METAPHI
MENTORING, EDUCATION, AND CLINICAL TOOLS FOR ADDICTION: PRIMARY CARE – HOSPITAL INTEGRATION

A guide to the use of depot buprenorphine

Authors: Katie Dunham NP, Meldon Kahan MD, Ken Lee MD, Jennifer Wyman MD
Reviewers: Joel Bordman MD, Christina Henry RN, Melissa Holowaty MD, Lori Regenstreif MD, Maria Zhang PharmD

Introduction

A subcutaneous 28-day depot buprenorphine injection (hereafter *depot buprenorphine*, trade name Sublocade) has recently been added to the Ontario Drug Benefit (ODB) formulary as a Limited Use drug (LU 577), as well as most other provincial formularies, the NIHB program, and most private plans. This product has an important role to play in the management of opioid use disorder (OUD). In this document, we summarize the evidence for depot buprenorphine's effectiveness and adverse effects and present a practical and concise guide for its use based on our collective initial experience with this product and research currently available; information here is subject to change as new research becomes available. For a full discussion of depot buprenorphine's pharmacology and side effects, please refer to the product monograph (1).

Evidence of effectiveness

Depot buprenorphine vs. placebo
An industry-sponsored phase three randomized trial showed that depot buprenorphine was **significantly more effective than placebo at reducing opioid use** (2). At week 24, 41% of the 100 mg group and 43% of the 300 mg group had urine samples negative for illicit opioids, compared to 5% for the placebo group ($p < 0.0001$). High-dose depot buprenorphine may be particularly effective for people who inject opioids. A post-hoc analysis (3) of an industry-sponsored phase three controlled trial (4) showed that people injecting opioids receiving 300 mg monthly had more days of continuous abstinence than those receiving 100 mg monthly. This difference was not found for subjects who were using oral opioids.

Depot buprenorphine vs. SL buprenorphine/naloxone
There has not been a head-to-head comparison of the depot formulation approved in Canada and SL buprenorphine/naloxone.

A 24-week placebo-controlled trial compared SL buprenorphine/naloxone to a different depot buprenorphine injection product not currently available in Canada (5). The proportion of opioid-negative urine samples was higher in the depot buprenorphine group (35.1%) than in the SL buprenorphine/naloxone group (28.4%, $p < 0.001$), and treatment completion rates in the two groups were similar. The results of this trial do not necessarily apply to the depot product approved in Canada.

Depot buprenorphine vs. methadone
To date, depot buprenorphine has not been directly compared to methadone in a head-to-head trial.

In a systematic review of treatment retention in controlled trials of opioid agonist medications, the average six-month retention rate for methadone was 74.0%, compared to 46.0% for SL buprenorphine/naloxone (6); other systematic reviews have had similar findings (7). The reviews did not find methadone to be more effective than SL buprenorphine/naloxone at maintaining opioid abstinence during treatment. Depot buprenorphine delivers a higher and steadier buprenorphine level than SL buprenorphine, but it is not yet known whether this results in higher treatment retention rates or lower opioid use. In a phase three randomized controlled trial comparing depot buprenorphine to placebo (2),

Version date: 19 November 2020

the six-month retention rate was around 63%; compared to the average retention rates in the systematic review, this is higher than daily SL buprenorphine/naloxone but lower than methadone.

Patient-centered outcomes

In a twelve-month follow-up on the phase three industry-sponsored randomized controlled trial (8), participants reported high rates of satisfaction with depot buprenorphine treatment and improvements in most life domains. In a qualitative study (9), patients with OUD were asked how they felt about long-acting depot buprenorphine preparations. The patients thought that depot medications would be less stigmatizing and less embarrassing, as they would not have to take medication in front of other customers at the pharmacy. They also thought it would allow them to live their daily lives more freely, and they would no longer have to have contact with other drug users. On the other hand, some stated that they would miss the daily routine of pharmacy attendance, and others felt they would be less likely to receive counselling and psychosocial support.

