CoLab Network

Rapid Review

# Buprenorphine Formulations for Opioid Use Disorder

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This rapid review was conducted by Michael Law through the Post Market Drug Evaluation CoLab Network.

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# Key Messages

**There are numerous buprenorphine formulations** available in Canada for treating opioid use disorder. This rapid review examines their relative clinical effectiveness, safety, and cost-effectiveness and offers an overview of their use in jurisdictions across Canada.

**The review includes 2 randomized controlled trials, 2 nonrandomized studies, and 1 economic evaluation**, all published since March 2019. The included studies all compared extended-release buprenorphine formulations to sublingual buprenorphine formations, including tablets and/or film.

**The findings are mixed on the clinical effectiveness** of extended-release injectable buprenorphine versus sublingual buprenorphine-naloxone.

**The economic evaluation suggests** that extended-release buprenorphine is less effective and more costly than sublingual formulations. As a result, sublingual formations dominated as a treatment strategy.

**All but 1 of the studies, including the economic evaluation, were conducted in other countries**, so their applicability to the Canadian population remains unclear.

**All studies had significant methodological concerns** and caution should be used in interpreting these results.

**Overall, the included studies did not offer a clear rationale for preference of 1 formulation** of buprenorphine on clinical effectiveness or safety grounds.

**The use of buprenorphine film and extended-release injections has been rising** among beneficiaries of Canadian drug programs, but it still only accounts for a small fraction of overall buprenorphine use. However, the use of both formulations is growing at a rapid rate in most provinces.

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# Abbreviations

| | |
|---|---|
| **CI** | confidence interval |
| **OUD** | opioid use disorder |
| **NPDUIS** | National Prescription Drug Utilization Information System |
| **QALY** | quality-adjusted life-year |
| **RCT** | randomized controlled trial |
| **SLB** | sublingual buprenorphine-naloxone and/or buprenorphine |
| **TSQM** | Treatment Satisfaction Questionnaire for Medication |
| **XRB** | extended-release buprenorphine |

# Introduction and Rationale

## Background

Opioid use disorder (OUD), which results from the compulsive and problematic use of opioid drugs, is a serious public health concern in Canada. Survey data from Statistics Canada suggests that use of opioid medications is widespread, and that problematic use can be identified in more than 350,000 people in the country.[1] Higher rates of use were found among individuals who are younger, male, and reported fair or poor mental health. The use of illicit opioids has led to significant morbidity and mortality in Canada, with 7,525 deaths attributable to opioid toxicity in 2022, and these numbers are increasing over time.[2]

This disease burden has led to a focus on identifying the best treatment approaches for OUD both in Canada and internationally. A cornerstone of treatment for OUD is opioid agonist therapies such as buprenorphine and methadone. Buprenorphine is often formulated in combination with naloxone to reduce the risk of misuse and diversion. In recent years, multiple formulations of buprenorphine have been approved for the treatment of OUD in Canada, including sublingual buprenorphine-naloxone (SLB) tablets, SLB film, and extended-release buprenorphine injection (XRB). These formulations offer different routes of administration and potentially different outcomes in terms of adherence, misuse, diversion, and convenience. They also differ substantially in cost.

## Policy Issue

With a multitude of formulations available for potential formulary listing, it is important to assess the comparative clinical effectiveness and cost-effectiveness of these different treatment options. The comparison of these different options has been touched upon in several past CADTH reviews:

1. A 2014 review identified 1 randomized controlled trial (RCT) that compared SLB tablets with SLB film.[3] This trial reported no differences between the 2 formulations on clinical effectiveness or adverse events.
2. A review completed in 2017 compared different formulations of buprenorphine and included 5 RCTs, 3 nonrandomized studies, and 1 economic analysis.[4] Overall, the review found similar clinical effectiveness between different buprenorphine formulations, with higher rates of misuse and diversion for SLB tablets. The economic analysis suggested buprenorphine implants have lower costs from a societal perspective. The review noted significant methodologic limitations with many of the clinical studies and with the economic analysis.
3. A 2019 review updated the evidence on buprenorphine formulations published since the previous reports.[5] The authors found 2 relevant systematic reviews, 3 RCTs, 6 nonrandomized studies, 2 economic evaluations, and 2 evidence-based guidelines. While the authors found some differences between formulations in these studies with respect to outcomes, they conclude that no consistent pattern appeared that would preference 1 over another. The results from the economic evaluations were also mixed. Similar to the previous review, this review noted significant issues with the literature, including that none of the studies were conducted in Canada.

4. Finally, a 2023 report specifically compared SLB tablets to SLB film in terms of clinical effectiveness based on literature from 2018 through September 2023.[6] The review identified 1 nonrandomized study for inclusion, which suggested no differences in clinical effectiveness and some potential advantages to film in terms of potential for misuse. This review also noted significant limitations in the literature comparing these 2 buprenorphine formulations.

In addition to these comparisons, CADTH has also reviewed the coverage status and overall use of different treatments for OUD across Canada.[7] While this report separated different drugs for comparison, it did not compare the utilization of different buprenorphine formulations in public drug plans across Canada by formulation or jurisdiction.

### Policy Questions

1. Which buprenorphine formulation for OUD should be funded and according to what criteria?
2. What are the trends in the utilization of the various buprenorphine formulations for OUD in Canadian jurisdictions?

## Purpose

This report has 2 purposes. One is to update the prior CADTH reviews to include evidence on other buprenorphine formulations that has been published since 2019, and the second is to provide insight into the use of different buprenorphine formulations in public drug plans across Canada.

**Main Takeaway**

OUD is a serious public health concern in Canada. Several formulations of buprenorphine have been approved for its treatment, but it is essential to assess their comparative clinical effectiveness and cost-effectiveness. Past reviews have found similar clinical effectiveness between different buprenorphine formulations, with higher rates of misuse for sublingual buprenorphine-naloxone tablets. The existing literature comparing buprenorphine formulations has significant limitations. This report aims to update prior reviews and provide insight into the utilization of different buprenorphine formulations in public drug plans across Canada.

## Research Questions

1. What is the comparative clinical effectiveness of various buprenorphine or buprenorphine-naloxone formulations versus other buprenorphine formulations for the treatment of OUD?
2. What is the comparative safety of various buprenorphine formulations for the treatment of OUD?
3. What is the comparative cost-effectiveness of various buprenorphine formulations for the treatment of OUD?

4. What are the evidence-based guidelines regarding the use of various buprenorphine formulations for the treatment of OUD?
5. What is the current utilization of different buprenorphine formulations in public drug plans across Canada?

# Methods

## Literature Search Methods

The research team used a modified version of the literature search strategy from a 2019 CADTH review on buprenorphine formulations.[5] This strategy consisted of a limited literature search on key resources including Medline via PubMed, the Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, and Canadian and major international health technology agencies, as well as a focused internet search. CADTH-developed search filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, indirect treatment comparisons, clinical trials or observational studies, economic studies, and guidelines. The search was limited to English-language documents published between March 21, 2019, and November 14, 2023.

## Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. As an update to a previous CADTH report, articles were included if they were made available since the previous search date and were not included in the 2019 CADTH report.[5] The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

## Table 1: Selection Criteria

| Criteria | Description |
|---|---|
| **Population** | Patients with opioid use disorder |
| **Potential subgroups** | All available formulations of buprenorphine (e.g., extended-release subcutaneous injection, sublingual, transdermal, intramuscular) or buprenorphine-naloxone combinations<br>Correctional population |
| **Intervention** | Q1, Q2, Q3: Various formulations of buprenorphine (e.g., extended-release subcutaneous injection, sublingual, implant, transdermal, intramuscular) or buprenorphine-naloxone combinations<br>Q4: No comparator necessary |
| **Comparator** | Q1, Q2, Q3: Various formulations of buprenorphine (e.g., extended-release subcutaneous injection, sublingual, implant, transdermal, intramuscular) or buprenorphine-naloxone combinations<br>Q4: No comparator necessary |

| Criteria | Description |
|---|---|
| **Outcomes** | Q1: Clinical effectiveness (e.g., reduction in opioid consumption, prevention of relapse, maintenance of abstinence, retention into treatment, urine drug screening results, adherence to medication, social functioning [e.g., return to school or work], emotional and psychological functioning [e.g., anxiety, depression, sleep])<br>Q2: Safety (e.g., reduction in misuse and diversion, reports or evidence of misuse, overdose, all-cause mortality)<br>Q3: Cost-effectiveness per health benefit gained<br>Q4: Guidelines on appropriate use of different formulations |
| **Setting** | Outpatient |
| **Study designs** | Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, nonrandomized studies, economic evaluations, and evidence-based guidelines |

## Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were included in prior CADTH reviews. Systematic reviews in which all relevant studies were captured in other more recent or more comprehensive systematic reviews were excluded. Primary studies retrieved by the search were excluded if they were captured in 1 or more included systematic reviews. Guidelines with unclear methodologies were also excluded.

