# Perioperative Pain Management Guidance for Patients on Chronic Buprenorphine Therapy Undergoing Elective or Emergent Procedures
# Supplemental Information
## February 2022

**VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives**

*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. 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 CLINICIAN SHOULD USE THIS GUIDANCE AND INTERPRET IT IN THE CLINICAL CONTEXT OF THE INDIVIDUAL PATIENT.*

The Product Information should be consulted for detailed prescribing information.
See the VA National PBM-MAP-VPE Monographs on these drugs at the *PBM INTERnet* or *PBM INTRAnet* site for further information.

## Introduction and Background

Buprenorphine is an opioid with formulations approved for chronic pain in buccal and transdermal dosage forms, and in injectable form for acute pain. It is available for opioid use disorder (OUD) in various transmucosal dosage forms as well as an extended release. The uniqueness of its pharmacokinetic and pharmacodynamic properties complicates the various risks in the perioperative setting for those taking it chronically. Despite recent expert panel and clinical practice guidance there is often confusion and lack of consensus on how to adequately and safely manage acute pain perioperatively in patients receiving chronic buprenorphine therapy.[1-8] The following recommendations and expert opinion are based on currently available evidence for the perioperative management of acute pain in patients chronically on buprenorphine therapy. It is strongly recommended that where available, waivered providers or an interdisciplinary team experienced with buprenorphine use be consulted to most effectively and safely help manage these patients. It is equally important in every single situation to communicate treatment plans with the buprenorphine prescriber, as this will allow for the best transition of care plan back to the community postoperatively. Clinical judgement is paramount regarding individual cases.

Buprenorphine was first approved in 1985 in the United States as the injectable formulation Buprenex®. Since then, eight additional buprenorphine-containing formulations have come to market (see Table 1 for further details). Six of those have specific indications for OUD (three of which are co-formulated with naloxone) and three have indications for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment.

Pharmacologically, buprenorphine's primary effects are caused by its partial agonism of mu-opioid receptors (MORs) and antagonism at kappa-opioid receptors (KORs). 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.[9-14] 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. 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.[5, 15-22] 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, thus lowering the risk of overdose when used without other central nervous system (CNS) depressants.[22-24]

Buprenorphine also has one of the highest binding affinities toward MORs compared to all other opioid, the only exception being naltrexone.[25-26] 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.[27-28] 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.[13] The slower dissociation may contribute to prolonged analgesia and less potential for withdrawal when used appropriately for chronic.[9]

From a pharmacokinetic perspective, buprenorphine is available in a multitude of different formulations, all with varying properties, mainly because of its poor oral bioavailability. The bioavailability differences between each formulation are important to consider because these directly relate to the amount of medication available for systemic absorption to exert therapeutic effects (see Table 1). The variability in elimination half-life of buprenorphine between each formulation is also relevant to consider given this will directly relate to when buprenorphine is expected to be completely eliminated from a patient's system. This varies widely between formulations, ranging from 1.2 to 7.2 hours after intravenous/intramuscular administration to 43 to 60 days after subcutaneous administration.[29]

The unique combined physiochemical, pharmacodynamic, and pharmacokinetic features of buprenorphine increase the complexity in treating pain perioperatively for patients on chronic buprenorphine therapy. The addition of a full MOR agonist perioperatively may exert some effect if it is able to grab and occupy unbound MORs; however, a full MOR will not displace buprenorphine from those receptors once fully saturated likely leaving the patient susceptible to increased pain and agitation. One way to overcome buprenorphine's tight binding to those receptors would be to increase the dose of the new MOR agonist. However, if buprenorphine were abruptly stopped in this situation without further adjustment to the new MOR agonist dose, the risk of side effects and opioid-induced respiratory depression (OIRD) could significantly increase as the patient's body eliminates all the buprenorphine in systemic circulation. This would eventually allow the new opioid to now occupy all available MORs. These risks highlight the importance for appropriate procedures and preemptive planning for surgical patients that are admitted with active or recently active (within the last 3-5 days) buprenorphine therapy.

Regardless of method chosen for perioperative management in patients on buprenorphine, providers should maximize all other non-opioid and non-pharmacological interventions and patients should be scheduled with their SUD provider or chronic pain provider after discharge for close follow-up. Warm hand-off for continued buprenorphine adherence may be required upon discharge, especially for high risk patients. Patients should be discharged with enough buprenorphine to last them until their next follow-up appointment.

**Table 1. Differences Between FDA-approved Buprenorphine Products** [29-37]

| Formulary Buprenorphine Products | | | | | |
|---|---|---|---|---|---|
| **Generic Name** | **Brand Name** | **Formulation** | **FDA-Approved Indications** | **Bioavailability** | **Elimination Half-Life** |
| Buprenorphine | Butrans® | Transdermal delivery system | Management of pain severe enough to require around-the-clock, long-term opioid treatment | ~15% | ~26 hours |
| Buprenorphine | Generically available | Sublingual tablet | Treatment of opioid dependence | ~30% | ~37 hours |
| Buprenorphine and naloxone | Zubsolv®, Generically available | Sublingual tablet | Treatment of opioid dependence | ~30% | 24 to 42 hours (buprenorphine) |

| Non-Formulary Buprenorphine Products | | | | | |
|---|---|---|---|---|---|
| Buprenorphine | Buprenex® | Intravenous or intramuscular | Management of pain severe enough to require opioid therapy | 100% | 1.2 to 7.2 hours |
| Buprenorphine | Belbuca™ | Buccal film | Management of pain severe enough to require around-the-clock, long-term opioid treatment | 46 to 65% | 11.2 to 27.6 hours |
| Buprenorphine | Sublocade® (BUP XR INJ®) | Abdominal subcutaneous injection | Treatment of moderate to severe opioid use disorder | 100% | 43 to 60 days |
| Buprenorphine | Subutex® | Sublingual film | Indicated for the treatment of opioid dependence and are preferred for induction. | ~30% | 31 to 35 hours |
| Buprenorphine and naloxone | Suboxone™ | Sublingual film | Treatment of opioid dependence | ~30% | 24 to 42 hours |
| Buprenorphine and naloxone | Generically available | Sublingual film | Treatment of opioid dependence | 12mg/3mg showed comparable relative bioavailability as the SL brand tablets | 24 to 42 hours (buprenorphine) |

## Purpose

This supplemental information document provides additional information supporting the Perioperative Pain Management Guidance for Patients on Chronic Buprenorphine Therapy Undergoing Elective or Emergent Procedures. (See Link ).