Pharmacokinetics and protective factors

Depot buprenorphine produces a steady serum level with no daily variation and bioavailability six to eight times higher compared with SL buprenorphine. The product monograph (1) states that the average plasma concentrations of depot buprenorphine at steady state are 3.21 ng/mL for the 100 mg dose and 6.54 ng/mL for the 300 mg dose. In an extensive review of brain imaging studies on buprenorphine receptor occupancy in heroin-using volunteers, the authors conclude that a buprenorphine serum level of around 1 ng/mL (achieved with a dose of less than 16 mg per day) is associated with 50% mu receptor occupancy, and will relieve withdrawal symptoms in most patients (10). A concentration of 2–3 ng/mL or above (greater than 16 mg, closer to 24 mg) is associated with 70–80% receptor occupancy, and will attenuate the reinforcing and euphoric effect of typical doses of commonly abused opioids (11, 12). These studies suggest that depot buprenorphine more effectively blocks the euphoric effects of opioids than sublingual buprenorphine, but in the absence of a head-to-head comparison it cannot be assumed that depot buprenorphine is more effective at reducing opioid use and retaining patients in treatment.

There is experimental evidence that higher buprenorphine levels may protect against fentanyl-induced respiratory depression. In an industry-sponsored study of eight subjects with high opioid tolerance (13), all subjects were given placebo, followed by intravenous buprenorphine infusions titrated to achieve serum levels of 1, 2, or 5 ng/mL. They were then given escalating doses of intravenous fentanyl up to 0.7 mg/kg. Seven of the eight subjects on placebo had apnea, and three had both apnea and low O2 sat. The 1 ng/mL group had declines in respiratory volume after fentanyl challenge, but the 2 ng/mL and 5 ng/mL groups did not. The depot formulation may provide better protection against fentanyl-induced respiratory depression than the SL form; at steady state the minimum serum level conferred by 100 mg depot buprenorphine is greater than 2 ng/mL, while even at 24 mg the SL formulation can provide a plasma concentration of less than 2 ng/mL (14).

Adverse effects, precautions, and contraindications

Adverse effects

In the pivotal phase three trial (2), between 5% and 10% of the subjects in the depot buprenorphine groups experienced headache, nausea, constipation, and/or pruritis at the injection site. Overall, these side effects were mild, and comparable to that documented for SL buprenorphine/naloxone (although no direct comparison has been conducted). The product monograph lists other common reactions (fatigue, insomnia, elevated hepatic enzymes) and less common reactions (blurred vision, dizziness,

postural syncope, euphoric mood). The actual incidence of adverse effects among the population of patients on depot buprenorphine is not known.

Precautions and contraindications

CNS and respiratory: Depot buprenorphine can be presumed to be safe in patients who show no sedation or respiratory impairment with SL buprenorphine at a dose of 8 mg or above. However, serum levels of buprenorphine slowly rise with depot buprenorphine and at steady state are significantly higher than with sublingual buprenorphine; it is possible, therefore, that **patients who are on benzodiazepines or other sedating drugs or who have respiratory impairment could experience sedation and respiratory depression when starting depot buprenorphine**. These patients require close monitoring, as do patients who are started on benzodiazepines while on depot buprenorphine. Patients should be advised to be cautious when driving for the first few months of depot buprenorphine therapy.

QT prolongation: Clinical studies of SL buprenorphine have not found cases of QT interval increase above 500 msecs (15, 16) or increased reporting of torsades de pointes in an adverse drug reaction database (17). However, the product monograph notes cases of increased QT interval, and one case of QT interval beyond 500 msec (1). Because serum levels of buprenorphine are higher with depot buprenorphine than with SL buprenorphine, the clinician might consider ordering an ECG before and after initiation if the patient has other risk factors for QT prolongation.

Bradycardia and hypotension: Clinically significant bradycardia has been reported; estimated incidence is < 1%.

