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SUMMARY WITH CRITICAL APPRAISAL

Buprenorphine for Opioid Use Disorder: A Review of Comparative Clinical Effectiveness, Safety, Cost-Effectiveness, and Guidelines

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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Abbreviations

AGREE II	Appraisal of Guidelines for Research & Evaluation 2
AMSTAR II	A Measurement Tool to Assess Systematic Reviews 2
BUP-NAL	the combination product of buprenorphine with naloxone, as a single preparation
COWS	Clinical Opiate Withdrawal Scale
CRISM	Canadian Research Initiative in Substance Misuse
DSM	Diagnostic and Statistical Manual of Mental Disorders
GRADE	Grading of Recommendations Assessment, Development and Evaluation
ICER	incremental cost-effectiveness ratio
OOWS	Objective Opiate Withdrawal Scale
OUD	opioid use disorder
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QALY	quality-adjusted life years
RCT	randomized controlled trial
SOWS	Subjective Opiate Withdrawal Scale
VA/DoD	Veterans Affairs/Department of Defense

Context and Policy Issues

The *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition* (DSM-V), describes opioid use disorder (OUD) as "a problematic pattern of opioid use leading to clinically significant impairment or distress […]"[1] that is diagnosed, and graded for severity, in the presence of various criteria.[1] Prior to the transition from the fourth to the fifth edition of the manual in 2013, "opioid dependence" and "opioid abuse" were considered separately.[2]. Opioid dependence was described as "[…] compulsive, prolonged self-administration of opioid substances that are used for no legitimate medical purpose or, if a general medical condition is present that requires opioid treatment, that are used in doses that are greatly in excess of the amount needed for pain relief".[2] Whereas the opioid abuse definition was nuanced by describing that "Persons who abuse opioids typically use these substances much less often than do those with dependence and do not develop significant tolerance or withdrawal".[2]

OUD may involve the use of illicitly manufactured opioids or prescription opioids that are obtained illicitly or used non-medically.[3] In 2017, the prevalence of opioid use disorder was estimated to be 1.01% in the Canadian population.[4] Young Canadians are disproportionately affected, causing premature morbidity and mortality, with 51,139.2 years of life lost in 2017.[5] Furthermore, based on 2014 data, males seem unequally burdened with a 1.6-fold prevalence and a death rate 2.3 times that of females.[6]

The clinical management of OUD depends on the desired treatment intensity, ranging from withdrawal management in low intensity cases, agonist therapies, and specialist-led alternative approaches in higher intensity cases.[3] Across this spectrum, the goal of therapy is to reduce or prevent opioid use and related harms.[3] Pharmacotherapy, in the form of opioid substitution therapy (such as with buprenorphine or methadone), is commonly used since these agents work to relieve opioid withdrawal symptoms and reduce cravings.[7] Buprenorphine is unique in that it offers several formulation choices and flexible administration options when compared with methadone. Its pharmacology is also different since it tightly binds to, and partially agonizes, the mu-opioid receptors in the central nervous system and elsewhere in the body.[7]

In Canada, several formulations of buprenorphine are available for the treatment of OUD, including the single ingredient buccal film, buprenorphine extended-release injection,

subcutaneous implant, as well as the combination product of buprenorphine with naloxone (BUP-NAL) in a sublingual tablet.[8] The presence of naloxone in this latter formulation is to deter the misuse of the drug through crushing and injecting, since the naloxone component would cause opioid withdrawal symptoms.[7] Depending on the formulation, treatment may start with an induction phase, where a low initial dose is given to determine tolerability and gradually increased over a short period to a target dose for the maintenance phase.[9]

CADTH has previously reviewed the evidence for the use of buprenorphine formulations for the treatment of OUDs.[10-12] One report was limited to pregnant populations,[11] another was a qualitative review of patient preferences and perspectives,[10] and the third was a summary of abstracts based on evidence available in 2017.[12] The objective of the current report is to evaluate the comparative clinical effectiveness, safety, cost-effectiveness and evidence-based guidelines regarding various buprenorphine or BUP-NAL formulations for the treatment of OUD.

Research Questions

1. What is the comparative clinical effectiveness of various buprenorphine or buprenorphine-naloxone (BUP-NAL) formulations versus other buprenorphine formulations for the treatment of opioid use disorder (OUD)?
2. What is the clinical evidence regarding the safety of various buprenorphine or BUP-NAL formulations for the treatment of OUD?
3. What is the cost-effectiveness of various buprenorphine or BUP-NAL formulations for the treatment of OUD?
4. What are the evidence-based guidelines regarding the use of various buprenorphine or BUP-NAL formulations for the treatment of OUD?

Key Findings

Two relevant systematic reviews, three randomized controlled trials (in four publications), six non-randomized studies, and two economic evaluations were identified regarding the clinical effectiveness, safety, and cost-effectiveness of various buprenorphine formulations for the treatment of OUD.

Though there were some instances where specific formulations of buprenorphine demonstrated statistically significant improvements in outcomes of interest compared to other formulations, no clear patterns emerged regarding the comparative clinical effectiveness of buprenorphine for the treatment of OUD. The economic evaluation concluded that buprenorphine implant did not provide cost-effective benefit over generic sublingual buprenorphine-naloxone (BUP-NAL). The second economic evaluation reported that implantable buprenorphine was cost-effective compared to sublingual buprenorphine. It remains uncertain whether the findings of the reviewed literature are generalizable to the Canadian population as all of the included studies were conducted outside of Canada.

Two evidence-based guidelines were identified regarding the use of various buprenorphine formulations for the treatment of OUD. One guideline recommends BUP-NAL as a first-line therapy for individuals who require opioid agonist treatment (strong recommendation based on high quality evidence). The second guideline recommends offering either BUP-NAL or methadone, while considering patient preferences, for individuals with OUD (strong recommendation).

The limitations of the included studies, such as several with lack of blinding to treatment or few studies from Canadian settings, and of this report should be considered when interpreting the results.

Methods

Literature Search Methods

This report makes use of a literature search strategy developed for a previous CADTH report.[15] For the current report, a limited literature search was conducted on key resources including Medline via OVID, the Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, economic studies, and guidelines. The search was limited to English-language documents published between January 1, 2014 and March 20, 2019.

Selection Criteria and Methods

Two reviewers screened citations and selected studies. In the first level of screening, titles and abstracts were evaluated by one reviewer. Studies clearly not relevant to the topic of interest, as well as those that failed to meet one or more criteria, were rejected. Potentially relevant articles were retrieved. The final selection of full-text articles was conducted independently by two reviewers based on the inclusion criteria presented in Table 1. Disagreements were resolved through discussion to achieve consensus. Study characteristics from a set of studies were extracted by one reviewer, and a second reviewer extracted study characteristics from the remaining studies.

Table 1: Selection Criteria

Population	Patients with opioid use disorder (i.e., Opioid Use Disorder [DSM-V], Opioid Abuse [DSM-IV], Opioid Dependence [DSM-IV]), in all settings.
Intervention	Various formulations of buprenorphine (e.g., extended-release subcutaneous injection, sublingual, implant, transdermal, intramuscular) or buprenorphine-naloxone combinations
Comparator	Q1, Q3: Various formulations of buprenorphine (e.g., extended-release subcutaneous injection, sublingual, implant, transdermal, intramuscular) or buprenorphine-naloxone combinations Q2: No comparator; various formulations of buprenorphine (e.g., extended-release subcutaneous injection, sublingual, implant, transdermal, intramuscular) or buprenorphine-naloxone combinations Q4: No comparator necessary
Outcomes	Q1: Clinical effectiveness (e.g., reduction in opioid consumption, prevention of relapse, maintenance of abstinence, retention into treatment, adherence to medication, social functioning [e.g., return to school or work], emotional and psychological functioning [e.g., anxiety, depression, sleep]) Q2: Safety (e.g., reduction in misuse and diversion, reports or evidence of abuse, urine drug screening results, overdose, all-cause mortality) Q3: Cost-effectiveness per health benefit gained Q4: Guidelines on appropriate use of different formulations
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, economic evaluations, and evidence-based guidelines

DSM = Diagnostic and Statistical Manual of Mental Disorders.

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2014. Systematic reviews that had relevant included studies fully captured in other, more recent and comprehensive systematic reviews were excluded. Systematic reviews that had broader inclusion criteria than the present review were examined in detail to ascertain whether data could be extracted from a relevant sub-set of included studies, rather than excluding the systematic review entirely. If it was not possible to identify relevant primary studies upon detailed investigation the systematic review was excluded. Primary studies retrieved by the search were excluded if they were captured in one or more included systematic reviews. Studies focused primarily on the use of buprenorphine in pregnancy were excluded. Finally, guidelines with unclear methodology were also excluded.