## Critical Appraisal of Individual Studies

The included publications were critically appraised by 1 reviewer using the Downs and Black checklist[8] for randomized and nonrandomized studies and the Drummond checklist[9] for economic evaluations. Summary scores were not calculated for the included studies; rather, the strengths and limitations of each included publication were described narratively.

## Utilization Data

Public drug claims data were sourced from the National Prescription Drug Utilization Information System (NPDUIS), including public drug plans from Alberta, British Columbia, New Brunswick, Newfoundland and Labrador, Nova Scotia, Ontario, Prince Edward Island, Saskatchewan, and Yukon Territory. Note that in British Columbia, Saskatchewan, and Manitoba, nonadjudicated claims are also included, which results in all community pharmacy dispensations being captured in these provinces. The drugs used for OUD were identified by the Drug Identification Numbers (DINs) assigned by Health Canada (Appendix 1), and the specific drugs plans and programs that contributed data are shown in Appendix 2. Claims data per year were extracted from the second quarter of 2018 to the first quarter of 2023 and stratified by jurisdiction. Trends in utilization over time were derived for each formulation (i.e., SLB film, SLB tablet, XRB). Utilization was defined as the number of individuals who were dispensed a prescription for a publicly funded buprenorphine formulation per quarter from 2018 to 2023.

The NPDUIS database does not include information related to prescriptions that were written but never dispensed or prescriptions that were dispensed but for which the associated drug costs were not submitted to, or not accepted by, the public drug programs listed in Appendix 2. In accordance with the Canadian

Institute of Health Information privacy policy, in cases in which the number of active beneficiaries were less than 5 (but greater than zero), this number and other associated values were suppressed to ensure confidentiality.

# Summary of Evidence

## Quantity of Research Available

A total of 940 citations were identified in the literature search. Following screening of titles and abstracts, 931 citations were excluded. Nine potentially relevant publications were retrieved from the internet search for full-text review, leading to a total of 18 potentially relevant reports. Of these, 13 were excluded for various reasons, and 5 publications met the inclusion criteria and were included in this report. Appendix 3 presents the PRISMA[10] flow chart of the study selection.

## Study Characteristics

Two RCTs,[11,12] 2 nonrandomized studies,[13,14] and 1 economic evaluation[15] were identified and included in this review. No relevant systematic reviews or evidence-based guidelines were identified. Additional details regarding the characteristics of included publications are provided in Appendix 4.

### Study Design

Four primary study reports comparing the clinical effectiveness and safety of different buprenorphine formulations for the treatment of OUD were identified. There were 2 RCTs in 2 publications: both were randomized open-label effectiveness studies that were published in 2021.[11,12] The 2 relevant nonrandomized studies both used retrospective cohort designs, 1 was published in 2021 and the other in 2023.[13,14]

The included economic evaluation study was published in 2023 and used a state transition model.[15] The clinical and cost inputs were derived from existing studies and pricing information from the US Federal Supply Schedule. The study was conducted from the perspective of the US health care system using a lifetime time horizon for a fixed cohort of 100,000 simulated patients. The model included transitions between 4 health states: active injection opioid use, active noninjection opioid use, nonactive injection opioid use, and nonactive noninjection opioid use.

### Country of Origin

The RCTs were conducted in the US[12] and Australia.[11] The nonrandomized studies were conducted in Canada[14] and the US.[13] Finally, the economic evaluation was conducted in the US.[15]

### Patient Population

The 2 RCT reports focused on different target populations. Lee and colleagues (2021)[12] focused on 52 currently incarcerated individuals in New York State who were currently taking daily SLB and who had a known release date. Potential participants were identified using electronic medical records. To be included, individuals had to be aged 18 or over, have no serious or uncontrolled psychiatric illness, and be able to

understand English. Participants were recruited from 2 correctional facilities, 1 of which was a facility for males and the other for females. The second RCT by Lintzeris et al. (2021),[11] the Depot Evaluation–Buprenorphine Utilization Trial (DEBUT), focused on a population of 119 individuals with OUD who were established on treatment with SLB. Participants aged 18 and older were recruited from 6 outpatient drug treatment centres in Australia. Participants were excluded if they had other serious medical conditions, were pregnant, breastfeeding, or planned to become pregnant during follow-up.

The 2 nonrandomized studies also used different data sources. Morgan et al. (2021)[13] used claims data from commercial insurers available through the MarketScan database from the US. Using this data from 2018 onward, they studied 14,358 patients who were initiated on 1 of 4 treatments for OUD following a 3-month washout period. For the purposes of this review, we focused on the comparison between 2 groups: XRB and SLB. The second study, an observational cohort study by Lee et al. (2023)[14] included 379 individuals at 9 clinics in the Canadian provinces of British Columbia and Ontario. Patients were identified through chart review, and had to be 18 years or older with moderate to severe OUD and have initiated treatment with buprenorphine or methadone after March 11, 2020. Patients were excluded if they were pregnant or planning to become pregnant when they started treatment.

The economic evaluation by Flam-Ross et al. (2023)[15] used the existing RESPOND model to assess the cost-effectiveness of XRB against SLB. The study used a simulated cohort of 100,000 patients based in the state of Massachusetts that was informed by estimates drawn from the existing literature and information drawn from the Massachusetts Public Health Data Repository that links data across 29 data sources. Patients were simulated over their lifetime, were 58% male, and had an average age of 48 years.

### Interventions and Comparators

All of the included studies were comparisons of XRB versus 1 or more forms of SLB (tablets and/or film, either exclusively coformulated with naloxone, or a combination of formulations with and without naloxone).

For the RCT studies, the intervention of interest in Lee et al. (2021)[12] was XRB, which was provided to patients monthly. The first injection was provided to participants at least 1 week before release, and subsequent injections were provided free of charge in a specific community clinic. The comparator population was continued on SLB tablets with naloxone through observed treatment clinic visits in the facility, and provided with a 7-day supply on release that was intended to bridge to a community prescription. Similarly, participants in the RCT conducted by Lintzeris et al.[11] were randomized 1:1 to receive either XRB or the comparator of SLB film or tablets, and most participants received SLB film with naloxone. XRB injections were conducted at the clinics, while the comparator group could receive treatment at either the trial clinic or a community pharmacy.

The 2 nonrandomized studies also compared XRB to SLB. The study by Morgan et al. (2021)[13] compared patients who were initiated on XRB to with a population initiated on SLB tablets or film, with either buprenorphine alone or buprenorphine coformulated with naloxone. Similarly, Lee et al. (2023)[14] compared patients who were initiated on XRB to those who were initiated on SLB tablets. The study report is not explicit

about whether these tablets were exclusively coformulated with naloxone, but the introduction makes reference to a specific product that does contain naloxone.

### Outcomes

The outcomes assessed in the RCT studies were varied. The primary outcomes of the 2 trials included the Treatment Satisfaction Questionnaire for Medication (TSQM),[11] and buprenorphine treatment retention at 8 weeks following release from incarceration.[12] Secondary outcomes in the studies included heroin and fentanyl use,[12] adverse events,[12] reincarceration,[12] the Patient Satisfaction–Visual Analogue Scale (PS-VAS),[11] the Patient Global Impression of Improvement (PGI-I) scale,[11] the Treatment Burden Questionnaire (TBQ),[11] the Opioid-Related Behaviours in Treatment (ORBIT) scale,[11] and the Substance Use Recovery Evaluator (SURE).[11]

The outcomes in the nonrandomized studies included nonfatal overdose,[14] opioid use (positive opioid urine tests combined with self-report),[14] and medication discontinuation (gap of > 14 days).[13]

Finally, in the economic evaluation the outcome of interest was the incremental cost per quality-adjusted life-year (QALY) gained.[15]

## Critical Appraisal

### Randomized Controlled Trials

The 2 RCT reports[11,12] had several strengths in common, including clear descriptions of objectives, interventions, main outcomes, population characteristics, potential confounders, eligibility criteria, and adverse events. Neither study was blinded to the participants or those collecting outcomes, which is a concern as many of the outcomes under study were subjective in nature. One study[11] reported a formal power calculation, while the other did not.[12] The studies were both conducted at multiple sites, although both were comparatively small at 2 jails[12] and 6 outpatient clinics.[11] Loss to follow-up was reported, but no characteristics of these patients were provided in either study. One study[12] did not report any formal statistical testing for any of the outcomes. The external validity of both studies to the Canadian context is unclear, as 1 studied incarcerated individuals in the US[12] and the other studied patients in several clinics in Australia.[11] One of the studies[11] was funded by a manufacturer of the intervention drug under study, while some authors of the other study reported industry funding from the manufacturers of the drugs under study.[12]