Serotonin syndrome: Although very rare, buprenorphine can cause serotonin syndrome when taken with medications that elevate serotonin. The risk is highest with triptans, MAO inhibitors, tricyclic antidepressants, tryptophan and other serotonin precursors, and tramadol and tramadol products. Buprenorphine should be avoided in patients on these medications if possible. SSRIs are not contraindicated, but the clinician should be aware of signs of serotonin syndrome: muscle rigidity, vomiting, sweating, tachycardia, and sedation.

Adrenal suppression: All opioids, including buprenorphine, have been reported to suppress ACTH, although this effect is rare. Adrenal suppression should be suspected and cortisol levels should be checked in patients who report fatigue, hypotension, and nausea.

Hepatic: There have been case reports of severe liver disease and death in patients taking buprenorphine; however, most cases had other factors that could have contributed or caused the liver disease, such as hepatitis C. Although SL buprenorphine was not associated with elevations in hepatic transaminases in randomized trials and cohort studies (18, 19), 7% of subjects in phase three trials receiving depot buprenorphine 300 mg maintenance dose had elevated transaminases, compared to 4.5% in the 100 mg group and 3% in the placebo group (2). Depot buprenorphine was discontinued due to possible hepatic injury in 1.5% of subjects in the 300 mg group, whereas it was not discontinued in either of the other groups. The product monograph states that hepatic impairment slows the metabolism of buprenorphine, causing significant elevations in serum buprenorphine levels (1). For this reason, the monograph recommends **that caution be used when administering depot buprenorphine to patients with moderate hepatic impairment, and its use is contraindicated in patients with severe hepatic impairment.** Moderate hepatic impairment should be assumed in patients with cirrhosis who have laboratory signs of impaired liver function: low albumin, high INR, low platelets, or high bilirubin. Severe hepatic impairment should be assumed in patients with overt signs of cirrhosis (firm liver edge,

spider nevi, jaundice) or in patients who have been in liver failure (i.e., encephalopathy, ascites, jaundice). Depot buprenorphine should not be delayed merely because of elevated transaminases in the absence of clinical or laboratory evidence of hepatic dysfunction.

Pregnancy: Depot buprenorphine is contraindicated in **people who are pregnant or who are planning to become pregnant.** While SL buprenorphine/naloxone is safe in pregnancy, depot buprenorphine contains an excipient that has been shown to be fetotoxic in animal studies, and the excipient crosses the placenta, although as yet there have been no reports of fetotoxicity among humans. Patients with the potential to become pregnant should be told about this risk and advised to use effective contraception if sexually active. Patients who indicate that they might be pregnant should be given a urine B-HCG test before receiving their injection. If a patient learns they are pregnant while taking depot buprenorphine, clinicians should have a discussion with them about whether the risks to the fetus of continuing with the monthly injections outweigh the risks of changing therapies.

All other contraindications to the use of buprenorphine products apply to this formulation; see the product monograph for a full list (1).

Guide for prescribing and administering depot buprenorphine

Certification

Prescribers must be certified (https://www.sublocadecertification.ca/) to prescribe depot buprenorphine. Once you have obtained certification, you may wish send your certificate to nearby pharmacies so that they can dispense the product to you.

Indications

Depot buprenorphine can be considered for patients who have been on a stable dose of SL buprenorphine/naloxone of 8–24 mg for at least seven days, and may be of particular benefit for patients with at least one of the following indications:

- Daily or frequent attendance at a pharmacy for observed dosing is difficult, because of distance, cost, family obligations, etc.
- Frequently miss their dose and relapse to opioid use.
- Persistent cravings and withdrawal symptoms while on the maximum dose of SL buprenorphine/naloxone.
- Persistent difficulty reducing use of illicit opioids while on SL buprenorphine/naloxone.
- At high risk for treatment discontinuation or relapse (e.g., about to be released from prison).
- Lack of acceptance of sublingual formulations (e.g., bad taste, long time to dissolve).
- Unable to safely store medication at home.
- Would derive psychological benefit from discontinuing a daily drug regimen.
- Want to taper and discontinue SL buprenorphine/naloxone (theoretically easier with depot buprenorphine because of its slower and smoother decline in serum levels).