Critical Appraisal of Individual Studies

The included systematic reviews and economic studies were critically appraised by one reviewer using AMSTAR II[16] and the Drummond checklist,[17] respectively. A second reviewer critically appraised clinical studies using the Downs and Black checklist[18] and guidelines with the AGREE II instrument.[19] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 781 citations were identified in the literature search. Following screening of titles and abstracts, 728 citations were excluded and 53 potentially relevant reports from the electronic search were retrieved for full-text review. In addition, 13 potentially relevant publications were retrieved from the grey literature search for full-text review. Of these 66 potentially relevant articles, 51 publications were excluded for various reasons, while 15 publications met the inclusion criteria and were included in this report. These comprised two systematic reviews,[20,21] three randomized controlled trials (RCTs) in four publications,[22-25] six non-randomized studies,[26-31] two economic evaluations (one of which was conducted within an included systematic review),[20,32] and two evidence-based guidelines.[13,14] Appendix 1 presents the PRISMA[33] flowchart of the study selection. Note that because both of the included systematic reviews had broader inclusion criteria than the present review (i.e., were wider in scope), only subsets of primary studies from the included systematic reviews that met the selection criteria for the present review are described. Additional references of potential interest are provided in Appendix 5.

Summary of Study Characteristics

Two systematic reviews,[20,21] three RCTs (in four publications),[22-25] six non-randomized studies,[26-31] two economic evaluations,[20,32] and two evidence-based guidelines[13,14] were identified and included in this review. No relevant health technology assessments or meta-analyses were identified. Detailed characteristics are available in Appendix 2, Table 2, Table 3, Table 4, and Table 5.

Study Design

The two included systematic reviews[20,21] had objectives and inclusion criteria that were broader than for the present report (i.e., wider in scope); only information from the subset of relevant studies is included here. Authors of one systematic review,[20] published in 2018, included literature searches for published and unpublished RCTs and non-randomized comparative studies up to September 25, 2018. The second review,[21] published in 2017 included RCTs and controlled clinical trials published before January, 2014. The first systematic review[20] included five relevant primary studies, and the review by Minozzi et al.[21] included one relevant RCT for a total of six unique primary studies (i.e., there was no primary study overlap between the included systematic reviews).

Ten primary study reports regarding the clinical effectiveness and safety of buprenorphine formulations for the treatment of OUD were identified. There were three RCTs in four publications: a randomized open-label study;[22] a prospective, randomized, multi-centre, blinded then open-label, parallel-group, active-control, noninferiority study,[24] a blinded, randomized, parallel-group, multi-centre, noninferiority study,[25] and a secondary analysis of this later study.[23] The six relevant non-randomized studies also utilized different methodologies: a retrospective cohort;[26] a multi-centre, open-label, prospective cohort;[28] a retrospective longitudinal study;[30] a retrospective cohort study,[29] and a prospective observational study.[31] The sixth study[27] was a multi-centre, open-label, uncontrolled, prospective cohort extension study.

The two economic evaluations[20,32] employed Markov models. The clinical inputs used in these models came from various systematic reviews or individual clinical studies, as selected by the authors. Cost inputs were informed by clinical studies, various databases, or were provided directly from drug manufacturers. One economic evaluation,[20] was conducted from the perspective of the United States health care sector using a five year time horizon (it also included a scenario analysis that took a modified societal perspective). The second economic evaluation[32] took a US societal perspective using a 12-month time horizon.

Two evidence-based guidelines were identified regarding the treatment of OUD that contained recommendations for the use of various buprenorphine or BUP-NAL formulations.[13,14] The first guideline, published in 2018 from the Canadian Research Initiative in Substance Misuse (CRISM), was based on two previous documents developed in British Columbia: "[…] the Vancouver Coastal Health/Providence Health Care Guideline for Clinical Management of Opioid Addiction released in November 2015, and the BC Centre on Substance Use/Ministry of Health Guideline for the Clinical Management of Opioid Use Disorder, released in February 2017".[13] They further updated the literature in 2016 and included meta-analyses of randomized clinical trials, clinical trials, observational reports, and expert opinion.[13] The second guideline, published in 2015, from the United States' Department of Veterans Affairs and the Department of Defense (VA/DoD) and is an update to their 2009 "Clinical Practice Guideline for the Management of Substance Use Disorders".[14] A systematic review was conducted to update the results from November 2007 onward, and included only systematic reviews or clinical studies (RCTs, prospective comparative studies).[14] They interpreted the results and carried forward recommendations from the previous guidelines modifying or adding as necessary. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool was used to evaluate the quality of evidence and strength of recommendations in both guidelines

(details in Table 5).[13,14] Recommendations were consensus-based and were developed with consideration of feedback from internal and external stakeholders and experts.[13,14]

Country of Origin

The included systematic reviews were by authors in the United States[20] and Italy.[21] Relevant primary studies included in the systematic reviews were conducted in the United States and published between 2008 and 2018.

The RCTs were conducted in the United Kingdom[22] and the United States.[23-25] The non-randomized studies were conducted in Australia,[26] the United States,[27-30] and Germany.[31]

The two economic evaluations were conducted in the United States. [20,32]

The guidelines were developed in Canada[13] and the United States.[14]

Patient Population

One systematic review[20] included studies that enrolled patients (≥ 16 years of age) with OUD in various treatment settings. The review by Minozzi et al.[21] examined adolescent patients (≤ 18 years of age) with opioid dependence. Neither systematic review excluded studies that included participants with co-morbid physical or psychological illness.

The four RCT reports focused on adults in different settings, such as: 36 participants with opioid dependency commencing buprenorphine maintenance in specialized clinical trials facilities and addictions treatment facilities;[22] 310 participants with opioid dependency in the past 12 months,[24] and similarly in 758 participants,[23,25]

The six non-randomized studies also focused on different populations and settings. Three studies evaluated all participants in large databases (i.e., 4,692 participants in a jurisdictional drug monitoring database,[26] 4,306 participants in a private insurance claims database,[29] and 495 eligible participant's electronic medical records[30]) and included all patients receiving treatment for opioid dependence.[26,29,30] Other studies were set in study centres (249 participants), or addiction medicine physician practice sites (384 participants).[31] The sixth study[27] included adult participants aged 18 to 65 years, with opioid dependence and having received buprenorphine-based opioid substitution therapy for at least 22 days.

The two economic evaluations[20,32] were conducted with patient populations in the United States. One study[20] assessed the cost-effectiveness of several drugs used for medication-assisted treatment among a cohort of patients who were considered for OUD treatment. The second study[32] analysed adults with OUD who were classified as clinically stabilized (i.e., those who achieved prolonged clinical stability on < 8 mg of daily transmucosal buprenorphine).

The target populations for the CRISM guidelines are adolescents, young adults, and adults with uncomplicated OUD and also included specific considerations for special populations.[13] The intended users are Canadian physicians, nursing and allied healthcare providers, medical educators, clinical care case managers, policymakers, healthcare administrators.[13] The VA/DoD guidelines apply to service members (18 years or older) and veterans with substance use disorder, and the intended users are VA/DoD health care providers, and others involved in the care of the target population [14]

Interventions and Comparators

In one systematic review[20] eligible medication interventions (i.e., buprenorphine subcutaneous extended-release injection, buprenorphine implant) were compared to other active treatments for patients with OUD (e.g., BUP-NAL in sublingual and buccal formulation). The Minozzi et al.[21] systematic review investigated the effectiveness of any opioid agonist treatment (including buprenorphine) alone or in conjunction with psychosocial interventions compared with no intervention, alternative opioid agonist treatments, other pharmacological interventions, any detoxification intervention, or psychosocial interventions alone.

One RCT evaluated buprenorphine oral lyophilisate wafers administered on the tongue compared to standard sublingual buprenorphine.[22] The three other studies evaluated BUP-NAL (rapid dissolving)[23,24] sublingual tablet[25] compared to either generic buprenorphine sublingual tablets,[24] or BUP-NAL sublingual film and generic buprenorphine sublingual tablets (for the induction phase).[23,25]

One non-randomized study evaluated buprenorphine compared to BUP-NAL.[26] Two studies did not have a comparator but evaluated BUP-NAL rapid dissolving sublingual tablet,[27] and BUP-NAL.[31] One study evaluated the conversion (i.e., switching patients from one formulation to another and where the dosages are not necessarily equal) from BUP-NAL sublingual tablet or film to BUP-NAL buccal film formulation.[28] Another,[30] compared sublingual buprenorphine to sublingual BUP-NAL and other opiate substitution therapies. The sixth study,[29] compared the BUP-NAL sublingual film formulation to the BUP-NAL sublingual tablet formulation.

One economic evaluation[20] compared the cost-effectiveness of several opioid substitution treatments (buprenorphine subcutaneous extended-release injection, naltrexone extended-release injectable suspension, buprenorphine implant) with generic sublingual BUP-NAL. The economic study by Carter et al. evaluated the cost-effectiveness of subdermal implantable buprenorphine compared to sublingual buprenorphine for the treatment of OUD, along with monthly psychosocial counselling in both groups.