## Additional Considerations

I. Recommendations for Preoperative Management of Patients on buprenorphine extended-release injection ([SUBLOCADE], BUP XR INJ):

Due to such low prevalence of veteran patients maintained on BUP XR INJ as well as it's unique pharmacokinetic properties, an extensive review of BUP XR INJ has been omitted from the guidance document. BUP XR INJ has an elimination half-life of 45-60 days, therefore it would have to be stopped and held for at least 3-4 months after last subcutaneous injection to allow for sufficient time for buprenorphine to be cleared from systemic circulation. This scenario is extremely impractical and risky and is not recommended for either elective or emergency surgery. For these patients, we recommend referring to options for continuing buprenorphine throughout the perioperative process (see **link** for further information)

II. Recommended Additional Opioids to be used with Buprenorphine Perioperatively:

In situations where a full MOR agonist medication is needed in addition to buprenorphine to adequately control perioperative pain, it is recommended that opioids with similar lipophilicity and binding affinity toward MORs be used. Theoretically, similarly lipophilic molecules may be able to penetrate the blood-brain barrier (BBB) to the same or better degree than buprenorphine and if they have similar binding affinity toward those receptors, they may be able to more effectively compete with buprenorphine. Fentanyl and Sufentanil are both available as IV formulations, both are highly lipophilic, and both have shown to have high binding affinity toward MORs when directly compared to other opioids, thus are theoretically more likely to compete with buprenorphine.[25, 38-39] Hydromorphone could also be a practical opioid to utilize, as it is available as both PO and IV, and has a high binding affinity toward MORs when directly compared to other opioids.[25]

III. Recommendations for naloxone education and counseling:

It has been documented that opioid mortality prevalence is higher in patients who have substance or polysubstance abuse history (including prescription, non-prescription/illicit drugs, and alcohol) and psychiatric comorbidities. One of the clinical tools available to aid in identification of patients at higher risk for fatal and non-fatal respiratory events is the Risk Index for Overdose or Serious Opioid-Induced Respiratory Depression (RIOSORD).[40] This tool has been validated for use in the Veteran and non-Veteran population for the accurate generation of a risk index predicting the probability of an overdose or OIRD in OUD and non-OUD pain patients.[40-41] The tool includes 17 questions with a total maximum score of 115 points (highest risk for overdose or OIRD) and can be calculated by any member of the interdisciplinary team or found online in the Stratification Tool for Opioid Risk Mitigation (STORM) database (Stratification Tool for Opioid Risk Mitigation (STORM) (sharepoint.com) ). Once the score has been calculated, the tool provides the OIRD probability and clinical judgment should be utilized for the decision to provide naloxone education and counseling prior to discharge from hospital.

It is important to consider the reasons why buprenorphine is being prescribed regarding assessing for need of naloxone. For those prescribed buprenorphine patch or buprenorphine buccal film for chronic pain without history of OUD or other SUD and have little to no risk for abusing other opioids, naloxone may not be needed unless IR opioids have been initiated in the post-operative setting with plans to discharge the patient with a supply of IR opioid. As aforementioned, there is reduced risk of OIRD with buprenorphine because of its unique mechanisms of action that limits MOR availability for a full agonist. Additionally, if a patient was to "overdose" on buprenorphine (hypothetically, as unlikely to occur from buprenorphine use alone), it would not be expected that naloxone doses used in rescue kits would be adequate to displace buprenorphine from MORs to "reverse" the overdose. As shown in several studies, the reversal of buprenorphine's respiratory depression effects by naloxone is very much dependent on both buprenorphine and naloxone doses.[42-44] In general, higher doses of naloxone are required to overcome buprenorphine's affinity; multiple doses of naloxone may be required to overcome buprenorphine's binding to the opioid receptor.[42-44] Patients may be at highest risk for overdose as they leave the hospital. Ideally, overdose education would occur during hospitalization and naloxone should be prescribed at discharge for those patients considered at risk for an opioid overdose. Patients should also receive instruction on how to use the naloxone product prescribed.

For more information on naloxone education and distribution, visit: (Naloxone HCL Recommendations for Use).

IV. Recommendation for screening for suicidal ideation prior to discharge:

It is recommended that all patients be assessed for suicidal ideation prior to discharge. Both chronic pain [7, 45-51] as well as SUD (including OUD)[51-62] represent individual risk factors for increased likelihood of suicide and/or suicidal behavior. These risks are only heightened in individuals with chronic pain, history of or active SUD, acute stresses to health, and behavioral health co-morbidities including but not limited to depression, anxiety, and PTSD. [48, 63-64] The Veteran population may be even more susceptible to these risks, given the higher incidence of behavioral health comorbidities than the general population, thus it may be even more prudent to assess risk in this population. A comprehensive review of assessing/screening for suicide is outside the scope of this protocol. However, we recommend that providers complete screen for suicide as part of the VA strategy for suicide risk identification per facility protocol.

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