Patients should be switched from depot buprenorphine to another form of OAT if they have intolerable side effects, if they have persistent severe cravings and withdrawal symptoms, or if their opioid use does not decline according to their goals.

Dosing

The depot buprenorphine product currently available in Canada is a subcutaneous injection (100 mg or

300 mg) that is administered by a trained health care professional every 28 days. Dose may be administered up to two days early; that is, a minimum of 26 days is required between consecutive doses. Doses may be administered up to fourteen days late without reinitiating SL buprenorphine. Doses should be administered as follows:

- Two loading doses of 300 mg 28 days apart.
    - Doses of SL buprenorphine/naloxone **may** be considered on days 14–28 after the first injection for patients who experience withdrawal due to a possible drop in the plasma concentration.
- A maintenance dose of 100 mg every 28 days.
    - Ongoing illicit opioid use, withdrawal, pain, or cravings can either be managed with small daily doses (2–4 mg) of SL buprenorphine/naloxone or with conversion to 300 mg depot as maintenance.

Injection technique

Depot buprenorphine comes as a pre-filled syringe with a #19-gauge needle supplied (do not change the needle). **The injection must be given subcutaneously**. When the contents of the pre-filled syringe are injected, depot buprenorphine forms a solid mass that can occlude blood vessels, causing clots or emboli. Intravenous and intramuscular injection must be avoided.

Use the following injection technique:

- See the product monograph for appropriate injection sites below the rib cage and above the pelvic brim.
- Avoid injecting into scars, including stretch marks.
- The patient should be in a supine position if possible.
- Tell the patient to expect a burning sensation at the injection site starting at ten seconds.
- Consider icing the area before and after the injection to reduce pain.
- Pinch and lift the skin to avoid injecting intramuscularly.
- Inject on a 45° angle into the abdomen for subcutaneous depot formation.
- Inject steadily over a minimum of ten to fifteen seconds (or longer if the patient prefers). The medication is very viscous and requires steady pressure.
- Advise the patient that they may have a palpable lump for several weeks to months, and not to rub/manipulate the area of the depot.
- Rotate injection sites (previous injection sites may still be palpable for up to four months).

Storage

Depot buprenorphine must be maintained in a cold chain, between 2–8°C, for storage and transportation, and must be delivered directly from the pharmacy to the clinic with no patient handling. It should be not be removed from the refrigerator until it has been confirmed that the patient will be receiving the injection, and it should be allowed to come to room temperature for at least fifteen minutes prior to injection. Once it is out of the refrigerator, it can be stored in the original packing at room temperature for seven days maximum (discard if left at room temperature any longer).

Cost

Depot buprenorphine costs $550 per dose (for 300 mg or 100 mg dose) + dispensing fees. It is covered

by most private insurance plans, NIHB, and ODB with Limited Use code 577. As many pharmacies do not regularly stock depot buprenorphine, notify the pharmacy/send a prescription prior to the planned injection date to ensure that the medication is available when needed.

Clinical Q&A

When should my patient take the last dose of SL buprenorphine before their first injection?

As buprenorphine concentrations will begin to rise immediately after the injection, patients should ideally take their last dose of SL buprenorphine the day before their first injection. If dosing was split throughout the day, doses that would have been administered before the injection can be provided; this will likely be beneficial for clinical stability and/or pain control until the injection is provided. If a full once-daily dose of SL buprenorphine was taken the day of the injection, it is likely still safe to proceed, as peak buprenorphine concentration will not be reached until 24 hours after the injection. Be mindful of the patient's high total daily dose and monitor for euphoric effects or sedation, which are likely to be felt a few hours after the injection is provided and last a few days

After the first dose of 300 mg, my patient experienced what they described as moderate-severe withdrawal symptoms around day 21. How should this and the second injection be managed?

The minimum buprenorphine concentration at day 28 after one 300 mg injection can fall below 2 ng/mL, putting the patient at risk of withdrawal and cravings. Consider providing 2–4 mg SL buprenorphine once daily to control symptoms until the next injection can be provided, which can be as early as 26 days after the previous injection. Tell your patient that this is likely to occur only after the first injection, as levels do not fall this low again after the second loading dose of 300 mg is provided.