The CRISM guidelines considered the following treatments for OUD: opioid agonists and antagonists, withdrawal management strategies, psychosocial interventions, and residential treatment.[13] The VA/DoD considered various OUD treatments, including pharmacological therapies, brief interventions, mutual help programs, psychotherapy, and psychosocial interventions.[14]

Outcomes

The outcomes considered in the SRs were illicit use of opioids,[20,21] opiate withdrawal symptoms[20] (e.g., COWS, SOWS), patient adherence and dropout (e.g., all-cause treatment discontinuation),[20,21] adverse events,[20] and mortality.[20]

In the RCTs, the outcomes of interest were opiate withdrawal symptoms[22-25] (e.g., COWS, SOWS, OOWS), patient adherence and dropout,[22,24,25] adverse events, [22-25] and mortality.[22,24]

The outcomes of interest in the non-randomized studies were illicit use of opioids,[30] health care utilization[26] (e.g. hospital or emergency department admissions), adverse events[27,28,31] (including anomalous liver function laboratory values [e.g., alkaline phosphatase, glutamic-

pyruvic transaminase, glutamate oxaloacetate transaminase, and gamma-glutamyl transpeptidase][27,28,31]), and mortality.[26-28,31]

In the economic evaluations, the outcome of interest was incremental cost per quality adjusted life-years gained.[20,32]

The three main symptom severity scales used for opiate withdrawal were: (1) the Clinical Opiate Withdrawal Scale (COWS), (2) the Objective Opiate Withdrawal Scale (OOWS), and (3) the Subjective Opiate Withdrawal Scale (SOWS). A brief description of these three scales is provided below.

(1) Clinical Opiate Withdrawal Scale (COWS; used in four studies[20,23-25]): A validated 11-item, clinician-administered tool used to reproducibly rate common signs and symptoms of opiate withdrawal.[34,35] Total scores range between 0 and 47, and withdrawal is classified as mild (5 to 12), moderate (13 to 24), moderately severe (25 to 36), or severe (>36).[34,35]

(2) Objective Opiate Withdrawal Scale (OOWS; used in one study[22]): A validated 13-item rating scale in which physically-observable symptoms (e.g., perspiration, tremor, vomiting, anxiety) are rated as present or absent.[36] Total scores range between 0 and 13. No clinically significant ranges or thresholds were mentioned in the identified literature.

(3) Subjective Opiate Withdrawal Scale (SOWS; used in five studies[20,22-25]): A validated 16-item symptom severity scale in which patients are asked to rate various opiate withdrawal symptoms on a scale of 0 (not at all) to 4 (extreme).[36] Total scores range between 0 and 64. No clinically significant ranges or thresholds were mentioned in the identified literature.

The outcomes of interest in the guidelines included OUD adherence with treatment, emergency department utilization, morbidity, mortality, overdoses, relapse, adverse events, cravings, substance consumption (e.g., alcohol, opioid), and quality of life.

Summary of Critical Appraisal

Additional details regarding the strengths and limitations of the included publications are provided in Appendix 3, Table 6, Table 7, Table 8, and Table 9.

Systematic Reviews

Strengths of both systematic reviews[20,21] included: clear objectives and inclusion criteria, report of key search terms and search strategies, provision of a list of included studies and summary of their characteristics, justification for eligible study designs, and detailed descriptions of the processes used for article selection, data extraction, and quality assessment. In addition, the Minozzi et al.[21] review included a list of excluded studies and reasons for exclusion. The authors of both systematic reviews[20,21] published detailed protocols containing their proposed methodologies prior to conducting the reviews. These strengths of reporting increase confidence in the findings and the reproducibility of the systematic reviews. In both reviews, multiple databases were used to identify relevant literature and various strategies to identify grey literature were performed by review authors, decreasing the risk of missing relevant, non-indexed studies. One systematic review[20] restricted the search to studies published in English and did not provide justification for this decision. Study selection and data extraction were performed individually by multiple

authors and any disagreements were resolved by group discussions in both systematic reviews.[20,21] The possibility of publication bias was discussed and investigated to the degree possible in both reviews,[20,21] and no evidence of publication bias was identified. The authors of both systematic reviews[20,21] disclosed their conflicts of interest and sources of funding, none of which were considered likely to have influenced the findings.

RCTs

There were several strengths common to all four RCT reports,[22-25] such as: clear descriptions of objectives, interventions, main outcomes, population characteristics, and eligibility criteria; participants appeared to be representative of the population of interest; and main outcome measures used were valid and reliable (e.g., COWS scores). Power calculations, and recruitment of adequate sample size, were performed in two studies,[24,25] and a description of the participant randomization process were provided. This contrasts with the two other studies,[22,23] where details on the methodology used to randomize were lacking and absence of allocation predictability could not be assessed. Three studies had the strength of being multi-centric.[23-25] Reported patients lost to follow-up or withdrawn were 16.7%,[22] 28.5%,[25] 30.9%,[23] and 35.8%,[24] but no associated patient characteristics were provided.[22-25] A further limitation present in all studies revolved around conflicts of interest. Strang et al.[22] reported conflicts of interest, including that key authors have patents on various novel naloxone formulations. The authors of Gunderson et al. 2016 and 2015 reported conflicts of interest, including that some authors have received funding from the manufacturer of their respective intervention.[23,25] Lastly, there was no disclosure of conflict of interest in one study, therefore possible conflicts of interest could not be assessed.[24]

Non-Randomized Studies

There were several strengths common to all six non-randomized studies,[26-31] such as: clear descriptions of objectives, interventions, main outcomes, population characteristics, eligibility criteria; participants appeared to be representative of the population of interest; and main outcome measures used were valid and reliable (e.g., COWS scores). All studies planned their data analyses at the outset,[26-31] and one study performed survival analyses for the primary outcomes to adjust for the different lengths of follow-up in the intervention and comparator groups.[26] None of the studies reported conducting an a priori power calculation.[26-31] Actual probability values (*P*-values) were not reported in three studies.[27,28,30] One study in particular,[27] suffered a 56.1% dropout rate mostly due to patients being lost to follow-up or patient nonadherence. A further limitation of some studies was that sources of funding were either not disclosed,[31] or disclosed,[27-29] included received funding from the manufacturer. Similarly, some study authors disclosed conflicts of interest which may have influenced the findings of the study,[27-29,31] including that some received funding from the manufacturer of their respective intervention.

Economic Evaluations

The research objectives, economic importance of the research question, time horizons, viewpoints of the analyses, and rationale for choosing interventions and comparators were clearly stated, in both economic evaluations. The five year time horizon used in one economic evaluation[20] was appropriate; however, the 12 month time horizon used in the Carter et al.[32] analysis may not be sufficiently long given that treatment for opioid use disorders often takes place over multiple years. The choice of form of economic evaluation was justified in both studies (four and five-state Markov models).

As for the methods of data collection, the sources of effectiveness estimates, transition probabilities, drug costs, and other relevant model inputs were included in both studies.[20,32] The primary outcome measures and methods to assign value to clinical benefits were described in detail. Both studies[20,32] provided details of currency and price adjustments for inflation. Although both studies stated the discount rates that were applied to their models, justification for selecting these rates was not provided. The Carter et al.[32] analysis made assumptions that may limit their findings: (1) both treatment cohorts received monthly psychosocial counselling if they were retained in treatment, and (2) the model did not consider the possibility of patients transitioning to an off treatment, not relapsed state (i.e., fully recovered). These assumptions, whilst simplifying the model, may not be truly accurate in reality, as treatment with monthly psychosocial counselling is likely to have some sort of dropout rate. Also, since the study did not examine the cost-effectiveness of the buprenorphine subdermal implant alone nor sublingual buprenorphine alone, but rather in combination with psychosocial counselling, the magnitude of effectiveness and the associated costs would both be anticipated to be different than with the intervention of interest alone. Additionally, the possibility of patients recovering from their condition, therefore no longer requiring opioid agonist maintenance treatment, should be considered.

The authors of the Carter et al.[32] economic evaluation disclosed conflicts of interest including former or current employment with manufacturers, and the study was funded by a manufacturer. The authors and expert reviewers of the second economic evaluation[20] reported no relevant conflicts of interest related to the analysis and disclosed sources of funding. The generalizability of these two economic evaluations[20,32] to the Canadian context is limited given they were conducted in the United States.

Evidence-Based Guidelines

In both guidelines[13,14] the scope and purpose were described. Developed in Canada, the CRISM guideline sought the views and preferences of the target population, provided an explicit link between the recommendations and the evidence, and indicated a procedure for updating the guideline in the future.[13] Overall, the methodology used to develop the guidelines were rigorous. Whereas only the VA/DoD guidelines employed systematic methods to search for evidence,[14] they both described thoroughness in selecting evidence, assessing quality of the evidence, and having the guideline document externally reviewed.[13,14] In both cases, the guideline development groups were comprised of experts and stakeholders who were required to declare conflicts of interest. [13,14] The recommendations were well presented and unambiguous and included information on the quality of the evidence and strength of the recommendations.[13,14] Neither guideline included discussion of facilitators or barriers to implementation, resource implications with respect to application, or monitoring and auditing criteria.[13,14] The views of the funding bodies did not appear to have influenced the content of the guidelines.[13,14] The generalizability of the VA/DoD guideline to the Canadian context is limited given that it was conducted for a specific target population and it was in the United States.[14]

Summary of Findings

A detailed summary of findings and recommendations is provided in Appendix 4, Table 10 and Table 13.