### Nonrandomized Studies

There were several strengths common to both nonrandomized studies,[13,14] including clear descriptions of objectives, main outcomes, patient characteristics, eligibility criteria, potential confounders, and estimates of random variability. The main outcome measures used were valid and reliable and actual P values were reported for some of the key outcomes in both studies. Loss to follow-up was 18.4% of the relevant groups in 1 analysis,[14] while it was not reported in the other study.[13] As both were observational studies, there was no blinding of participants, and there were some important differences in reported baseline characteristics in both studies. For example, the SLB group in 1 study had higher historical rates of nonfatal overdose compared to XRB.[14] P values were not reported for some outcomes in both studies, including differences in

opioid use over the follow-up period in 1 study[14] and pairwise comparisons of treatment discontinuation in the other.[13] The external validity of both studies is unclear, as 1 focused on 9 clinics in Canada,[14] while the other examined commercially insured individuals in the US.[13] As the patients and/or their clinicians chose the treatments in both studies, there may be unobserved differences between the groups that are related to the outcomes under study. One study was funded by the manufacturer of a buprenorphine formulation,[14] while the other was publicly funded and the authors reported no conflicts of interest.[13]

### Economic Evaluations

The economic evaluation[15] clearly stated the research question, economic importance, viewpoint, alternatives, and form of economic analysis being conducted. The model assumptions were all clearly stated and several sensitivity analyses were undertaken to test key assumptions on a range of variables. While the source of clinical outcomes and drug cost data were clearly described, the costing of nondrug expenditures and the derivation of QALY measures for different health states was not clear. The use of a lifetime time horizon was appropriate given that OUD can impact individuals for many years. While the discount rate (3%) was documented, it was not justified in the report. The generalizability of the study to Canada may be limited given that it was conducted in the US. Finally, the study was publicly funded and none of the authors disclosed any financial relationships with drug manufacturers.

Additional details regarding the strengths and limitations of the included publications are provided in Appendix 5.

**Main Takeaway**

All studies had significant methodological concerns, including a lack of blinding, generalizability (i.e., few studies from Canada), and a lack of formal statistical testing for several outcomes, suggesting that caution should be used in interpreting the results.

## Findings

Appendix 6 presents the main study findings. In the following, the results are separated into the 2 studies that compared XRB with SLB tablets with naloxone and those that compared XRB to SLB tablets and film, both with and without naloxone.

### Clinical Effectiveness of Extended-Release Buprenorphine Versus Sublingual Buprenorphine-Naloxone Tablets

#### *Retention in Treatment*

Two studies compared XRB with SLB tablets with naloxone. One RCT study[12] that compared XRB to SLB tablets with naloxone only reported point estimates for the key outcomes. It found that patients who were released from incarceration being treated with XRB had higher retention in treatment at 8 weeks (69.2% versus 34.6%). The second comparison was in a nonrandomized study[14] and found retention rates were higher in the XRB group than in the SLB tablets with naloxone comparator group (86.7% versus 71.9%, not statistically tested).

### *Opioid Use*

There was a higher percentage of negative urine tests for nonprescribed opioids in the XRB group versus the SLB tablets with naloxone group in 1 RCT study (55.4% versus 38.5%).[12] However, these differences were not statistically tested and it was also assumed that missing tests were positive and there were many more missing tests in the SLB tablets with naloxone group (43.1% for SLB versus 22.3% for XRB).

### *Reincarceration*

In the RCT study of individuals recently released from incarceration, fewer participants were reincarcerated during follow-up in the XRB group compared to the SLB tablets with naloxone comparator (8% versus 15%).[12] This difference was not subjected to formal statistical testing.

### *Nonfatal Overdose*

One nonrandomized study reported that nonfatal overdose was less frequent in the XRB group than in the SLB tablets with naloxone group (1.6% versus 5.8%; P = 0.0115).[14]

## Clinical Effectiveness of Extended-Release Buprenorphine Versus Sublingual Buprenorphine Film or Tablets (With or Without Naloxone)

### *Retention in Treatment*

One nonrandomized study[13] found that the median time to discontinuation of treatment was shorter for individuals receiving XRB (47 days; interquartile range, 28 to 73) than for those receiving SLB tablets or film (71 days; interquartile range, 36 to 122). While differences in discontinuation time were statistically tested, this was only done across all 4 study groups (including the extended-release naltrexone and methadone groups in addition to the 2 buprenorphine groups). As a result, it is unclear whether there was a statistical difference between these 2 groups specifically.

### *Opioid Use*

One RCT study reported a lower percentage of negative urine tests for nonprescribed opioids in the XRB intervention group (69.9%; 95% confidence interval [CI], 60.6% to 79.3%) versus the SLB tablets or film comparator group (73.5%; 95% CI, 64.1% to 82.9%).[11] This difference, however, was not statistically tested. The same RCT found no statistically significant differences between XRB and SLB tablets or film on both the Opioid-Related Behaviours in Treatment (ORBIT) scale of opioid-related behaviours and the Substance Use Recovery Evaluator (SURE) scale of recovery evaluation (P = 0.12 and 0.30, respectively).

### *Patient Satisfaction*

One RCT found some differences between XRB and SLB tablets or film on measures of treatment satisfaction using the TSQM.[11] This included a global treatment satisfaction summary score that was 8.6 points higher for the XRB group (the TSQM; 95% CI, 3.3 to 13.9; P = 0.002) and a 17.8 point higher summary score measuring treatment convenience (95% CI, 13.0 to 22.6; P < 0.001). Other scales measuring treatment behaviours and recovery showed no statistically significant differences between the study arms.

### Evidence Regarding the Safety and Cost-Effectiveness of Extended-Release Buprenorphine Versus Sublingual Buprenorphine Film or Tablets

#### *Adverse Events*

No participants ceased treatment due to adverse effects in 1 RCT, but the incidence of such events was somewhat higher in the intervention XRB group compared to the comparator SLB tablet or film group (90.0% versus 83.1%).[11] These were reported to be largely injection-site reactions of mild intensity.

#### *Cost-Effectiveness of Extended-Release Buprenorphine Versus Sublingual Buprenorphine Film or Tablets*

The cost-effectiveness analysis by Flam-Ross et al. (2023)[15] found that treatment with XRB resulted in fewer QALYs gained (27.44 versus 27.39) and higher costs (US$308,700 versus US$304,700). The combined decrease in QALYs and higher cost meant that XRB was dominated by SLB film or tablets. These findings were robust to sensitivity analyses around the demographic and epidemiological factors in the model, but were sensitive to changes in both the price of the medications and retention in treatment when they were comparatively large.

**Main Takeaways**

**Clinical effectiveness:** The studies lacked statistical testing, with mixed findings in treatment retention and opioid use and recovery. There were trends in 1 RCT to suggest that XRB may reduce nonfatal overdose, decrease reincarceration rates, and have higher patient satisfaction compared to SLB film or tablets. However, no firm conclusions can be made.

**Safety:** As reported in 1 RCT, no participants had stopped treatment due to adverse effects, but the frequency of events was somewhat higher in the XRB group compared to the SLB group.

**Cost-effectiveness:** The economic evaluation suggests that XRB is less effective and more costly than SLB formulations.

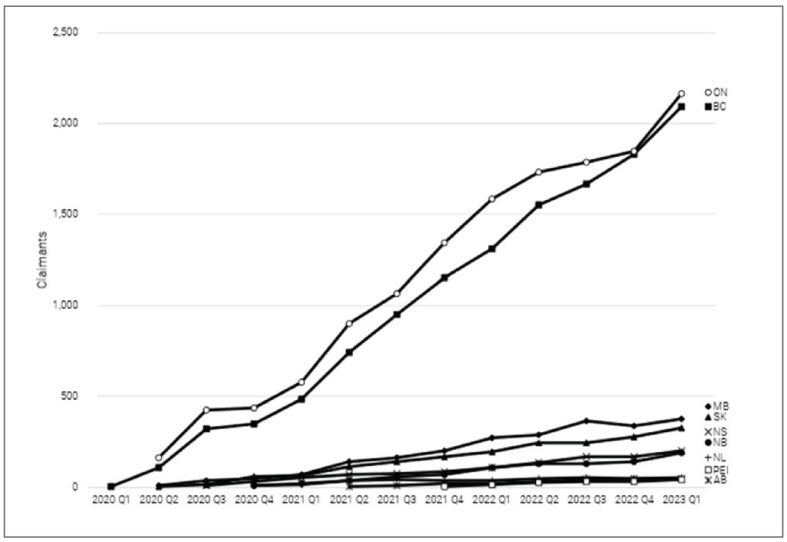
## Utilization Data

Figure 1, Figure 2, and Figure 3 show the longitudinal user prevalence of different buprenorphine formulations for OUD in Canadian public drug plans. Some jurisdictions may be underrepresented in the overall Canadian picture because NPDUIS only captures select public program data serving specific populations such as seniors (refer to Appendix 2), which may contain lower proportions and absolute numbers of patients with OUD. Appendix 7 contains a table with all of the data shown in the figures.