My patient continues to experience withdrawal symptoms with the 100 mg maintenance doses. How do I decide between offering SL buprenorphine and increasing the maintenance dose to 300 mg?

If a patient is experiencing any withdrawal, cravings, or pain while on the 100 mg maintenance dose, it is worth considering an increase to the 300 mg maintenance dose. If the patient's symptoms are suspected to be situational and likely to resolve, low doses (2–4 mg) of SL buprenorphine can be provided for symptom management until the next injection can be provided. If the symptoms last for more than two weeks during the injection period and/or if they recur, the patient likely needs a maintenance dose of 300 mg.

My patient will be travelling and unavailable between days 26 and 42 after their last injection. Can I give them their dose early or delay it beyond this window?

It is best to plan dose adjustments well ahead of the travel days to ensure safe dose timing and to reduces the risk of complications during travel, such as withdrawal or cravings. For example, if a patient will be away during the 26- to 42-day window of their fourth injection, provide the third injection one to two weeks late to avoid this. The length of the delay and any concurrent opioid use should be considered. If the patient misses the 42-day window, you will need to ensure the patient's tolerance to 8–24 mg SL buprenorphine before resuming the injections; consider a return to the initial 300 mg doses.

How should I use SL buprenorphine if a patient's injection must be delayed indefinitely (e.g., due to a shortage of depot buprenorphine)?

If an injection is impossible, start the patient on 4 mg SL buprenorphine based on a COWS assessment of their withdrawal symptoms. Reassess the patient at least weekly and increase the dose as needed for

control of withdrawal symptoms. The maintenance SL dose will not necessarily be the same as the dose they were on prior to conversion to depot buprenorphine.

What if my patient wants to get high sometimes? Are there any risks associated with the opioid blockade combined with additional opioids?

It is best to discuss your patient's goals when considering depot buprenorphine. Some patients struggle with the goal of abstinence when they know that they can skip their SL dose and use illicit opioids. Depot buprenorphine is a good option in these situations, as the constant release of medication combined with the opioid blockade frees the patient from this daily decision. However, if the patient does not wish to be abstinent and is on OAT for harm reduction, the opioid blockade of the depot may be too strong to achieve euphoria with other opioids, leading patients to escalate their use. If this occurs on the 300 mg maintenance dose, considering lowering the dose to 100 mg. If this occurs on the 100 mg maintenance dose, SL buprenorphine may be a better choice. Work with your patient to find the option that works best for their individual goals.

Conflicts of interest

Katie Dunham: Has received honoraria for speaking engagements on the topic of depot buprenorphine (Sublocade).

Meldon Kahan: No conflicts to declare.

Ken Lee: Has received honoraria for speaking engagements on the topic of depot buprenorphine (Sublocade).

Jennifer Wyman: No conflicts to declare.

1. Sublocade product monograph [Internet]. Health Canada. 2020. Available from: https://health-products.canada.ca/dpd-bdpp/info.do?lang=en&code=97348.
2. Haight BR, Learned SM, Laffont CM, Fudala PJ, Zhao Y, Garofalo AS, et al. Efficacy and safety of a monthly buprenorphine depot injection for opioid use disorder: a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2019;393(10173):778-90.
3. Wiest K, Andom A, Fox N-L, Learned SM, Zhao Y. Abstinence response to 300mg vs 100mg RBP-6000 among opioid injection users. American Society of Addiction Medicine 2019; 4-7 Apr 2019; Orlando, FL2019.
4. Ling W, Nadipelli VR, Solem CT, Ronquest NA, Yeh YC, Learned SM, et al. Patient-centered Outcomes in Participants of a Buprenorphine Monthly Depot (BUP-XR) Double-blind, Placebo-controlled, Multicenter, Phase 3 Study. J Addict Med. 2019;13(6):442-9.
5. Lofwall MR, Walsh SL, Nunes EV, Bailey GL, Sigmon SC, Kampman KM, et al. Weekly and Monthly Subcutaneous Buprenorphine Depot Formulations vs Daily Sublingual Buprenorphine With Naloxone for Treatment of Opioid Use Disorder: A Randomized Clinical Trial. JAMA Intern Med. 2018;178(6):764-73.
6. Timko C, Schultz NR, Cucciare MA, Vittorio L, Garrison-Diehn C. Retention in medication-assisted treatment for opiate dependence: A systematic review. J Addict Dis. 2016;35(1):22-35.
7. Mattick RP, Breen C, Kimber J, Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. Cochrane Database Syst Rev. 2014;2:CD002207.
8. Ling W, Nadipelli VR, Solem CT, Ronquest NA, Yeh Y-C, Learned SM, et al. Effects of monthly buprenorphine extended-release injections on patient-centered outcomes: A long-term study. J Subst Abuse Treat. 2020;110:1-8.