Clinical Effectiveness of Various Buprenorphine or Buprenorphine-Naloxone Formulations versus Other Buprenorphine Formulations for the Treatment of Opioid Use Disorder

Illicit Use of Opioids

Evidence regarding the comparative effectiveness of various buprenorphine formulations for reducing the illicit use of opioids was available from two systematic reviews[20,21] and one non-randomized study.[30] In general, the evidence regarding illicit use of opioids was inconsistent, with some comparisons suggesting that illicit opioid use was reduced in patients treated with buprenorphine, but others comparisons finding no difference between formulations.

One systematic review[20] included three primary studies that compared prevalence of urine samples testing negative for illicit opioids among participants treated with buprenorphine subcutaneous extended-release injection versus those treated with sublingual BUP-NAL. The findings indicated that participants treated with buprenorphine subcutaneous extended-release injection demonstrated significantly greater improvements in their illicit use of opioids at various time points (as assessed using urine samples) compared to individuals treated with sublingual BUP-NAL. The same systematic review[20] included two additional primary studies that compared buprenorphine implant and sublingual BUP-NAL with respect to prevalence of urine samples testing negative for illicit opioids. One primary study observed a significantly higher number of patients who had opioid-negative urine samples at week 24 in the buprenorphine implant group compared to patients treated with sublingual BUP-NAL. The second study did not observe a statistically significant between-group difference in the number of patients who tested negative for illicit use of opioids following treatment with buprenorphine implant and sublingual BUP-NAL.

The Minozzi et al.[21] systematic review included one primary study that compared BUP-NAL maintenance versus buprenorphine detoxification in adolescents with OUD. A significant difference between treatment strategies in promoting abstinence from illicit use of opioids, as detected with a urine test, was not observed; however, participants in the maintenance group had significantly lower rates of self-reported heroin use at 12-month follow-up.

The non-randomized study by Proctor et al.[30] did not observe significant differences in the number of patients with opioid-positive urine between participants treated with buprenorphine or BUP-NAL.

Measures of Opioid Withdrawal Symptoms

Information regarding the comparative effectiveness of various buprenorphine formulations for severity of opiate withdrawal symptoms was available from one systematic review[20] and four RCT reports.[22-25] Overall, the evidence regarding measures of opioid withdrawal symptoms was inconsistent, with some comparisons suggesting that BUP-NAL tended to improve opioid withdrawal, while others suggest no difference between formulations.

The systematic review[20] did not report any statistically significant differences between participants treated with buprenorphine subcutaneous extended-release injection and sublingual BUP-NAL with respect to opioid craving or COWS scores (one primary study). The systematic review[20] included one primary study that reported a significantly greater improvement in symptoms of opioid withdrawal (COWS and SOWS scores) in participants treated with sublingual BUP-NAL compared to those treated with buprenorphine implant.

One RCT[22] reported no significant between-group differences for symptoms of opiate withdrawal (OOWS and SOWS scores) in participants treated with buprenorphine oral lyophilisate wafer or sublingual buprenorphine. A second RCT[23] reported no significant differences in three measures of opiate withdrawal symptoms (COWS scores, SOWS

scores, and opioid craving scores) between patient groups treated with BUP-NAL rapid dissolving sublingual tablet and a BUP-NAL film formulation. Similarly, the Webster et al.[24] RCT did not observe a significant difference in participants treated with either BUP-NAL rapid dissolving sublingual tablet or generic buprenorphine with respect to opiate withdrawal symptom or craving scores. The fourth RCT report,[25] did not detect a statistically significant between-group difference in opioid withdrawal symptoms or opioid cravings in participants treated with either BUP-NAL or buprenorphine.

Health Care Utilization

Evidence regarding the comparative effectiveness of various buprenorphine formulations with respect to hospitalizations was available from two non-randomized studies.[26,29] In brief, the evidence regarding health care utilization was inconsistent among the various BUP-NAL formulations.

One non-randomized study[26] noted that participants treated with BUP-NAL were more likely to be admitted to the hospital ($P < 0.001$) and to the emergency department ($P < 0.001$) than participants treated with buprenorphine alone. The non-randomized study by Clay et al.[29] reported non-significant differences in pharmacy claims and outpatient visits between participants treated with BUP-NAL sublingual film or BUP-NAL sublingual tablet; however, participants treated with the film formulation of BUP-NAL were significantly less likely to have at least one hospitalization.

Patient Adherence and Dropout

Evidence regarding the comparative effectiveness of various buprenorphine formulations with respect to patient adherence and dropouts was available from two systematic reviews,[20,21] three RCTs,[22,24,25] and two non-randomized studies.[29,30] In general, evidence regarding patient adherence and dropout was inconsistent, with most comparisons suggesting no difference between formulations, while some comparisons favoured BUP-NAL formulations.

One systematic review[20] did not observe any significant differences in all-cause treatment discontinuation rates between those treated with buprenorphine subcutaneous extended-release injection and sublingual BUP-NAL. Similarly, no difference was observed in all-cause discontinuations between patients treated with either buprenorphine implant or sublingual BUP-NAL. The systematic review by Minozzi et al.[21] reported that adolescent patients who were treated with BUP-NAL maintenance were significantly less likely to drop out of treatment than those treated with buprenorphine detoxification.

One RCT[22] did not observe statistically significant differences in treatment retention rates between patients treated with buprenorphine oral lyophilisate wafer and standard sublingual buprenorphine. The RCT by Webster et al.[24] noted that participants treated with generic buprenorphine sublingual tablets were more likely to be retained in treatment after three days compared with those who received induction BUP-NAL rapid dissolving sublingual tablet. The third RCT[25] did not detected statistically significant differences in treatment retention rates between patients treated with either BUP-NAL sublingual tablet or BUP-NAL film.

One non-randomized study[29] reported significantly higher treatment persistence rates at six months in patients treated with a BUP-NAL sublingual tablet formulation compared to those treated with a BUP-NAL sublingual film formulation. The non-randomized study by Proctor et al.[30] did not observe significant differences in rates of treatment retention in patients

treated with sublingual BUP-NAL sublingual versus those treated with sublingual buprenorphine.

Clinical Evidence Regarding the Safety of Various Buprenorphine or Buprenorphine-Naloxone Formulations for the Treatment of Opioid Use Disorder

Adverse Events

Evidence regarding the safety of various buprenorphine formulations with respect to adverse events was available from one systematic review,[20] four RCT reports,[22-25] and three non-randomized studies.[27,28,31]

The systematic review[20] noted the rates of serious adverse events and the number of patients who had at least one opioid overdose events in patients treated with either buprenorphine subcutaneous extended-release injection or sublingual BUP-NAL. Serious adverse events were experienced by 2.3% of individuals treated with buprenorphine subcutaneous extended-release injection and 6% of individuals treated with sublingual BUP-NAL in one primary study. The second primary study reported serious adverse event rates of 1.8% and 14.5% in individuals treated with buprenorphine subcutaneous extended-release injection and sublingual BUP-NAL, respectively. As for the proportion of patients who had at least one opioid overdose event, the two primary studies reported rates of 2.3% and 4.5% in individuals who were treated with sublingual BUP-NAL. Neither primary study reported opioid overdose events in indivduals who were treated with buprenorphine subcutaneous extended-release injection. The statistical significance of between-group comparisons for these outcomes was not reported. The review also included two primary studies that compared the rates of serious adverse events patients treated with buprenorphine implant or sublingual BUP-NAL. Serious adverse events were observed in 2.3% of individuals treated with buprenorphine implant and in 3.4% or individuals treated with sublingual BUP-NAL in one primary study. The second primary study noted serious adverse events rates of 5.3% and 5.9% in individuals who were treated with buprenorphine implant and sublingual BUP-NAL, respectively. However, once again the statistical significance of these rates was not reported.

One RCT[22] reported no significant differences in the number of serious, severe, moderate, and mild adverse events in patients treated with buprenorphine oral lyophilisate wafer versus the sublingual formulation. The second RCT[23] reported similar rates of treatment-related adverse events between patients treated with BUP-NAL rapid dissolving sublingual tablet and those who were treated with BUP-NAL sublingual film; however, between-group differences were not tested statistically. In the RCT by Webster et al.,[24] there were no significant differences in the number of adverse events experienced by patients who were treated with BUP-NAL rapid dissolving sublingual tablet versus those treated with generic buprenorphine. The fourth RCT report,[25] reported no significant difference in the prevalence of treatment-emergent adverse events between patients treated with BUP-NAL sublingual tablet and those who were treated with BUP-NAL film.