XRB claimants are increasing in all jurisdictions, with Ontario and British Columbia having the most users. SLB film is also a new formulation that has increased in use, but it is still only available in a handful of jurisdictions (Newfoundland, Nova Scotia, Saskatchewan, Manitoba, British Columbia) and claimants represent only a fraction (1% to 10%) of total SLB users. Numbers of users of SLB tablets (both branded and generic tablet versions) have been more stable over time. In most jurisdictions, a surge of demand was

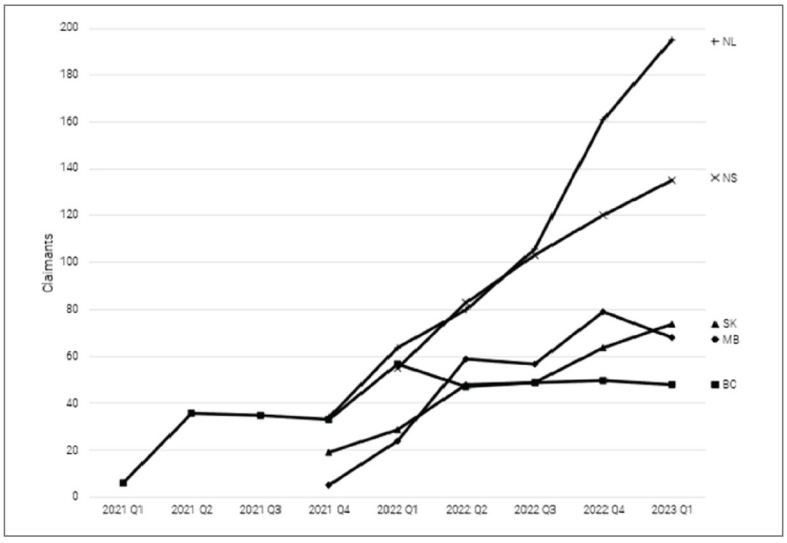
observed before the COVID pandemic, which then plateaued for 2 years, and has slowly increased since. Again, patients from Ontario and British Columbia form the bulk of prevalent users of SLB tablets.

## Figure 1: Utilization of Buprenorphine Depot in Canada



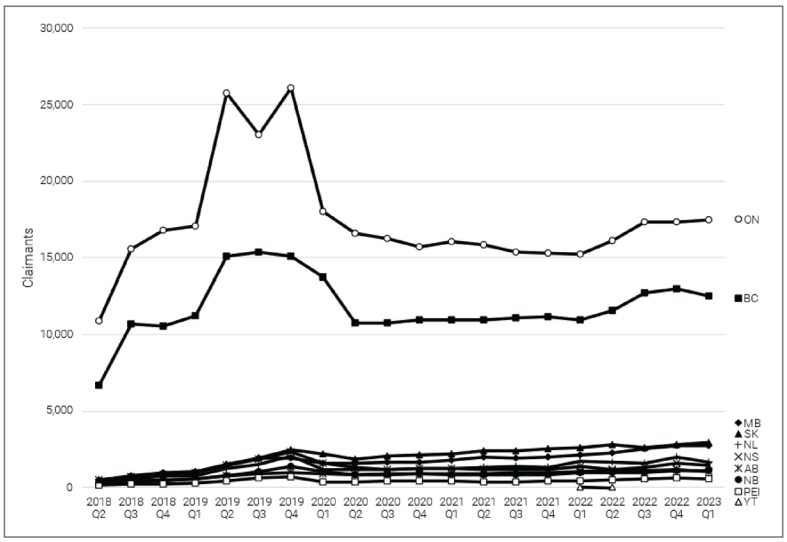

AB = Alberta; BC = British Columbia; MB = Manitoba; NB = New Brunswick; NL = Newfoundland and Labrador; NS = Nova Scotia; ON = Ontario; PEI = Prince Edward Island; SK = Saskatchewan; YT = Yukon Territory.

## Figure 2: Utilization of Buprenorphine-Naloxone Film in Canada




AB = Alberta; BC = British Columbia; MB = Manitoba; NB = New Brunswick; NL = Newfoundland and Labrador; NS = Nova Scotia; ON = Ontario; PEI = Prince Edward Island; SK = Saskatchewan; YT = Yukon Territory.

### Figure 3: Utilization of Buprenorphine-Naloxone Tablets in Canada




AB = Alberta; BC = British Columbia; MB = Manitoba; NB = New Brunswick; NL = Newfoundland and Labrador; NS = Nova Scotia; ON = Ontario; PEI = Prince Edward Island; SK = Saskatchewan; YT = Yukon Territory.

## Limitations

Overall, the major limitations of the evidence synthesized in this report comprise risk of internal bias, external validity of the findings, a lack of statistical testing in many studies, and conflicting findings between industry-sponsored and other studies.

In terms of risks to internal validity, there are several key limitations to the included studies. In all of the studies, participants were not blinded to their treatment. This is particularly problematic in the case of self-reported outcomes. Similarly, the selection of treatment in the nonrandomized studies was based on patient and clinician choice. Therefore, participants could have been unbalanced across treatment groups in both observed and unobserved characteristics, resulting in residual confounding. Notably, many of the reported outcomes in the various study reports were not subject to formal statistical testing and should thus be interpreted with significant caution. Finally, industry funding or conflicts were present in 3 of the 5 studies.[11,12,14] Notably, these were the only 3 studies to report any positive outcomes for XRB in relation to other available formulations of buprenorphine.

Overall, the studies included different populations, but the applicability of many of the results to the Canadian context remains unclear. Four of the 5 included studies were conducted in other countries, and some of these were in very specific populations, such as incarcerated individuals scheduled for release. In addition, the enrolled population in all of the studies was predominantly male, so the results may not generalize to females. Finally, the generalizability of the included economic evaluation is uncertain given the different prices for medicines and medical treatment in the US.

## Conclusions and Implications for Decision- or Policy-Making

We identified clinical and cost-effectiveness evidence comparing different buprenorphine formulations for the treatment of OUD. Two RCTs,[11,12] 2 nonrandomized studies,[13,14] and 1 economic evaluation[15] were included. All of these studies compared XRB to 1 or more forms of SLB. Overall, these studies reached mixed conclusions regarding the clinical effectiveness, safety, and cost-effectiveness of various buprenorphine formulations for individuals with OUD. Our results also demonstrated that while use of SLB film and XRB is increasing in Canada, they remain very small in comparison to SLB tablets.

Regarding clinical effectiveness, there was no instance where multiple studies reported the same direction of effect for comparisons between XRB and various forms of SLB. For example, 1 RCT[12] and 1 nonrandomized study[14] found point estimates indicating better retention on treatment for XRB, while another nonrandomized study[13] found the opposite result. For most other outcomes, including reincarceration,[12] nonfatal overdose,[14] and patient satisfaction,[11] the results tended to favour XRB, but were all derived from single studies. Differences in adverse events between the different formulations were also only reported in 1 study.[11]

The single economic evaluation[15] found that treatment with XRB was both more expensive and less effective than SLB, and was thus dominated. This result was highly robust to reasonable changes in the model parameters. However, as the study was conducted in the US and used costs that would be different in Canada, it is unclear if it would extrapolate to Canadian policy settings. It worth noting, however, that the monthly cost for XRB in Canada reimbursed by public plans is substantially higher than SLB, even at high doses of SLB.[16,17]

Overall, these findings are very similar to past CADTH work on this topic, which has also identified no clear patterns in the evidence on clinical effectiveness between various forms of buprenorphine.[3-6] It is also consistent with past results on the mixed cost-effectiveness evidence around the use of newer formulations.[5]

The limitations of the included studies are significant and should be taken into account when considering how the results can be used for reimbursement decisions. Additional research on the comparative safety, effectiveness, and cost-effectiveness of these different formulations would be valuable in reducing the decision uncertainty in this clinical area.

