Buprenorphine for the Management of Acute Pain

National Guidance

June 2025

VA National Formulary Committee, and Pharmacy Benefits Management Services, In collaboration with the National Anesthesia Acute Pain Management Committee, the Pain Management Opioid Safety and PDMP program, and National Emergency Medicine program.

Purpose: To establish guidance for the administration of buprenorphine for the management of acute pain including both transmucosal and parenteral products. At this time, administration of parenteral buprenorphine solution for injection is restricted to Veterans under the care of an Anesthesia Service provider or facility designated experts.

Disclaimer: To be consistent with the purpose of this general guidance and not to be overly proscriptive, this guidance allows facilities the flexibility to exercise modifications as necessary to operationalize the use of buprenorphine for treating acute pain.

Background

The overarching principles of acute pain management are to reduce pain, to facilitate interventions and assessments that support medical stabilization, participation in treatment, and accelerate the body's recovery response. Opioids are reserved for pain that has not responded to prior step treatments or is expected to be severe enough to require opioid management.

Buprenorphine intravenous solution for injection (i.e. BUPRENEX) has a 6-decade track record of being at least as effective for management of post-operative pain and providing a longer duration of action than other formulary parenteral opioids as well as safety advantages due to its unique pharmacologic profile.[1,2] Due to these advantages buprenorphine solution for injection was added to the VA national formulary in March 2025 and multidisciplinary Subject Matter Expert working group comprised of representatives from multiple VHA program offices was established to create pragmatic guidance for U.S. providers who may not be familiar with the role buprenorphine can play in the management of acute pain.

Buprenorphine in Acute Pain: Advantages and Misconceptions

The safety advantages of buprenorphine have been well documented due to its unique ceiling effects on respiratory depression and addiction potential. However, this may have also resulted in a misconception that due to its classification as a partial agonist at the mu opioid receptor it only provides partial analgesia. Buprenorphine's high lipophilicity and high binding affinity for the mu-opioid receptor makes it one of the most potent opioid analgesics in our armamentarium. No analgesic ceiling effect has been reported across dose ranges studied. Additionally, transmucosal formulations have a fairly rapid onset of action and compare favorably to IV opioids across a range of acute pain conditions. As such this document provides guidance to the field to support use of IV and transmucosal buprenorphine formulations for the management of acute pain episodes where an opioid would be appropriate.

Departments Affected

Pharmacy, Nursing, Emergency Departments/Urgent Care, Anesthesia/Pain, Surgery/Dental, Medicine, Critical Care, and Physical Medicine and Rehabilitation services

Patient Selection –

Veterans who may be appropriate for buprenorphine

In general, patients for whom a usual formulary opioid would be considered (e.g. fentanyl, hydromorphone, oxycodone, morphine) for the management of acute pain, buprenorphine in either its parenteral or transmucosal formulation can be considered. Buprenorphine may offer safety advantages especially in Veterans with known risk factors for hospital Opioid Related Adverse Events (ORADES) as detailed in table below. Veterans already on a buprenorphine pain formulation as an outpatient (e.g. buccal or transdermal), veterans with impaired renal function (dose adjustment not required), Veterans who are opioid naïve with other medical risks (e.g. COPD, advanced age), Veterans at high risk for opioid dependence (e.g. co-occurring chronic pain syndromes), and patients who may be more sensitive to the GI side effects of both opioids and surgical procedures.

Risk factors for in-hospital Opioid Related Adverse Event (ORADES)[3,4]	
Advanced age (OR 1.18)	Substance use disorders (OR 2.74)
Female (OR 1.29)	Concurrent CNS depressants (OR 1.06)
Renal impairment OR 1.22)	High opioid doses (OR 3.51)
Pulmonary diseases (OR 1.71)	Multiple opioid types (OR 1.38)
Cardiac diseases (OR 1.13)	Obesity (OR 1.20)
Mental health disorders (OR 1.26)	Chronic opioid use (OR 1.20)

Veterans who may NOT be appropriate for buprenorphine

In general, veterans with pain not severe enough (or expected to be severe enough) to require opioid therapy should also not be considered for buprenorphine. In patients who are already on high-dose opioid therapy, prescribed or illicit, or long-acting opioid antagonist treatment (e.g. Vivitrol) the exact role of pain formulations of buprenorphine is not well known at this time. However, the microgram doses and plasma levels achieved from the buprenorphine products approved for pain (e.g. parenteral, buccal, transdermal) would not be expected to cause precipitated withdrawal in patients who are on baseline full-agonist opioids. There is significant interest from the field on a current or prior dose of opioid that would affect buprenorphine's ability to provide analgesia. There is a lack of evidence to support an MEDD dose threshold that may indicate buprenorphine is either ineffective or may precipitate withdrawal and emerging evidence indicates those risks are less than previously thought. [5]