One non-randomized study[27] reported on a number of adverse events that were experienced by patients treated with rapidly dissolving BUP-NAL sublingual tablets. The most frequent complaints were headache and constipation, which occurred in 21 and 20 patients, respectively (the total number of patients in the study was 258). A second non-randomized study[28] assessed the tolerability and safety of treatment with BUP-NAL buccal film. Treatment–emergent adverse events were experienced in 192 of the 249 participants; however, there were no deaths, two serious adverse events, and 11 withdrawals due to an

adverse event, suggesting that treatment was overall well tolerated. The study by Soyka et al.[31] monitored laboratory markers for liver safety of patients treated with BUP-NAL. A number of safety outcomes, including patients' levels of alkaline phosphatase, glutamic-pyruvic transaminase, glutamate oxaloacetate transaminase, and gamma-glutamyl transpeptidase were measured throughout the study. The authors concluded that the treatment appears to be safe.

Mortality

Evidence regarding the safety of various buprenorphine formulations with respect to mortality was available from one systematic review,[20] two RCTs,[22,24] and four non-randomized studies.[26-28,31]

No deaths were reported in patients treated with buprenorphine oral lyophilisate wafer,[22] buprenorphine sublingual tablet,[22] generic buprenorphine,[24] buprenorphine implant,[20] BUP-NAL buccal film,[28] BUP-NAL tablet.[31]

One non-randomized study[26] that compared patient cohorts treated with buprenorphine or BUP-NAL noted that there were no statistically significant differences in mortality rates per 1,000 patient years between the groups after adjustment for pre-treatment hospitalizations and gender (P = 0.055). The non-randomized study by Hoffman et al.[27] reported two deaths resulting from severe adverse events in patients treated with BUP-NAL rapid dissolving sublingual tablet. The study included a total of 665 patients, 292 of which completed the study (reasons for withdrawal included loss to follow-up, patient nonadherence, and patient request for discontinuation).

Cost-Effectiveness of Various Buprenorphine or Buprenorphine-Naloxone Formulations versus Other Buprenorphine Formulations for the Treatment of Opioid Use Disorder

Incremental Cost-Effectiveness Ratios

Evidence regarding the comparative cost-effectiveness of various buprenorphine or BUP-NAL formulations versus other buprenorphine formulations for the treatment of OUD using ICERs was available from two economic evaluations.[20,32]

One economic analysis[20] compared buprenorphine subcutaneous extended-release injection versus generic sublingual BUP-NAL; however, an ICER could not be estimated due to the lack of a list price or net price for buprenorphine subcutaneous extended-release injection. The same systematic review[20] also compared buprenorphine implant versus generic sublingual BUP-NAL. The results indicated that buprenorphine implant offered marginal improvements in QALYs relative to generic BUP-NAL, with an incremental cost of $265,000 per QALY gained. The authors concluded that this value would fall outside of commonly cited cost-effectiveness thresholds.

The second economic analysis[32] examined the cost-effectiveness of subdermal implantable buprenorphine versus sublingual buprenorphine for the treatment of OUD. The comparison suggests that treatment with subdermal implantable buprenorphine resulted in decreased costs to society and increased QALYs; therefore it dominated treatment with sublingual buprenorphine.

Evidence-Based Guidelines Regarding the Use of Various Buprenorphine or Buprenorphine-Naloxone Formulations for the Treatment of Opioid Use Disorder

Two evidence-based guidelines[13,14] were identified regarding recommendations for the use of various buprenorphine or BUP-NAL formulations for the treatment of OUD.

The first from the Canadian Research Initiative in Substance Misuse, recommends initiating treatment with BUP-NAL to "reduce the risk of toxicity, morbidity and mortality, as well as to facilitate safer take-home dosing".[13] This is a strong recommendation, based on high quality evidence. [13]

Guidelines from the United States' VA/DoD, recommend considering patient preference between BUP-NAL or methadone in treatment initiation.[14] They further recommend considering patients' preferences for the clinical setting in which they are treated, either office-based or opioid treatment program in a specialized clinic.[14] Both of these were strong recommendations; however, there is no explicit link between the recommendation and the quality evidence.[14]

Limitations

A number of limitations were identified in the critical appraisal (Appendix 3, Table 6, Table 7, Table 8, and Table 9), however, additional limitations exist. The main limitations of this review are related to risk of bias, limited study populations and generalizability of findings.

A primary limitation that should be considered when interpreting these results is that participants and outcome assessors were not blinded to the treatment received in a majority of the reviewed studies. Given that several of the outcomes reported in these trials were based on subjective measures (e.g., SOWS scores, opioid craving visual analogue scale scores, self-reported use of heroin), the findings of open-label studies may be at risk for bias in either direction depending on the perceptions and expectations of participants and clinicians involved.

Only one included study[20] contained information specific to pediatric or adolescent populations with OUD; therefore, the comparative clinical effectiveness, safety, and cost-effectiveness of various buprenorphine formulations in children is largely unknown. The applicability of the evidence to Canadian settings is unclear as all relevant clinical studies[20-32] were conducted outside of Canada. Furthermore, it may be difficult to generalise the results in women since most studies enrolled a disproportionately higher number of men.[22,24,26-29,31] There is also uncertainty around the generalizability of the cost-effectiveness findings due to the potential for significant differences in drug prices and associated costs between Canada and the United States, where the economic studies took place.

Conclusions and Implications for Decision or Policy Making

This report identified clinical and cost-effectiveness evidence and evidence-based guidelines regarding the use of buprenorphine formulations for the treatment of OUD. Two relevant systematic reviews,[20,21] three RCTs (in four publications),[22-25] six non-randomized studies,[26-31] two economic evaluations (one of which was conducted within an included systematic review),[20,32] and two evidence-based guidelines were identified.[13,14]

The identified literature[13,14,20-32] revealed mixed conclusions regarding the clinical effectiveness, safety, and cost-effectiveness of various buprenorphine formulations for individuals with OUD.

With respect to the clinical effectiveness of treatment, several studies[20,21,26,29] observed statistically significant differences in outcomes of interest between patients treated with various buprenorphine formulations; however, whether these differences were clinically meaningful was unclear and no clear patterns suggesting one formulation was superior to another emerged.

With respect to the safety of various formulations, none of the included studies[20-32] reported statistically significant differences in the safety profiles of buprenorphine formulations. For the most part, findings in this report suggest that buprenorphine formulations are a relatively safe and tolerable treatment options for patients with opioid use disorder.

The identified economic evaluations[20,32] suggested that treatment with implantable buprenorphine in combination with psychosocial therapy did not provide cost-effective benefit over generic BUP-NAL in combination with psychosocial therapy,[20] but that is was cost-effective compared to sublingual buprenorphine in combination with psychosocial therapy.[32]

Two evidence-based guidelines were identified that provide recommendations regarding the use of buprenorphine for OUD.[13,14] Both guidelines provide strong recommendations for the use of BUP-NAL,[13,14] for treatment initiation or maintenance.

The limitations of the included studies and of this report should be considered when interpreting the results. The findings highlighted in this review come with a high degree of uncertainty. Further research investigating the comparative clinical and cost-effectiveness of buprenorphine formulations, especially through the use of large, methodologically-sound RCTs or well-designed meta-analyses, would help reduce this uncertainty.

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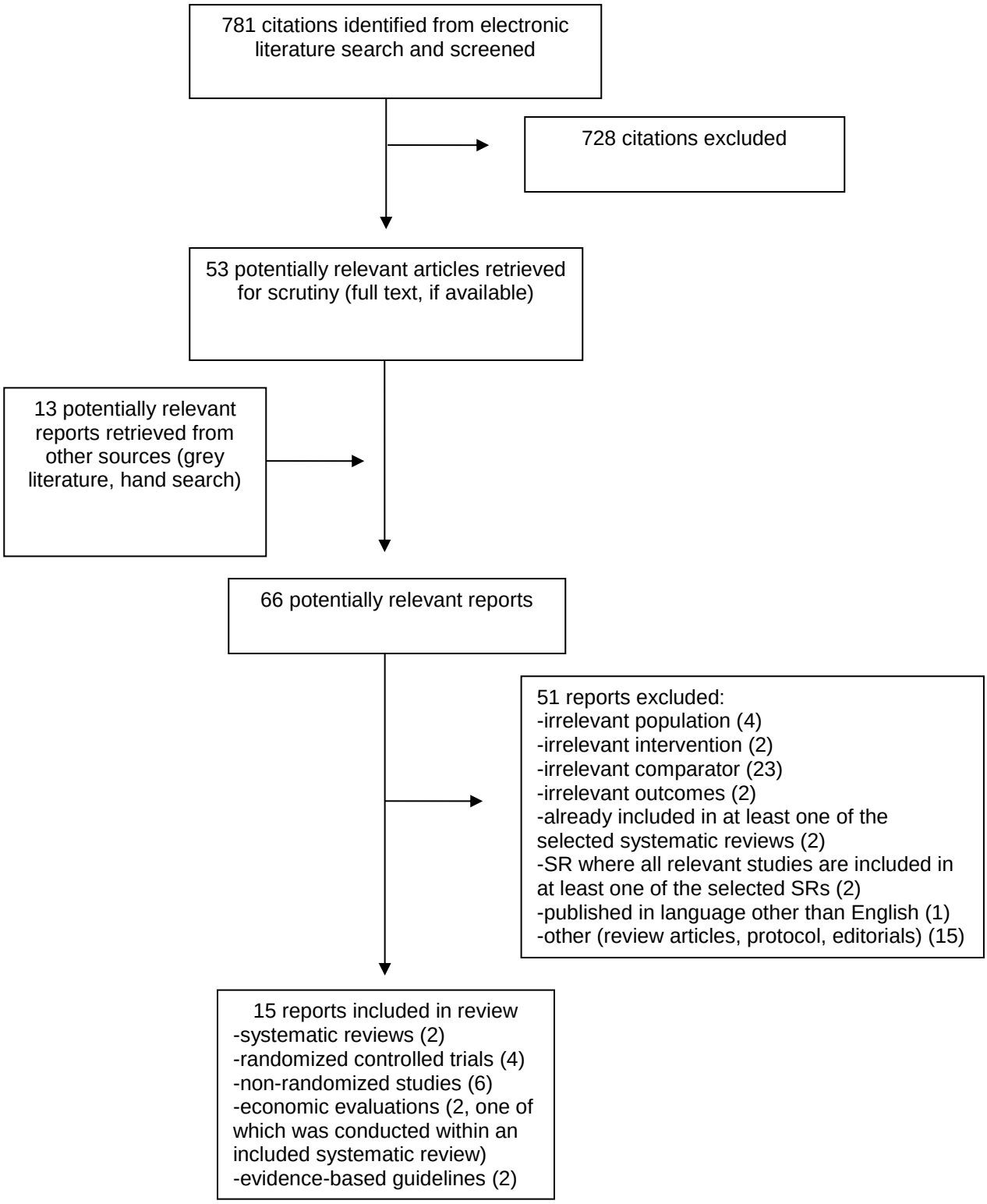
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Systematic Reviews