**Main Takeaways**

The included studies did not provide conclusive evidence to favour 1 formulation of buprenorphine over another in terms of either clinical effectiveness or safety. Buprenorphine film and extended-release injection are gaining in popularity among patients in Canada with OUD in many provinces, but still account for only a small fraction of overall buprenorphine use.

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# Authors and Contributors

## Authors

**Michael Law** contributed to the conception and design, acquisition of data, analysis and interpretation of results, and drafting the report, and was accountable for all aspects of his contribution.

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### Conflicts of Interest

This individual disclosed the following conflicts of interest:

**Michael Law**
Consulted for Health Canada, CADTH, and iTAD Limited.

Acted as an expert witness for the Federation of Post-Secondary Educators and the Durham Police Association.

No other conflicts of interest were declared.

# Appendix 1: NPDUIS

Note that this appendix has not been copy-edited.

## Table 2: Included Drugs

| Formulation | DIN | Strength | DIN Holder |
|---|---|---|---|
| Buprenorphine-naloxone tablet | 02453908 | 0.5 mg | Teva |
| | 02453916 | 2 mg | Teva |
| | 02424851 | 0.5 mg | Pharmascience |
| | 02424878 | 2 mg | Pharmascience |
| | 02295695 | 0.5 mg | Indivior |
| | 02295709 | 2 mg | Indivior |
| Buprenorphine-naloxone film | 02502313 | 0.5 mg | Indivior |
| | 02502348 | 2 mg | Indivior |
| | 02502356 | 3 mg | Indivior |
| Extended-release buprenorphine subcutaneous depot | 02483084 | 100 mg | Indivior |
| | 02483092 | 300 mg | Indivior |

DIN = drug identification number

# Appendix 2: List of Public Drug Plans and Programs Included in Utilization Analysis

Note that this appendix has not been copy-edited.

## Table 3: Provincial Public Drug Plans and Programs With Claims Data Contained Within the National Prescription Drug Utilization Information System Database

| Jurisdiction | Plan/Program Code-Description |
|---|---|
| **Alberta** | Non-Group |
| | Seniors |
| | Palliative Care |
| **British Columbia** | Assurance Program |
| | Children in the At Home Program |
| | Cystic Fibrosis |
| | Fair PharmaCare |
| | Nicotine Replacement Therapies |
| | Palliative Care |
| | Psychiatric Medication Program |
| | Recipients of British Columbia Income Assistance |
| | Residential Care |
| | Non-Adjudicated (Pharma Net) |
| **Manitoba** | Employment and Income Assistance Program |
| | Palliative Care |
| | Pharmacare |
| | Personal Home Care/Nursing Homes |
| | Non-Adjudicated (Drug Program Information Network) |
| **New Brunswick** | New Brunswick Prescription Drug Program, including:<br>• Seniors<br>• Nursing Home Residents<br>• Social Development Clients<br>• Individuals in Licensed Residential Facilities<br>• Children in Care of the Minister Social Development and Children With Disabilities<br>• Multiple Sclerosis<br>• HIV/AIDS<br>• Cystic Fibrosis<br>• Organ Transplant Recipients<br>• Growth Hormone Deficiency |
| | New Brunswick Drug Plan |

| Jurisdiction | Plan/Program Code-Description |
|---|---|
| | Medical Abortion Program |
| | Extra-Mural Program |
| | Tuberculosis Drug Plan |
| | Pharmacy Administered Publicly Funded Vaccines, Testing and Drug Therapies Program |
| **Newfoundland and Labrador** | Foundation Plan |
| | 65 Plus Plan |
| | Access Plan |
| | Select Needs/Cystic Fibrosis Plan |
| | Select Needs/Growth Hormone Plan |
| | Assurance Plan |
| | Pandemic Plan |
| **Nova Scotia** | Department of Community Services Programs |
| | Diabetes Assistance Program |
| | Drug Assistance for Cancer patients |
| | Family Pharmacare Program |
| | Palliative Care Drug Program |
| | Seniors' Pharmacare Program |
| | Under 65 – Long-Term Care Pharmacare Plan |
| **Ontario** | Ministry of Children, Community and Social Services |
| | MOHLTC Ontario Drug Benefit Program |
| **Prince Edward Island** | Catastrophic Drug Program |
| | Children-In-Care Drug Program |
| | Diabetes Drug Program |
| | Family Health Benefit Drug Program |
| | Financial Assistance Drug Program |
| | Generic Drug Program |
| | High Cost Drugs Program |
| | Immunization Program |
| | Nursing Home Drug Program |
| | Opioid Replacement Therapy Drug Program |
| | Seniors' Drug Program |
| | Sexually Transmitted Diseases Drug Program |
| | Smoking Cessation Program |
| **Saskatchewan** | Universal Program |

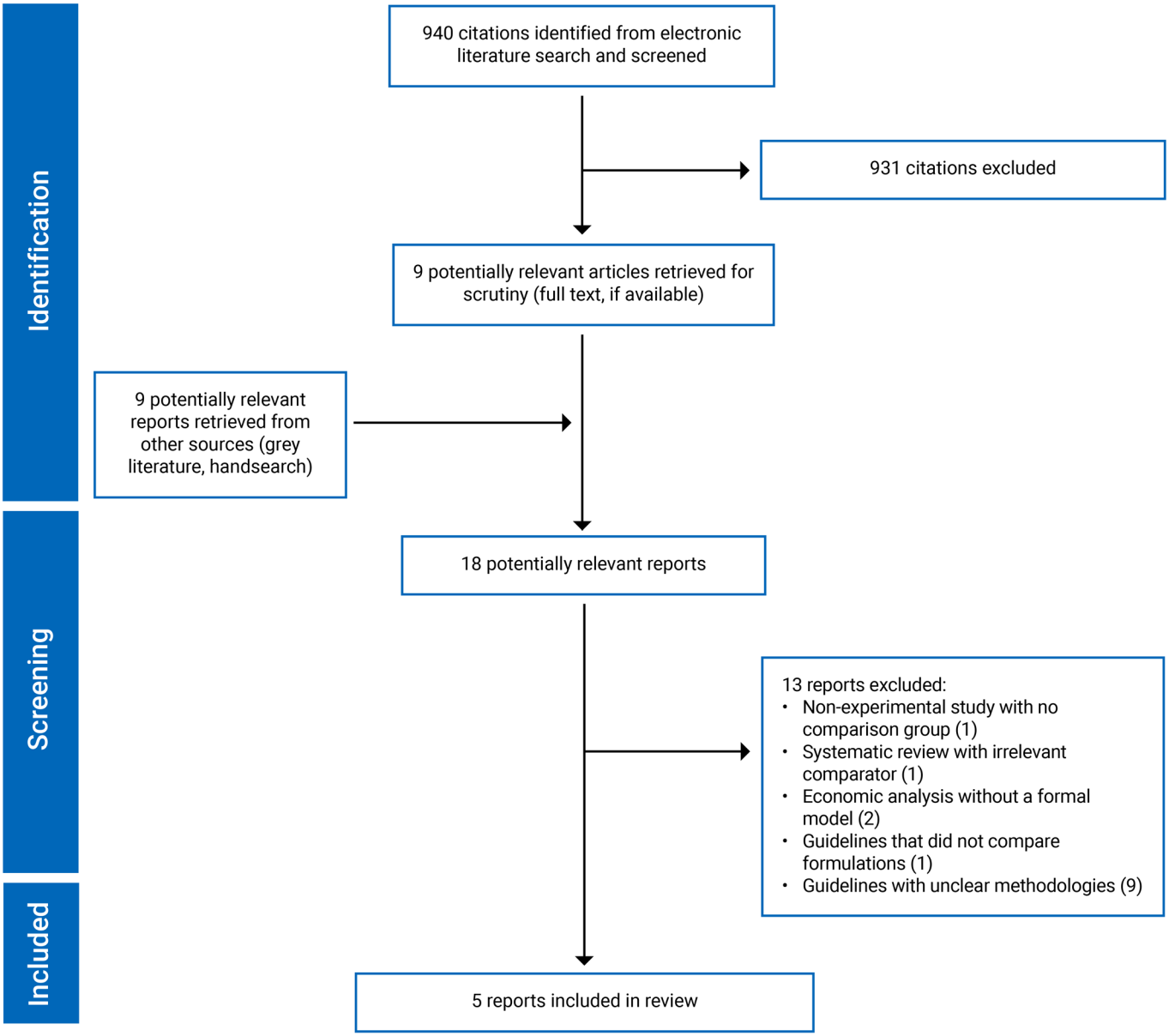
| Jurisdiction | Plan/Program Code-Description |
|---|---|
| | Non-Adjudicated (Drug Information System) |
| **Yukon** | Chronic Disease Program |
| | Children's Drug and Optical Plan |
| | Pharmacare |

MOHLTC = Ministry of Health and Long-Term Care.

