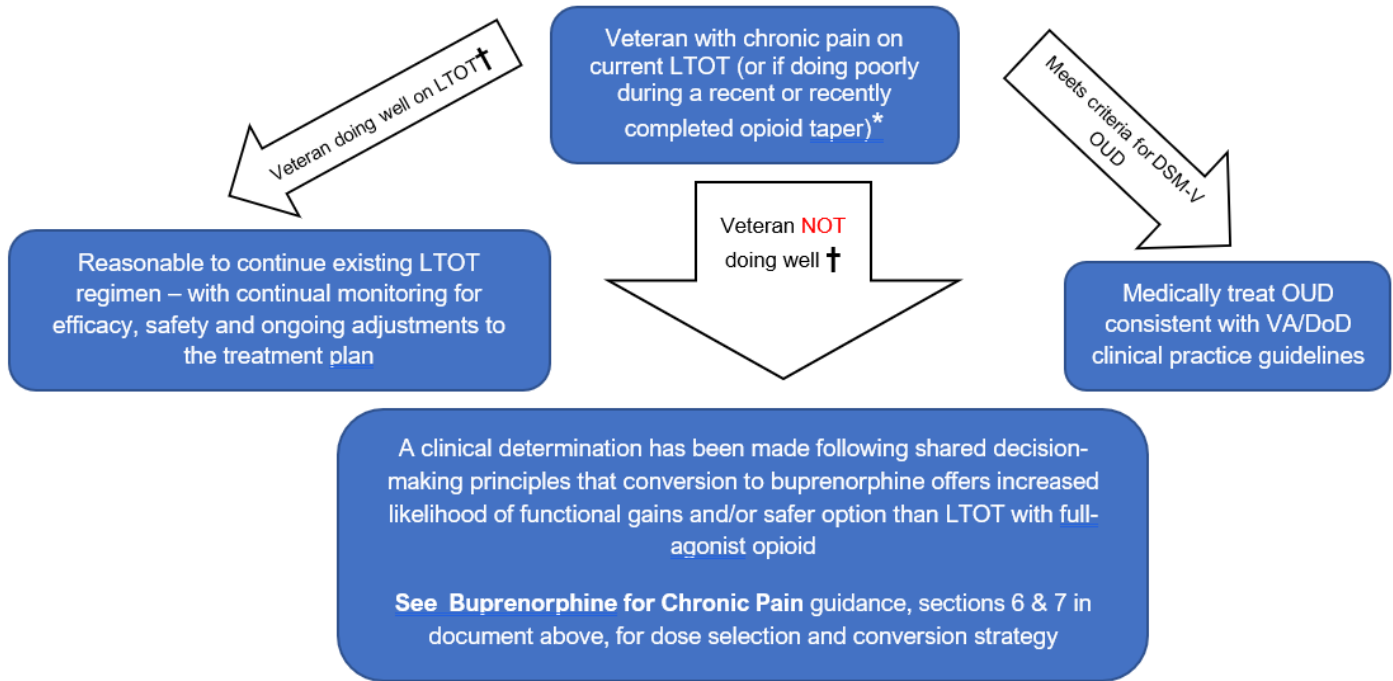
disorder and the concurrent care of their infants and children: literature review to support national guidance. *J Addict Med* 2017; 00: 1-13.

62. Maeda A, Bateman BT, Clancy CR, et al. Opioid abuse and dependence during pregnancy: temporal trends and obstetrical outcomes. *Anesthesiology* 2014; 121:1158–1165
63. Jones HE, Kaltenbach K, Heil SH, et al. Neonatal abstinence syndrome after methadone or buprenorphine exposure. *N Engl J Med* 2010; 9: 2320-31
64. ACOG Committee Opinion No 711. Opioid Use and Opioid Use Disorder in Pregnancy; 2017 [Opioid Use and Opioid Use Disorder in Pregnancy | ACOG](#)
65. NIH, US National Library of Medicine, TOXNET Toxicology Data Network. [buprenorphine - Books - NCBI \(nih.gov\)](#) Accessed June 2021

APPENDIX B – EXAMPLES OF TRANSITION STRATEGIES FROM LONG-TERM OPIOID THERAPY (LTOT) TO BUPRENORPHINE



APPENDIX C – FLOW CHART TO FACILITATE CLINICAL DECISION MAKING FOR CONSIDERATION OF BUPRENORPHINE FOR LONG-TERM OPIOID THERAPY (LTOT)



*NOTE: The clinical determination of functional status and assessment of benefits vs. risks, especially in context of what may be years of LTOT for chronic pain, can often be diagnostically challenging. Facility Pain Management Teams (PMTs) and/or VISN Clinical Resource Hubs are available to assist with both the evaluation of and treatment planning for veterans with chronic pain on LTOT (or LTOT taper).

†ADDITIONAL CONSIDERATIONS – There is no definition of “doing well” or “not doing well with LTOT.” The 2022 CDC and VA/DoD clinical practice guidelines on opioid therapy^{1,2} both recommend evaluating function to determine benefit of LTOT. No specific or preferred means to do this are described and, although rating scales, qualitative interviews, clinical judgment, shared decision-making, etc. can all be used, there is no evidence base to support use of any approach as better than another. The 2023 NICE safe prescribing guidelines for medicines associated with dependence or withdrawal recommend evaluating on risks and benefits similarly without any specific means of how to do so.³ Manhapra and colleagues recently suggested using function compared to an age related peer and presence or absence of high-risk events (or future risk of high-risk events) as at least a practical starting point to evaluate functional benefit of LTOT in setting of chronic pain⁴ and during the PMOP Buprenorphine SME workgroup there was general agreement that approaching the assessment of how a veteran is doing should be consistent with Whole Health Principles (e.g. Personal Health Inventory, Wellbeing Signs may be helpful).⁵ Until an evidence base or specific guidance exists to provide clarity on best means of evaluating the functional benefit of LTOT, VHA local pain management teams, VISN Telepain teams, and PMOP initiative resources are available to assist with care planning for the veteran with chronic pain on LTOT. Additional resources may be found here [VHA Pain Management, Opioid Safety, and Prescription Drug Monitoring Program \(PMOP\) \(sharepoint.com\)](https://www.sharepoint.com/VHA/Pain-Management-Opioid-Safety-and-Prescription-Drug-Monitoring-Program-PMOP)

1. CDC Clinical Practice Guidelines for Prescribing Opioids MMWR 2022; 2. VA/DoD Clinical Practice Guideline: [The Use of Opioids in the Management of Chronic Pain 2022](#) Accessed Jan 2024; 3. National Institute for Health Care Excellence [NICE: Prescribing medications associated with dependence or withdrawal -- 2023](#); 4. Manhapra, A. et. al., Are Opioids effective analgesics and is physiological opioid dependence benign? Revising current assumptions to effectively manage long-term opioid therapy and its deprescribing [Brit J Clinical Pharma 2023 1-15](#); 5. PMOP Buprenorphine Subject Matter Experts Guideline development sequester and document draft meeting, Fall 2023