First Author, Publication Year, Country	Study Designs, Search Strategy, Numbers of Studies Included, Quality Assessment Tool, and Objective	Population Characteristics	Intervention and Comparator(s)	Outcomes, Length of Follow-Up
Institute for Clinical and Economic Review, 2018[20] United States	**Study design**: SR of relevant published and unpublished RCTs and non-randomized comparative studies **Literature search strategy**: Authors performed literature searches in MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials up to September 25, 2018. These searches were supplemented by a manual search of the reference lists of included trials and reviews. Key stakeholders were also asked to share potentially relevant references. Finally, a grey literature search of conference proceedings, regulatory documents, information submitted by manufacturers, and other sources was conducted. **Number of studies included**: In total, 23 studies were included, with 5 relevant for this review **Quality assessment tool**: Quality assessment was based on US Preventive Services Task Force criteria **Objective**: To assess the effectiveness and value of new medication options (i.e., buprenorphine subcutaneous extended-release injection, buprenorphine implant, naltrexone intramuscular extended-release injection) in patients with OUD	Patients (≥ 16 years of age) with OUD in various treatment settings.	**Interventions**: Buprenorphine subcutaneous extended-release injection, buprenorphine implant, naltrexone intramuscular extended-release injection **Comparators**: Other common medications used in the treatment of OUD Studies relevant to the present report compared various formulations of buprenorphine to each other or to BUP-NAL combinations	**Relevant Outcomes:** - Illicit use of opioids - Opioid withdrawal syndrome - Craving/desire for opioids - Mortality (e.g., overdose deaths, suicide) - Adherence/treatment discontinuation - AEs **Follow-up:** Studies of any follow-up duration were included
Minozzi, 2014[21] Italy	**Study design**: SR of relevant RCTs and controlled clinical trials (i.e., non-randomized comparative studies)	Adolescents (≤ 18 years of age) who are opiate-dependent. There	**Interventions**: Any opioid agonist treatment (e.g., methadone, buprenorphine,	**Relevant Outcomes:** - Drop-out rates - Use of primary substance - Number of relapses at the

Table 2: Characteristics of Included Systematic Reviews

First Author, Publication Year, Country	Study Designs, Search Strategy, Numbers of Studies Included, Quality Assessment Tool, and Objective	Population Characteristics	Intervention and Comparator(s)	Outcomes, Length of Follow-Up
	Literature search strategy: Authors searched the Cochrane Drugs and Alcohol Group's Trials Register, the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (PubMed), EMBASE, CINAHL, and Web of Science from inception to January, 2014. Ongoing clinical trials were identified using Current Controlled Trials, Clinical Trials.gov, and the International Clinical Trials Registry Platform. These searches were supplemented by a manual search of the reference lists of relevant trials and by expert consultations for identification of other potentially relevant published, unpublished, or incomplete controlled trials. **Number of studies included**: In total, 2 studies were included, with 1 relevant for this review **Quality assessment tool**: Conducted using methodology outlined in the *Cochrane Handbook for Systematic Reviews of Interventions*[37] **Objective**: "To assess the effectiveness of any maintenance treatment alone or in combination with psychosocial intervention compared to no intervention, other pharmacological intervention or psychosocial interventions for retaining adolescents in treatment, reducing the use of substances and improving health and social status."[21] (*p7*)	were no restrictions on participants with co-morbid physical or psychological illness.	LAAM, heroin) alone or in conjunction with psychosocial intervention for maintenance treatment **Comparators:** No intervention, alternative opioid agonist treatments, other pharmacological interventions, any detoxification intervention, psychosocial interventions alone The study relevant to the present report compared BUP-NAL maintenance versus buprenorphine detoxification.	end of follow-up - Use of other substances of abuse **Follow-up:** NR

AE = adverse event; ED = emergency department; HRQoL = health-related quality of life; LAAM = levo-alpha-acetylmethadol; MA = meta-analysis; NR = not reported; OUD = opioid use disorder; PCP = primary care physician; RCT = randomized controlled trial; SR = systematic review.

Table 3: Characteristics of Included Primary Clinical Studies

First Author, Publication Year, Country	Study Design, Setting, and Objective	Patient Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Randomized Controlled Trials				
Strang, 2017[22] United Kingdom	**Study design**: Randomized (2:1) open-label study **Setting**: Specialized clinical trials facility and addictions treatment facility **Objective**: To test the safety of buprenorphine oral lyophilisate wafer versus the sublingual formulation	Participants with opioid dependency commencing buprenorphine maintenance. **Number of patients**: 36 (23 in the intervention group; 13 in the comparator group) **Mean age (SD)**: 42.0 (8.0) in the intervention group; 42.0 (10.0) in the comparator group **Sex**: 20 males in the intervention group; 11 males in the comparator group	**Intervention**: Buprenorphine oral lyophilisate wafer administered on the tongue **Comparator**: Standard sublingual buprenorphine tablet	**Outcomes**: - Retention in treatment - Dose adequacy - OOWS - SOWS - Respiratory function - Oral disintegration time - Various laboratory indicators, including urine drug screens, liver function tests, pregnancy test - ECG **Follow-up**: Ongoing monitoring; retention in treatment at end of titration (study day 7) and end of the maintenance period (study day 14)
Gunderson, 2016[23] United States	**Study design**: Secondary analysis of a blinded, randomized, parallel-group, multi-center, noninferiority trial, extension of Gunderson, 2015[25] **Setting**: 43 centres in the US **Objective**: Examine the effect of switching treatments between a BUP-NAL rapid dissolving sublingual tablet and a BUP-NAL film formulation	Adults aged 18 to 65 years, opioid dependent in the past 12 months. **Number of patients**: 758 (383 in the intervention group; 375 in the comparator group) **Mean age (SD)**: 35.7 (11.26) in the intervention group; 35.6 (11.28) in the comparator group **Sex**: 56.4% male in the intervention group; 62.9% female in the comparator group	**Intervention**: BUP-NAL rapid dissolving sublingual tablet **Comparators**: BUP-NAL sublingual film, and generic buprenorphine sublingual tablets (for the induction phase)	**Outcomes**: - Retention in treatment at each visit - COWS - SOWS - Opioid cravings - AEs **Follow-up**: Ongoing assessments up to day 22