Note: For more information about NPDUIS, refer to this report.

# Appendix 3: Selection of Included Studies

## Figure 4: Selection of Included Studies



# Appendix 4: Characteristics of Included Publications

## Table 4: Characteristics of Included Primary Clinical Studies

| Study citation, country, funding source | Study design | Population characteristics | Intervention and comparator(s) | Clinical outcomes, length of follow-up |
|---|---|---|---|---|
| **Randomized Controlled Trials** | | | | |
| Lee et al. (2021)[12]<br>United States<br>**Funding sources:** National Institute on Drug Abuse, New York University | **Study design:** Randomized (1:1), open-label effectiveness study<br>**Setting:** Two jail facilities in the US<br>**Objective:** Compare retention on treatment between SLB and XRB | Incarcerated adults aged over 18 years, diagnosed with OUD, incarcerated with a known release date, currently on sublingual BUP-NAL, no serious psychiatric illnesses, able to understand English<br>**Number of Patients:** 52 (26 in intervention group, 26 in the comparator group)<br>**Mean age (SD):** 43.1 (9.2) in the intervention group; 42.3 (10.8) in the comparator group<br>**Sex:** 23 (88%) male in the intervention group; 22 (85%) male in the comparator group | **Intervention:** XRB<br>**Comparator:** SLB tablets with naloxone | **Outcomes:** Buprenorphine treatment retention<br>**Follow-up:** 8 weeks |
| Lintzeris et al. (2021)[11]<br>Australia<br>**Funding sources:** Camurus AB | **Study design:** Randomized (1:1), open-label effectiveness study<br>**Setting:** 6 outpatient clinics in Australia<br>**Objective:** Compare patient satisfaction between SLB and XRB | Adults aged over 18 years, diagnosed with OUD, receiving SLB<br>**Number of Patients:** 119 (60 in intervention group, 59 in the comparator group)<br>**Mean age (SD):** 43.6 (10.4) in the intervention group; 45.3 (10.6) in the comparator group<br>**Sex:** 34 (56.7%) male in the intervention group; 36 (61%) male in the comparator group | **Intervention:** XRB<br>**Comparator:** SLB tablets or film, with or without naloxone[a] | **Outcomes:** Treatment satisfaction, quality of life, health outcomes, opioid use, retention in treatment, safety<br>**Follow-up:** 24 weeks |
| **Nonrandomized Studies** | | | | |
| Morgan et al. (2021)[13]<br>United States<br>**Funding Sources:**<br>National Institutes of Health | **Study design:** Retrospective cohort study of administrative data<br>**Setting:** Commercially insured individuals | Commercially insured individuals and their dependents[b]<br>**Number of Patients:** 14,358 (204 on XRB, 12,171 on SLB)<br>**Age:** 76 (37%) under 30 in the intervention | **Intervention:** XRB<br>**Comparator:** SLB tablets or film, with or without naloxone | **Outcomes:** Medication discontinuation (gap of more than 14 days)<br>**Follow-up:** Up to 300 days |

| Study citation, country, funding source | Study design | Population characteristics | Intervention and comparator(s) | Clinical outcomes, length of follow-up |
|---|---|---|---|---|
| | **Objective:** Compare discontinuation between XRB, SLB, naltrexone, and methadone | group; 3924 (32%) under 30 in the comparator group<br>**Sex:** 128 (63%) male in the intervention group; 7,802 (64%) male in the comparator group | | |
| Lee et al. (2023)[14]<br>Canada<br>**Funding Sources:**<br>Indivior UK Ltd. | **Study design:** Retrospective cohort study<br>**Setting:** Nine clinics in British Columbia and Ontario<br>**Objective:** Compare nonfatal overdose rates between XRB, SLB, and methadone | Adults aged over 18 years, diagnosed with moderate to severe OUD, initiated on one of the three treatments on or after March 11, 2020<br>**Number of Patients:** 379 individuals (128 initiated on XRB, 139 on SLB, 112 other treatments)<br>**Mean age (SD):** 39.9 (10.3) in the intervention group; 39.4 (11.0) in the comparator group<br>**Sex:** 80 (62.5%) male in the intervention group; 36 (66.2%) male in the comparator group | **Intervention:** XRB<br>**Comparator:** SLB tablets with naloxone | **Outcomes:** Nonfatal overdose, opioid use (combined urine screening and patient-reported use)<br>**Follow-up:** 6 months |

XRB = Extended-release buprenorphine; SLB = sublingual buprenorphine; OUD = Opioid use disorder

Note: This table has not been copy-edited.

[a]The formulations of buprenorphine included both tablets and film, both with and without naloxone; most received film with naloxone.

[b]A diagnosis of OUD was required for one drug (naltrexone), but not for any buprenorphine formulations.

## Table 5: Characteristics of the Included Economic Evaluation

| Study citation country, funding source | Type of analysis, time horizon, perspective | Population characteristics | Intervention and comparator(s) | Approach | Source of clinical, cost, and utility data used in analysis | Main assumptions |
|---|---|---|---|---|---|---|
| Flam-Ross et al. (2023)[15]<br>US<br>**Funding source:** National Institute of Drug Abuse | **Analysis:** Cost-utility analysis<br>**Time horizon:** Lifetime<br>**Perspective:** Health care system | 100,000 simulated patients, 58% male, average age 48 years | **Intervention:** XRB<br>**Comparator:** SLB[a] | Cohort-level state transition model based on Massachusetts | Existing studies, Federal Supply Schedule | Patients could transition between use and non-use of opioids and treatment |

XRB = Extended-release buprenorphine; SLB = sublingual buprenorphine

Note: This table has not been copy-edited.

[a]The study report is not explicit about the breakdown between tablets and film, or whether formulations without naloxone were included in this group

# Appendix 5: Critical Appraisal of Included Publications

Note that this appendix has not been copy-edited.

## Table 6: Strengths and Limitations of Clinical Studies Using the Downs and Black Checklist[8]

| Strengths | Limitations |
|---|---|
| **Lee et al. (2021)[12] RCT** | |
| **Reporting**<br>• Objectives, main outcomes, patient characteristics, interventions, potential confounders, findings, estimates of random variability, and adverse events all clearly reported<br>**Internal validity (bias)**<br>• Time period between intervention and collection was the same for both groups, and the outcomes used were likely valid and reliable<br>**Internal validity (confounding)**<br>• Study participants were drawn from the same population, over the same period of time<br>• Participants were randomized to intervention and comparator groups | **Reporting**<br>• Characteristics of patients lost to follow-up not described, and no p-values were reported<br>• Loss to follow-up was 22.3% for the intervention group and 43.1% in the comparator group<br>**External validity**<br>• Study populations may not be representative of that in the target population<br>  ◦ Study populations only included two correctional facilities in one US State<br>**Internal validity (bias)**<br>• The intervention was not blinded for either participants or those measuring outcomes<br>• No statistical tests were conducted for any of the differences in effectiveness outcomes<br>Internal validity (confounding)<br>• There was no adjustment for confounding in the analyses<br>**Power**<br>• No formal power calculation was conducted |
| **Lintzeris et al. (2021)[11] RCT** | |
| **Reporting**<br>• Objectives, main outcomes, patient characteristics, interventions, potential confounders, findings, estimates of random variability, and adverse events were all clearly reported<br>• Actual p-values were reported for main outcomes<br>**Internal validity (bias)**<br>• Time period between intervention and collection was the same for both groups, the outcomes used were likely valid and reliable, and statistical tests were used for most comparisons<br>**Internal validity (confounding)**<br>• Study participants were drawn from the same population, over the same period of time, and were randomized to intervention and comparator groups<br>**Power**<br>• A formal power calculation was reported | **Reporting**<br>• Characteristics of patients lost to follow-up not described<br>**External validity**<br>• Study populations may not be representative of that in the target population<br>  ◦ Study populations only included six clinics in Australia<br>  ◦ Unclear how representative these clinics are of the broader community of services<br>• Not clear how representative patients were of the broader population being studied<br>**Internal validity (bias)**<br>• The intervention was not blinded for either participants or those measuring outcomes |