Precipitated Withdrawal

Even in patients transitioning from high-dose full-agonist opioids to milligram doses of buprenorphine, the incidence of precipitated withdrawal occurs in approximately <5% of patients,[5] less common than

often perceived. Microgram dosing of buprenorphine for acute pain, either parenterally or buccally, would not be expected to result in precipitated withdrawal. In patients who are on large doses of full agonist opioids, milligram doses of buprenorphine (e.g. Suboxone) results in the rapid displacement of the traditional opioid from the mu-receptor with an abrupt onset of severe opioid withdrawal symptoms. Titration schedules using microgram doses of buprenorphine are employed to transition patients from high-dose opioids to buprenorphine without precipitating withdrawal. Note that it is not the purpose of this guidance document to review opioid transitions, but that the example is made to point out that a microgram dose of buprenorphine would be unlikely to result in a precipitated opioid withdrawal even if the patient was known to be taking large doses of opioids. However, the analgesic benefit of buprenorphine for patients already on high dose opioids is not well-known. Additionally, giving full agonist opioids to a patient that has already received buprenorphine is also not expected to precipitate withdrawal.

Management Strategies if Buprenorphine is Ineffective or Insufficient

Management strategies for ineffective or insufficient buprenorphine treatment may raise concerns among providers about its high-potency binding to mu receptors and that full agonist opioids (FAO) would be essentially blocked from occupying the mu receptor. However, research indicates that even at doses up to 24 mg/day, some mu opioid receptors remain unoccupied by buprenorphine.[6] Practical guidance suggests using a high-potency FAO if buprenorphine has been previously used. However, there is a RCT in post-abdominal surgery demonstrating that morphine is fully effective even when used as a bolus adjunct to a buprenorphine continuous infusion.[7] It's important to note that the doses of parenteral and buccal buprenorphine used for acute pain management are significantly lower, and conventional FAO is expected to be fully effective even if microgram doses of buprenorphine prove ineffective. Considering buprenorphine is an opioid, if it is not working, it may indicate opioid refractoriness, necessitating the optimization of non-opioid management strategies and use of high-potency full-agonist opioids (FAO).[8]

Pharmacokinetics

a. Onset of analgesia – within 5-15 minutes (IV), 15 minutes (IM), 20 minutes (buccal and sublingual)
b. Duration – 6-8 hours (parenteral); 12-24 hours transmucosal
    a. NOTE – duration may be longer with repeated administration
c. Half-life – 12-24 hours
d. Elimination – Hepatic and fecal. Dose adjustments not required in kidney disease.

TABLE – 1 Approximate dose equivalency of various buprenorphine formulations with approved or established use for analgesia

Route of Administration (BRAND)	**Bio-availability (%)**	**Equivalent Doses**	**Typical Pain Dosing**	**FDA Approved Indications**
IV, IM (BUPRENEX)	100	0.3 mg IV or IM	0.3mg q6h	Acute pain
Sublingual (SUBOXONE, SUBUTEX)	30	1 mg (1mg = ***HALF* TABLET**)	TID	OUD
Buccal (BELBUCA)	46-65	450 mcg	BID	Chronic Pain
Transdermal (BUTRANS)	15	20 mcg/h* (TAKES 24 HOURS FOR ONSET)	7d patch	Chronic Pain

Table 1. Buprenorphine formulations used for pain management with approximate bioavailability and dose equivalencies. *Transdermal bioavailability is already factored into the labeling, thus a 20mcg/h patch would be roughly equivalent to 1.6 mg SL over 24h. FDA = Food and Drug Administration, OUD = opioid use disorder, mg = milligram, mcg = microgram, d = day, Q6-8h = every 6-8 hours, h = hour, BID = twice daily, TID = three times daily.

Indication

a. Acute Pain
b. Intractable Pain

Contraindications

Significant respiratory depression*, acute or severe bronchial asthma in an unmonitored setting, known or suspected GI obstruction including paralytic ileus, or hypersensitivity to buprenorphine

**NOTE: Buprenorphine has been reported to reverse opioid overdoses similar to naloxone*[9]

Precautions

Buprenorphine has similar precautions to other full-agonist opioids (e.g. additive risk with concomitant CNS depressants).