Table 3: Characteristics of Included Primary Clinical Studies

First Author, Publication Year, Country	Study Design, Setting, and Objective	Patient Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Webster, 2016[24] United States	**Study design**: Prospective, randomized, multi-centre, blinded (induction), open-label (maintenance), parallel-group, active-controlled, noninferiority trial **Setting**: 13 centres in the US **Objective**: Evaluate whether BUP-NAL rapid dissolving sublingual tablet was noninferior to generic buprenorphine during the induction phase of treatment	Adults aged 18 to 65 years, opioid dependent in the past 12 months. **Number of patients**: 310 (155 in the intervention group; 155 in the comparator group) **Mean age (SD)**: 38.9 (10.55) in the intervention group; 38.0 (10.90) in the comparator group **Sex**: 64.5% male in the intervention group; 66.5% in the comparator group	**Intervention**: Buprenorphine/ naloxone rapid dissolving sublingual tablet **Comparator**: Generic buprenorphine sublingual tablets	**Outcomes**: - Retention in treatment at day 3 (primary) and each study visit (secondary) - Time to treatment discontinuation - COWS - SOWS - Opioid cravings - AEs **Follow-up**: Ongoing assessments up to day 29
Gunderson, 2015[25] United States	**Study design**: A blinded, randomized, parallel-group, multi-centre, noninferiority trial **Setting**: 43 centers in the US **Objective**: Assess the efficacy of a BUP-NAL sublingual tablet, generic buprenorphine, and a BUP-NAL film formulation	Adults aged 18 to 65 years, opioid dependent in the past 12 months. **Number of patients**: 758 (383 in the intervention group; 375 in the comparator group) **Mean age (SD)**: 35.7 (11.26) in the intervention group; 35.6 (11.28) in the comparator group **Sex**: 56.4% male in the intervention group; 62.9% female in the comparator group	**Intervention**: BUP-NAL sublingual tablet **Comparators**: BUP-NAL sublingual film, and generic buprenorphine sublingual tablets (for the induction phase)	**Outcomes**: - Retention in treatment at days 3 and 15 - COWS - SOWS - Opioid cravings - AEs - Vital signs measurements, physical examination and laboratory tests **Follow-up**: Ongoing assessments up to day 15
Non-Randomized Studies				
Kelty, 2018[26] Australia	**Study design**: Retrospective cohort **Setting**: Western Australia **Objective**: Examine and compare rates of morbidity	All patients treated with buprenorphine or BUP-NAL for opioid dependence in Western Australia for the first time prior to December 2010. **Number of patients**: 2,432 in	**Intervention**: Buprenorphine **Comparator**: BUP-NAL	**Outcomes**: - Crude mortality rates - Cause-specific fatalities - Crude rates of hospital and ED visits - Cause-specific hospital and ED attendances

Table 3: Characteristics of Included Primary Clinical Studies

First Author, Publication Year, Country	Study Design, Setting, and Objective	Patient Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
	and mortality in opioid dependent patients treated with buprenorphine and BUP-NAL	the buprenorphine group; 2,260 in the BUP-NAL group **Mean age (SD)**: 30.9 (±8.2) in the buprenorphine group; 33.3 (±7.9) in the BUP-NAL group **Sex**: 63.7% male in the buprenorphine group; 65.6% male in the BUP-NAL group		**Follow-up**: A total of 24,788 patient-years
Hoffman, 2017[27] United States	**Study design**: Multi-centre, open-label, uncontrolled, extension of Gunderson, 2015[25] and Webster, 2014[38] **Setting**: 50 study centres in the US **Objective**: Assess the safety of rapidly dissolving BUP-NAL sublingual tablets in participants with opioid dependency.	Adults aged 18 to 65 years, opioid dependent, having received buprenorphine-based opioid substitution therapy for at least 22 days. **Number of patients**: 668 **Mean age (SD)**: 36.8 (11.3) **Sex**: 61.1% male	**Intervention**: BUP-NAL rapid dissolving sublingual tablet **Comparator**: None	**Outcomes**: - Incidence of AEs - Severity of opioid addiction: cravings, CGI-I - Vital signs - Laboratory values **Follow-up**: Approximately 24 weeks
Sullivan, 2015[28] United States	**Study design**: Multi-centre, open-label, prospective cohort **Setting**: 10 study centres in the US **Objective**: Assess the safety, tolerability, symptom control, and patient acceptance of BUP-NAL buccal film in participants with opioid dependency, and confirm conversion ratios between the buccal film and sublingual tablet or film formulations.	Adults aged 18 to 65 years, opioid dependent, having been maintained on a stable BUP-NAL sublingual tablet or film dose for at least 30 days. **Number of patients**: 249 **Mean age**: 38.7 **Sex**: 65.9% male	**Intervention**: BUP-NAL buccal film **Comparator**: BUP-NAL sublingual tablet or film	**Outcomes**: - Vital signs - Incidence of AEs - Risk of suicide - Oral mucosa - COWS - Laboratory values - Urine toxicology - ECG **Follow-up**: Throughout the 12 weeks of treatment and at one week after

Table 3: Characteristics of Included Primary Clinical Studies

First Author, Publication Year, Country	Study Design, Setting, and Objective	Patient Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Clay, 2014[29] United States	**Study design**: Retrospective cohort study **Setting**: Private insurance claims database (Invision DataMart) in the US **Objective**: Compare persistence in treatment, healthcare resource utilization, and total health care costs between patients treated with BUP-NAL sublingual film and the sublingual tablet formulation	Patient having evidence of treatment with BUP-NAL sublingual film or sublingual tablet formulation. **Number of patients**: 2,796 in the film group, and 1,510 in the tablet group **Mean age (SD)**: 34.34 (11.83) in the film group, and 35.65 (12.32) in the tablet group **Sex**: 65.62% male in the film group, 62.72% male in the tablet group	**Intervention**: BUP-NAL sublingual film formulation **Comparator**: BUP-NAL sublingual tablet formulation	**Outcomes**: - Time to discontinuation of BUP-NAL - Persistence rates - Switch rates - Average daily dose - Resource utilization - Healthcare costs **Follow-up**: From 56 months before to 27 months after the launch of the BUP-NAL sublingual film formulation
Proctor, 2014[30] United States	**Study design**: Retrospective longitudinal study **Setting**: 34 substance use treatment facilities throughout the US operated by a large health care provider (CRC Health Group Inc.) **Objective**: Compare the effectiveness of methadone, buprenorphine, and BUP-NAL in reducing illicit drug use and retaining patients in treatment	Active and discharged patients admitted for medication-assisted treatment for opioid dependence to the facilities during the period of July 1, 2012, through July 1, 2013. **Number of patients**: 3,233 (393 in the buprenorphine sublingual group, and 102 in the BUP-NAL group **Mean age (SD)**: 31.6 (9.33) in the buprenorphine group, 31.8 (8.47) in the BUP-NAL group, and 33.1 (9.48) in the methadone group **Sex**: 57.8% male in the buprenorphine group, 50.0% male in the BUP-NAL group, and 55.9% male in the methadone group	**Intervention**: Buprenorphine sublingual **Comparator**: BUP-NAL sublingual	**Outcomes**: - Urine drug screens for opioids - Urine drugs screens for non-opioids - Patient retention in treatment **Follow-up**: Six months or until treatment discharge, whichever came first

Table 3: Characteristics of Included Primary Clinical Studies

First Author, Publication Year, Country	Study Design, Setting, and Objective	Patient Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Soyka, 2014[31] Germany	**Study design**: Prospective observational study **Setting**: 69 addiction medicine physician practices in Germany **Objective**: Assess liver safety of treatment with BUP-NAL in participants with opioid dependency.	Participants with opioid dependency **Number of patients**: 384 **Mean age (SD)**: 35.1 (8.8) **Sex**: 76.6% of eligible patients (n = 337) were male	**Intervention**: BUP-NAL **Comparator**: None	**Outcomes**: - Various liver laboratory values - AEs **Follow-up**: 12 months

AE = adverse event; CGI-I = Clinical Global Impression of Improvement; COWS = Clinical Opiate Withdrawal Scale; ECG = electrocardiogram; ED = emergency department; OOWS = Objective Opiate Withdrawal Scale; SD = standard deviation; SOWS = Subjective Opiate Withdrawal Scale.

Table 4: Characteristics of Included Economic Evaluations

First Author, Publication Year, Country	Type of Analysis, Approach, Time Horizon, Perspective	Decision Problem	Population Characteristics	Interventions and Comparators	Clinical and Cost Data Used in Analysis	Main Assumptions
Institute for Clinical and Economic Review, 2018[20] United States Note: This was conducted as part of an included SR, see	**Analysis**: Cost-effectiveness analysis using a 5 state Markov model. The model ran in 1-month cycles. **Approach**: Model-based **Time horizon**: 5 years **Perspective**: US health care sector perspective	"The primary aim of this analysis was to estimate the lifetime cost-effectiveness of certain drugs used for medication-assisted treatment among a cohort of patients who were considered for OUD treatment, from a US health care sector perspective."[20] (*p*51)	Adults diagnosed with OUD seeking medication-assisted treatment. **Mean age**: 36 years **Sex**: 30% female **Percent Illicit Use of Prescription Opioids**: 50.7% 5 state Markov model: 1. On treatment with no illicit use of opioids 2. On treatment with illicit use of opioids 3. Off treatment with no illicit use of opioids 4. Off treatment with illicit use of opioids 5. Dead	**Interventions**: Buprenorphine subcutaneous extended-release injection, naltrexone for extended-release injectable suspension, buprenorphine implant **Comparator**: Generic sublingual BUP-NAL	- Treatment efficacy - Treatment discontinuation - Comorbidities associated with OUD - Mortality - Health state utilities - Averse events - Drug acquisition costs - Administration and monitoring costs - Health care utilization costs - Societal costs	- Patients continue receiving ancillary counseling services while on medication-assisted treatment, irrespective of whether they maintain abstinence or relapse - Long-term discontinuations for all interventions was assumed the same as seen in the trials - 10% of all patients who remained in the "treatment with no illicit use of opioids" health state for at least 12 months transitioned to an "off treatment with no illicit use of opioids" health state - Opioid overdose-related mortality was assumed to occur only during periods of illicit use of opioids - Mortality from opioid overdose was held constant over time - The model assumed a constant disutility associated with HIV infection and related treatment - Serious AE-related costs or disutilities were not included in the model