| Strengths | Limitations |
|---|---|
| **Lee et al. (2023)[14] Cohort Study** | |
| **Reporting**<br>• Objectives, main outcomes, patient characteristics, interventions, potential confounders, findings, estimates of random variability, and adverse events were all clearly reported<br>• p-values were reported for some of the key outcomes<br>**Internal validity (bias)**<br>• Time period between intervention and collection was the same for both groups, and statistical tests were used for most comparisons<br>**Internal validity (confounding)**<br>• Study participants were drawn from the same population, over the same period of time | **Reporting**<br>• Characteristics of patients lost to follow-up not described<br>• p-values were not reported for differences in opioid use over the follow-up period<br>**External validity**<br>• Study populations may not be representative of that in the population<br>  ◦ Study populations only included nine clinics in Canada, so it is unclear how representative these clinics are of the broader community of services<br>• Not clear how representative patients were of the broader population being studied<br>**Internal validity (bias)**<br>• The intervention was not blinded for either participants or those measuring outcomes<br>**Internal validity (confounding)**<br>• Patients and clinicians could choose the treatment, which may have led to unobserved differences between the groups<br>**Power**<br>• A formal power calculation was not reported |
| **Morgan et al. (2021)[13] Cohort Study** | |
| **Reporting**<br>• Objectives, main outcomes, patient characteristics, interventions, potential confounders, findings, estimates of random variability were all clearly reported<br>• Actual p-values were reported for some of the key outcomes<br>**Internal validity (bias)**<br>• Time period between intervention and collection was the same for both groups, and statistical tests were used for some comparisons<br>**Internal validity (confounding)**<br>• Study participants were drawn from the same population, over the same period of time | **Reporting**<br>• The number or characteristics of patients lost to follow-up not described<br>• p-values were not reported for any pairwise comparisons of treatment discontinuation<br>• No reporting of adverse events was included<br>**External validity**<br>• Study populations may not be representative of that in the target population<br>  ◦ Study populations only included individuals with commercial insurance, who are likely healthier and wealthier on average<br>**Internal validity (bias)**<br>• The intervention was not blinded for either participants or those measuring outcomes<br>**Internal validity (confounding)**<br>• Patients and clinicians could choose the treatment, which may have led to unobserved differences between the groups<br>• Baseline differences were present between the groups, particular on age and use of other illicit drugs<br>**Power**<br>• A formal power calculation was not reported |

RCT = randomized controlled trial

## Table 7: Strengths and Limitations of the Economic Evaluation Using the Drummond Checklist[9]

| Strengths | Limitations |
|---|---|
| **Flam-Ross et al. (2023)[15]** | |
| **Study Design**<br>• The research question, importance, viewpoints, alternatives, and form of economic analysis are all clearly stated<br>**Data Collection**<br>• Most sources of data are well-described, outcomes are identified, and methods for quantities, estimation, price, and the model are reported<br>**Analysis and Interpretation**<br>• Model assumptions are clearly stated, including the discount rate, approach to sensitivity analysis, and range of variables<br>• Several sensitivity analyses were conducted, including on key parameters of interest (e.g., treatment retention, price of medication)<br>• Reporting and interpretation are consistent with the data that is presented | **Data Collection**<br>• The source of costing data for non-drug expenses is not well-described, nor is information on the derivation of QALY values for different health states<br>• Data were largely collected from one US State, so it is not clear how they would extrapolate to other jurisdictions<br>• Retention values appear to be derived from one study of a commercially-insured population<br>**Analysis and Interpretation**<br>• The choice of discount rate (3%) is not justified |

QALY = quality-adjusted life-year

# Appendix 6: Main Study Findings

Note that this appendix has not been copy-edited.

## Table 8: Retention in Treatment

| BUP formulation | Lee et al., 2021[12] RCT | | Lee et al. 2023[14] Cohort | | Morgan et al. 2021[13] Cohort | |
|---|---|---|---|---|---|---|
| | Percentage (95% CI) | Relative risk (95% CI) | Percentage | Difference (95% CI) | Days | Difference (95% CI) |
| — | Retention at 8 weeks | | Retention at 6 months on any OAT treatment | | Median time to discontinuation of treatment[a] | |
| XRB | 69.2% (50% to 84%) | NR | 86.7% | NR | 47 (IQR: 28 to 73) | NR[b] |
| SLB | 34.6% (19% to 54%) | | 71.9% | | 71 (IQR 36 to 122) | |

BUP = buprenorphine; RCT = randomized controlled trial; CI = confidence interval; NA = not applicable; NR = not reported; SLB = sublingual buprenorphine; XRB = extended-release buprenorphine

[a]Discontinuation was defined as a gap of 14 days or more from the end of one prescription to the start of the next

[b]The authors report a Wilcoxon rank test of homogeneity that was statistically significant, but it referred to differences between all 4 groups, not just the 2 groups that were given different formulations of buprenorphine

## Table 9: Opioid Use

| BUP formulation | Lee et al., 2021[12] RCT | | Lintzeris et al. 2021[11] RCT | |
|---|---|---|---|---|
| | Percentage (95% CI) | Difference | Outcome | Difference |
| **Opioid-negative Urine Tests (%)** | | | | |
| XRB | 55.4% (47 to 64)[b] | NR | 69.9% (60.6% to 79.3%)[c] | NR |
| SLB[a] | 38.5% (30 to 47)[b] | | 73.5% (64.1% to 82.9%)[c] | |
| **Opioid-Related Behaviours in Treatment (ORBIT) Scale** | | | | |
| XRB | — | — | 0.8 | 1.0 (−0.2 to 2.2), P = 0.12 |
| SLB | — | | 1.2 | |
| **Substance Use Recovery Evaluator (SURE) Scale** | | | | |
| XRB | — | — | 53.0 | −1.7 (−5.2 to 1.7), P = 0.30 |
| SLB | — | | 54.2 | |

BUP = buprenorphine; RCT = randomized controlled trial; CI = confidence interval; NA = not applicable; NR = not reported; SLB = sublingual buprenorphine; XRB = extended-release buprenorphine; NA = not applicable; NR = not reported

[a]The Lee et al. study included just SLB tablets with naloxone, whereas the Lintzeris et al. study included SLB tablets and film, both with and without naloxone

[b]Note that tests with missing information (22.3% in the XRB group and 43.1% in the SLB group) were assumed to be positive in this calculation

[c]This was a combined measure based on both urine testing and self-report

## Table 10: Reincarceration

| BUP formulation | Lee et al., 2021[12] RCT | |
|---|---|---|
| | Percentage (95% CI) | Difference |
| **Percentage Reincarcerated** | | |
| XRB | 8% (2% to 24%) | NR |
| SLB | 15% (6% to 34%) | |

BUP = buprenorphine; CI = confidence interval; SLB = sublingual buprenorphine; RCT = randomized controlled trial; XRB = extended-release buprenorphine; NR = not reported

## Table 11: Nonfatal Overdose

| BUP formulation | Lee et al., 2023 Cohort Study[14] | |
|---|---|---|
| | > = 1 Nonfatal Overdose | Risk-adjusted Difference (95% CI) |
| **Nonfatal Overdose[a]** | | |
| XRB | 1.6% | 6.51% (1.46 to 11.56), P = 0.0115 |
| SLB | 5.8% | |

BUP = buprenorphine; CI = confidence interval; SLB = sublingual buprenorphine; XRB = extended-release buprenorphine

[a]Only the results for the comparison between XRB and SLB are included in the data table

## Table 12: Patient Satisfaction

| BUP formulation | Lintzeris et al., 2021[11] RCT | |
|---|---|---|
| | Score | Difference (95% CI) |
| **Treatment Satisfaction Questionnaire for Medication (TQSM) Global Satisfaction** | | |
| XRB | 82.4 | 8.6 (3.3 to 13.9), P = 0.002 |
| SLB | 73.8 | |
| **TQSM Effectiveness** | | |
| XRB | 80.0 | 5.4 (−0.2 to 10.9), P = 0.06 |
| SLB | 74.6 | |
| **TQSM Convenience** | | |
| XRB | 87.4 | 17.8 (13.0 to 22.6), P < 0.001 |
| SLB | 69.6 | |
| **TQSM Side Effects** | | |
| XRB | 87.5 | −0.3 (−6.2 to 5.6), P = 0.91 |
| SLB | 88.2 | |
| **Patient Global Impression of Improvement (PS-VAS)** | | |
| XRB | 83.9 | 7.9 (1.5 to 14.3), P = 0.02 |

| BUP formulation | Lintzeris et al., 2021[11] RCT | |
|---|---|---|
| | Score | Difference (95% CI) |
| SLB | 76.0 | |
| **Treatment Burden Questionnaire (TBQ)** | | |
| XRB | 13.4 | 9.9 (5.7 to 14.2), P < 0.001 |
| SLB | 28.3 | |