Adverse Effects

In meta-analysis, adverse effects of buprenorphine were similar to other parenteral opioids, with some demonstrating less pruritus in the buprenorphine group.

a. Common – sedation, nausea/vomiting
b. Rare – excess sedation,

Product Selection and Dose (in various settings and transitions of care)

a. **Pre/Peri-operative and PACU settings**
   - Buprenorphine 0.3mg slow IV (over 2 minutes) pre-op
   - Repeat 0.3mg slow IV during PACU recovery prn, may repeat x1 additional dose at 30 minutes if necessary
   - Consider post-operative continuation with transmucosal formulation, if opioids are appropriate as part of analgesic plan
   - An example of an ERAS analgesic pathway involving buprenorphine is provided in appendix A

b. **PACU to ward** -- if buprenorphine IV effective, consider continuing a transmucosal formulation (e.g. Belbuca 300 to 450mcg bid), scheduled for duration of admission. May dose adjust as appropriate.* Continue all other analgesic protocol components including usual prn opioids
   - ***NOTE**: Buprenorphine buccal formulations are available in multiple strengths (75mcg to 900mcg per film). Select transmucosal dose based on observed patient response to PACU administered buprenorphine dose*

c. **Discharge Home** – If buprenorphine is effective and additional discharge opioids are indicated, consider continuing buprenorphine buccal*, two to three times daily prn for the expected duration of time that opioids would normally be provided after the surgical procedure. Continue all other non-opioid protocol components.
   - *NOTE - select outpatient buprenorphine dose based on the observed effective minimum dose during the inpatient episode of care

d. **Emergency Department** – Buprenorphine (primarily transmucosal) has been studied in renal colic and fractures compared directly to parenteral NSAID and FAO. Specific use guidance in the Emergency Department setting is outside scope of this document but pertinent trials are referenced[10, 11]

e. **Patients actively treated with milligram doses of buprenorphine (8-32mg/day or LAI)** -- In general, buprenorphine being taken in milligram doses for OUD or complex dependency + pain pre-encounter should NOT be stopped for management of acute pain where FAO may be used. In most cases the buprenorphine should continue at maintenance dose and both non-opioid and high-potency FAO may be used as needed for acute pain. In some cases, the buprenorphine dose may be reduced (25-50%) to allow for mu-opioid receptors to "open up" in the subsequent 12-24 hours. However, both the risk of overdose and withdrawals increases when using this strategy so close monitoring should be employed. See linked documents for detailed additional information:
   Buprenorphine Perioperative Guidance_508.pdf
   Buprenorphine Perioperative Guidance Supplemental Information_508.pdf

Clinical Pearls

A.) Tapering and discontinuing buprenorphine for acute pain should not be needed. Due to long half-life, buprenorphine self-tapers. Advise patients of long duration of action, that they may stop taking buprenorphine if they feel pain is well managed with non-opioid only

Clinical Pearls (continued)

B.) Onset of action is within 20 minutes (faster with parenteral). Full effect of transmucosal products may take 1-3 hours.

C.) The buccal formulation has the benefit of mucoadherence. Unlike SL, it requires no patient participation and can be administered to a patient in the operating room under anesthesia. If buccal mucosa is very dry it can be moistened with a gloved finger prior to application. Preoperative fasting may also limit a patient's ability to produce sufficient saliva for SL administration. Both SL and buccal buprenorphine are attractive options for NPO patients.

D.) Application of buccal films –yellow side goes on cheek

   a. Belbuca self-admin video https://www.belbuca.com/resources?wvideo=p41cton4dx

E.) Don't eat or drink while transmucosal formulation is dissolving. Rinse mouth after complete

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APPENDIX A

BUPRENOPRHINE: Example of pharmacologic interventions for a post-surgery analgesia strategy