9. Tompkins CNE, Neale J, Strang J. Opioid users' willingness to receive prolonged-release buprenorphine depot injections for opioid use disorder. J Subst Abuse Treat. 2019;104:64-71.
10. Greenwald M, Johanson CE, Bueller J, Chang Y, Moody DE, Kilbourn M, et al. Buprenorphine duration of action: mu-opioid receptor availability and pharmacokinetic and behavioral indices. Biol Psychiatry. 2007;61(1):101-10.
11. Greenwald MK, Comer SD, Fiellin DA. Buprenorphine maintenance and mu-opioid receptor availability in the treatment of opioid use disorder: implications for clinical use and policy. Drug Alcohol Depend. 2014;144:1-11.
12. Nasser AF, Heidbreder C, Gomeni R, Fudala PJ, Zheng B, Greenwald MK. A population pharmacokinetic and pharmacodynamic modelling approach to support the clinical development of RBP-6000, a new, subcutaneously injectable, long-acting, sustained-release formulation of buprenorphine, for the treatment of opioid dependence. Clin Pharmacokinet. 2014;53(9):813-24.
13. Wiest K, Algera H, Moss LM, van Valzen M, Dobbins R. High therapeutic buprenorphine levels reduce IV fentanyl respiratory depression. American Society of Addiction Medicine 2019; 4-7 Apr 2019; Orlando, FL2019.
14. Lintzeris N, Dunlop A, Masters D. Clinical guidelines for use of depot buprenorphine (Buvidal® and Sublocade®) in the treatment of opioid dependence. New South Wales, Australia: New South Wales Ministry of Health; 2019.
15. Poole SA, Pecoraro A, Subramaniam G, Woody G, Vetter VL. Presence or Absence of QTc Prolongation in Buprenorphine-Naloxone Among Youth With Opioid Dependence. J Addict Med. 2016;10(1):26-33.
16. Woody GE, Poole SA, Subramaniam G, Dugosh K, Bogenschutz M, Abbott P, et al. Extended vs short-term buprenorphine-naloxone for treatment of opioid-addicted youth: a randomized trial. JAMA. 2008;300(17):2003-11.
17. Kao DP, Haigney MC, Mehler PS, Krantz MJ. Arrhythmia associated with buprenorphine and methadone reported to the Food and Drug Administration. Addiction. 2015;110(9):1468-75.
18. Vergara-Rodriguez P, Tozzi MJ, Botsko M, Nandi V, Altice F, Egan JE, et al. Hepatic safety and lack of antiretroviral interactions with buprenorphine/naloxone in HIV-infected opioid-dependent patients. J Acquir Immune Defic Syndr. 2011;56 Suppl 1:S62-7.
19. Tetrault JM, Tate JP, Edelman EJ, Gordon AJ, Lo Re V, 3rd, Lim JK, et al. Hepatic Safety of Buprenorphine in HIV-Infected and Uninfected Patients With Opioid Use Disorder: The Role of HCV-Infection. J Subst Abuse Treat. 2016;68:62-7.