BUP = buprenorphine; CI = confidence interval; RCT = randomized controlled trial; SLB = sublingual buprenorphine; XRB = extended-release buprenorphine

[a]Note that tests with missing information (22.3% in the intervention group and 43.1% in the comparator group) were assumed to be positive in this calculation

## Table 13: Summary of Findings of Included Economic Evaluation

| Main study findings | Authors' conclusion |
|---|---|
| **Flam-Ross et al. (2023)[15]** | |
| XRB vs. SLB resulted in<br>• fewer remaining undiscounted life-years per person (27.44 vs 27.39 life-years)<br>• a decrease of 0.03 QALYs<br>• discounted lifetime costs per person ($308 700 vs $304 700)<br>"The treatment with extended-release buprenorphine strategy was therefore dominated." | "In this economic evaluation of extended-release buprenorphine compared with transmucosal buprenorphine for patients with OUD, we found that extended-release buprenorphine was not a cost-effective treatment option when transmucosal buprenorphine was available" |

XRB = extended-release buprenorphine; SLB = sublingual buprenorphine; QALY = quality-adjusted life-year; OUD = opioid use disorder

# Appendix 7: Data From Jurisdictions

## Table 14: NPDUIS Utilization Data (2018 to 2020)

| Province | 2018 Q2 | 2018 Q3 | 2018 Q4 | 2019 Q1 | 2019 Q2 | 2019 Q3 | 2019 Q4 | 2020 Q1 | 2020 Q2 | 2020 Q3 | 2020 Q4 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **BUP depot** | | | | | | | | | | | |
| AB | – | – | – | – | – | – | – | – | – | – | – |
| BC | – | – | – | – | – | – | – | 6 | 108 | 320 | 348 |
| MB | – | – | – | – | – | – | – | – | 11 | 37 | 49 |
| NB | – | – | – | – | – | – | – | – | – | – | 11 |
| NL | – | – | – | – | – | – | – | – | – | – | 12 |
| NS | – | – | – | – | – | – | – | – | – | 12 | 33 |
| ON | – | – | – | – | – | – | – | – | 166 | 427 | 435 |
| PEI | – | – | – | – | – | – | – | – | – | – | – |
| SK | – | – | – | – | – | – | – | – | 6 | 15 | 57 |
| **BUP-NAL film** | | | | | | | | | | | |
| BC | – | – | – | – | – | – | – | – | – | – | – |
| MB | – | – | – | – | – | – | – | – | – | – | – |
| NL | – | – | – | – | – | – | – | – | – | – | – |
| NS | – | – | – | – | – | – | – | – | – | – | – |
| SK | – | – | – | – | – | – | – | – | – | – | – |
| **BUP-NAL tablet** | | | | | | | | | | | |
| AB | 323 | 493 | 533 | 541 | 748 | 880 | 979 | 903 | 826 | 878 | 912 |
| BC | 6,694 | 10,695 | 10,544 | 11,215 | 15,084 | 15,374 | 15,107 | 13,704 | 10,731 | 10,755 | 10,931 |
| MB | 479 | 775 | 950 | 1,055 | 1,454 | 1,958 | 1,960 | 1,558 | 1,579 | 1,642 | 1,656 |

| Province | 2018 Q2 | 2018 Q3 | 2018 Q4 | 2019 Q1 | 2019 Q2 | 2019 Q3 | 2019 Q4 | 2020 Q1 | 2020 Q2 | 2020 Q3 | 2020 Q4 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| NB | 252 | 383 | 468 | 555 | 764 | 1,079 | 1,399 | 1,033 | 852 | 875 | 882 |
| NL | 368 | 564 | 749 | 771 | 1,223 | 1,528 | 2,071 | 1,156 | 1,197 | 1,211 | 1,222 |
| NS | 484 | 729 | 861 | 978 | 1,438 | 1,842 | 2,351 | 1,597 | 1,303 | 1,208 | 1,240 |
| ON | 10,882 | 15,570 | 16,812 | 17,081 | 25,765 | 23,039 | 26,061 | 18,023 | 16,576 | 16,255 | 15,721 |
| PEI | 149 | 221 | 232 | 296 | 467 | 620 | 696 | 380 | 372 | 404 | 444 |
| SK | 513 | 728 | 866 | 1,046 | 1,501 | 1,909 | 2,444 | 2,206 | 1,852 | 2,042 | 2,159 |
| YT | — | — | — | — | — | — | — | — | — | — | — |

AB = Alberta; BC = British Columbia; BUP = buprenorphine; MB = Manitoba; NAL = naloxone; NB = New Brunswick; NL = Newfoundland and Labrador; NS = Nova Scotia; ON = Ontario; PEI = Prince Edward Island; SK = Saskatchewan; YT = Yukon Territory

Note: This table has not been copy-edited.

## Table 15: NPDUIS Utilization Data (2021 to 2023)

| Province | 2021 Q1 | 2021 Q2 | 2021 Q3 | 2021 Q4 | 2022 Q1 | 2022 Q2 | 2022 Q3 | 2022 Q4 | 2023 Q1 |
|---|---|---|---|---|---|---|---|---|---|
| **BUP depot** | | | | | | | | | |
| AB | – | 6 | 9 | 23 | 19 | 30 | 42 | 48 | 51 |
| BC | 484 | 744 | 951 | 1,155 | 1,312 | 1,552 | 1,666 | 1,831 | 2,093 |
| MB | 71 | 143 | 163 | 202 | 271 | 290 | 366 | 341 | 378 |
| NB | 20 | 40 | 62 | 68 | 107 | 132 | 129 | 144 | 190 |
| NL | 18 | 38 | 41 | 39 | 39 | 49 | 56 | 51 | 52 |
| NS | 53 | 71 | 77 | 88 | 111 | 137 | 169 | 171 | 199 |
| ON | 581 | 904 | 1,066 | 1,345 | 1,582 | 1,730 | 1,789 | 1,845 | 2,164 |
| PEI | – | – | – | 6 | 18 | 27 | 31 | 34 | 45 |
| SK | 63 | 114 | 139 | 168 | 194 | 245 | 245 | 278 | 327 |
| **BUP-NAL film** | | | | | | | | | |
| BC | 6 | 36 | 35 | 33 | 57 | 47 | 49 | 50 | 48 |
| MB | – | – | – | 5 | 24 | 59 | 57 | 79 | 68 |
| NL | – | – | – | 34 | 64 | 80 | 106 | 161 | 195 |
| NS | – | – | – | | 55 | 83 | 103 | 120 | 135 |
| SK | – | – | – | 19 | 29 | 48 | 49 | 64 | 74 |
| **BUP-NAL tablet** | | | | | | | | | |
| AB | 926 | 943 | 986 | 984 | 1,021 | 1,085 | 1,110 | 1,158 | 1,055 |
| BC | 10,955 | 10,950 | 11,068 | 11,156 | 10,988 | 11,568 | 12,735 | 12,981 | 12,533 |
| MB | 1,783 | 1,977 | 1,955 | 2,001 | 2,139 | 2,275 | 2,549 | 2,726 | 2,712 |
| NB | 853 | 876 | 855 | 871 | 1,008 | 1,006 | 978 | 1,115 | 1,091 |
| NL | 1,256 | 1,343 | 1,380 | 1,329 | 1,698 | 1,626 | 1,591 | 1,970 | 1,668 |

| Province | 2021 Q1 | 2021 Q2 | 2021 Q3 | 2021 Q4 | 2022 Q1 | 2022 Q2 | 2022 Q3 | 2022 Q4 | 2023 Q1 |
|---|---|---|---|---|---|---|---|---|---|
| NS | 1,241 | 1,168 | 1,193 | 1,156 | 1,389 | 1,198 | 1,285 | 1,576 | 1,436 |
| ON | 16,016 | 15,857 | 15,365 | 15,307 | 15,238 | 16,108 | 17,337 | 17,346 | 17,502 |
| PEI | 422 | 398 | 389 | 409 | 424 | 517 | 595 | 654 | 547 |
| SK | 2,220 | 2,380 | 2,437 | 2,562 | 2,604 | 2,841 | 2,621 | 2,839 | 2,979 |
| YT | — | — | — | — | 6 | 5 | — | — | — |

AB = Alberta; BC = British Columbia; BUP = buprenorphine; MB = Manitoba; NAL = naloxone; NB = New Brunswick; NL = Newfoundland and Labrador; NS = Nova Scotia; ON = Ontario; PEI = Prince Edward Island; SK = Saskatchewan; YT = Yukon Territory

Note: This table has not been copy-edited.

# Appendix 8: References of Potential Interest

Note that this appendix has not been copy-edited.

## Previous CADTH Reports

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