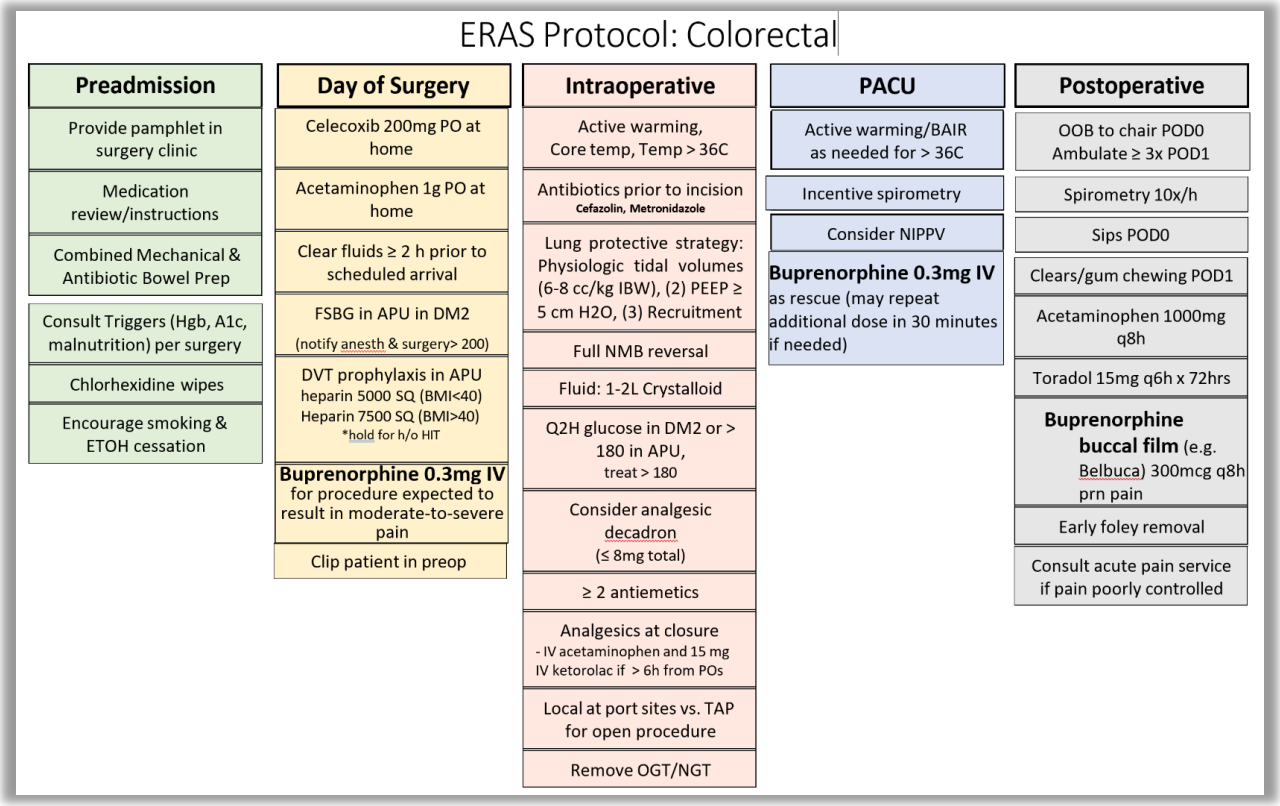
Enhanced Recovery After Surgery strategies are designed to achieve early recovery after major surgery by implementing evidence-based practices across the perioperative care pathway. A core component of the ERAS analgesia strategy is to reduce opioid adverse effects. Comprehensive strategies have been published across many surgeries and can be found at ERAS Society (https://erassociety.org/guidelines). Here we focus on the key analgesia elements and suggest a place for buprenorphine, when opioids are required.

Multimodal analgesia is essential across all surgery expected to result in more than moderate pain, emphasizing the most evidence-based interventions: acetaminophen, NSAID, and regional/neuraxial blocks when indicated. Risk/benefit, including consideration of contraindications and comorbidities, should be addressed in all cases. For example:

TABLE A-1 Pharmacologic Framework for ERAs protocol

Drug	Preoperative	Intraoperative	PACU	Postoperative
NSAID	PO (or IV NSAID)	Redose after 6h	Redose NSAID if indicated based on duration of surgery	Continued scheduled NSAID if not contraindicated
Acetaminophen (APAP)	PO (or IV) APAP	Redose 1g after 6h	Redose after 6h if not done in OR	Scheduled APAP
Buprenorphine	0.3mg IV or buccal (e.g., 300-450mcg)		0.3mg IV or buccal (e.g., 300-450mcg). Can redose 0.3mg IV in 30-60min if persistent pain requiring opioids	If opioids routinely utilized – scheduled buccal BID to TID (e.g., 300 – 450mcg per dose); If opioids NOT routinely utilized -- can consider PRN for breakthrough (e.g., 300 – 450mcg per dose q8h as needed)
Other opioid	Full agonist opioids (FAO) can be utilized adjunctively and concomitantly with buprenorphine for acute pain (e.g. Buprenorphine buccal 450mg bid scheduled plus hydrocodone/APAP q6h prn breakthrough pain). However, consideration should be noted that ineffectiveness of buprenorphine may represent an insufficient titration or an opioid refractory state instead of buprenorphine failure.			

Figure A-1 : Example of Buprenorphine Incorporated Into an established ERAS Pathway for Colorectal Surgery



APPENDIX B

BUPRENOPRHINE: Sample steps for Anesthesia and Pharmacy to coordinate to stock for Operating Room (OR) use

1.) Anesthesia team member determine approximate case load per month to estimate an initial par level
2.) Communicate with OR pharmacist (or Pharmacy Operations Chief) buprenorphine formulary status and intent to utilize buprenorphine for acute, surgical pain. Discuss with local Pharmacy and Therapeutics Committee if necessary.
    a. *NOTE: at this point in time, buprenorphine IV is only available via open market sources*
3.) Work with pharmacy operations staff to determine storage and day of surgery distribution (e.g. within a locked automated dispensing cabinet or as part of anesthesia surgical supply tray)
4.) Work with Clinical Applications Coordinator to add buprenorphine pain formulations to the PACU order set menus
5.) Facilitate local training with key partners and team members