First Author, Publication Year, Country	Type of Analysis, Approach, Time Horizon, Perspective	Decision Problem	Population Characteristics	Interventions and Comparators	Clinical and Cost Data Used in Analysis	Main Assumptions
Carter, 2017[32] United States	**Analysis**: Cost-effectiveness analysis using a 4 state Markov model. The model ran in 1-month cycles. **Approach**: Model-based **Time horizon**: 12 months **Perspective**: US societal perspective	The analysis was developed as a resource for interested parties to assess the cost-effectiveness of subdermal implantable buprenorphine versus sublingual buprenorphine for the treatment of OUD	Adults with OUD who were classified as clinically stabilized (i.e., those who achieved prolonged clinical stability on < 8 mg of daily transmucosal buprenorphine) **Mean age**: NR **Sex**: NR 4 state Markov model: 1. On treatment, not relapsed 2. On treatment, relapsed 3. Off treatment, relapsed 4. Dead	**Intervention**: Subdermal implantable buprenorphine plus monthly psycosocial counselling **Comparator**: Sublingual buprenorphine plus monthly psycosocial counselling	- Data to derive transition probabilities - State-dependent penalties associated with relapse and continued illicit opioid use - Clinical and societal penalties of relapse and illicit opioid use - Health state utilities - Health care utilization costs - Indirect non-medical and mon-medical costs	- The model did not consider the possibility of patients transitioning to an off treatment, not relapsed state - Both treatment cohorts received monthly psychosocial counselling if they were retained in treatment - Intravenous misuse (and associated costs) and accidental pediatric poisoning (and the costs associated with the management of accidental ingestion of the patient's home supply) with buprenorphine was possible in both groups. This was possible in the subdermal implantable buprenorphine group as a proportion of the cohort received supplemental oral buprenorphine

AE = adverse events; NR = not reported; OUD = opioid use disorder; SR = systematic review.

Table 5: Characteristics of Included Guidelines

Intended Users, Target Population	Intervention and Practice Considered	Major Outcomes Considered	Evidence Collection, Selection, and Synthesis	Evidence Quality Assessment	Recommendations Development and Evaluation	Guideline Validation
CRISM, 2018[13]						
Intended users: Canadian physicians, nursing and allied healthcare providers, medical educators, clinical care case managers, policymakers, healthcare administrators **Target population**: Adults, young adults, and adolescents with uncomplicated OUD. Also includes specific considerations for pregnant people.	Various OUD treatments including: opioid agonists and antagonists, withdrawal management strategies, psychosocial interventions, and residential treatment.	Various outcomes, including: abstinence, adverse events, costs, cravings, criminality, fatal and non-fatal overdose, health service utilization, HIV and hepatitis C infections, mental health, morbidity, mortality, patient preference, quality of life, retention in treatment, risk behaviours, side effects, social functioning	"The national guideline expanded on two previous documents developed in British Columbia: the Vancouver Coastal Health/Providence Health Care Guideline for Clinical Management of Opioid Addiction released in November 2015, and the BC Centre on Substance Use/Ministry of Health Guideline for the Clinical Management of OUD, released in February 2017"[13] Updated literature searches were performed in 2016 in PubMed, ISI Web of Science, and the Cochrane Library.	**GRADE quality of evidence:** • High • Moderate • Low • Very low **GRADE strength of recommendation:**[39] • Strong • Weak	Iterative consensus via an interdisciplinary committee of 43 individuals; external review with international experts and national stakeholder groups.	internal and external peer review with international experts and national stakeholder groups

Table 5: Characteristics of Included Guidelines

Intended Users, Target Population	Intervention and Practice Considered	Major Outcomes Considered	Evidence Collection, Selection, and Synthesis	Evidence Quality Assessment	Recommendations Development and Evaluation	Guideline Validation
Department of Veterans Affairs/Department of Defense, 2015[14]						
Intended users: US VA/DoD health care providers, and others involved in the care of the target population. **Target population**: Department of Defence service members (18 years or older) and veterans with substance use disorder	Various OUD treatments, including pharmacological therapies, brief interventions, mutual help programs, psychotherapy, psychosocial interventions,	Various outcomes, including: adherence with treatment, adverse events, emergency department utilization, morbidity, mortality, overdoses, relapse, side effects, substance consumption (alcohol, opioid), treatment retention quality of life,	"The current document is an update to the 2009 VA/DoD Clinical Practice Guideline for the Management of Substance Use Disorders"[18] A systematic review was conducted to update the results from November 2007 onward.	**GRADE quality of evidence:**[39] • High • Moderate • Low • Very low **GRADE strength of recommendation:**[39] • Strong • Weak Using these elements, the grade of each recommendation is presented as part of a continuum:[14] • "Strong For (or "We recommend offering this option …")"[14] • "Weak For (or "We suggest offering this option …")"[14] • "Weak Against (or "We suggest not offering this option …")"[14] • "Strong Against (or "We recommend against offering this option …")"[14]	Three clinical leaders and a working group defined the inclusion and exclusion criteria and assessed the level and quality of the evidence. They interpreted the results and carried forward recommendations from the previous guidelines modifying or adding as necessary. An external contractor (The Lewin Team) supported the development and evidence review.	Internal and external peer review with international experts and national stakeholder groups

BC = British Columbia; GRADE = Grading of Recommendations Assessment, Development and Evaluation; ISI = Institute for Scientific Information; VA/DoD = Veterans Affairs/Department of Defense.

Appendix 3: Critical Appraisal of Included Publications

Table 6: Strengths and Limitations of Systematic Reviews using AMSTAR II[16]

Strengths	Limitations
Institute for Clinical and Economic Review, 2018[20]	
• The objectives and inclusion/exclusion criteria were clearly stated and included components of population, intervention, comparator, and outcomes • Multiple databases were searched (MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials). In addition, a manual search of references from identified literature was performed • Search terms and dates were provided (September 25, 2018) • Grey literature searching of conference proceedings, regulatory documents, information submitted by manufacturers, and other sources was conducted • A detailed protocol of the methods was registered on Prospero (CRD42018103836) prior to the conduct of the review • The choice of included study designs was justified • Study selection was completed in duplicate and described in detail • Data extraction was completed by one researcher and independently verified by another researcher • A list of included studies was provided and the characteristics of included studies were described in detail • The quality of included studies was assessed based on US Preventive Services Task Force (USPSTF) criteria • The possibility of publication bias was investigated (there was no evidence of any publication bias) • Review authors reported on source of funding for the included studies • Review authors considered risk of bias in individual studies when interpreting and discussing the results • The authors and expert reviewers stated that they had no conflicts of interest related to this review • Sources of funding were disclosed (government grants and non-profit foundations) and were unlikely to have influenced the findings of the review	• A list of excluded studies was not provided (although the reasons for exclusion were) • Studies were excluded if they were not published in the English language, no justification provided • The five relevant primary studies were conducted in the US; findings may not be generalizable to the Canadian setting
Minozzi, 2014[21]	
• The objectives and inclusion/exclusion criteria were clearly stated and included components of population, intervention, comparator, and outcomes • Multiple databases were searched (Cochrane Drugs and Alcohol Group's Trials Register, the Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, CINAHL, and Web of Science). Ongoing clinical trials were identified using Current Controlled Trials, Clinical Trials.gov, and the International Clinical Trials Registry Platform. In addition, a	• Review authors did not report on source of funding for the included studies • The one relevant primary studies was conducted in the US; findings may not be generalizable to the Canadian setting

Table 6: Strengths and Limitations of Systematic Reviews using AMSTAR II[16]

Strengths	Limitations
manual search of references from identified literature was performed • Additional searching for non-indexed studies (grey literature) was conducted • Search terms and dates were provided (from inception to January, 2014) • All searches included non-English language literature (translation was done when studies were considered likely to meet inclusion criteria) • A detailed protocol of the methods was registered prior to the conduct of the review • The choice of included study designs was justified • Study selection was completed in duplicate (triplicate for full-text screening) and described in detail • Data extraction was independently conducted by three review authors (any disagreement was discussed and resolved by consensus) • A list of included studies was provided and the characteristics of included studies were described in detail • A list of excluded studies and their reasons for exclusion was provided • The quality of included studies was assessed using methodology outlined in the *Cochrane Handbook for Systematic Reviews of Interventions*[37] • The possibility of publication bias was discussed and investigated to the degree possible • Review authors considered risk of bias in individual studies when interpreting and discussing the results • The authors stated that they had no conflicts of interest related to this review • Sources of funding were disclosed (Department of Epidemiology ASL RM E, Italy) and were unlikely to have influenced the findings of the review	

Table 7: Strengths and Limitations of Clinical Studies using the Downs and Black Checklist[18]

Strengths	Limitations
Randomized Controlled Trials	
Strang, 2017[22]	
• The study's aim, intervention, and main outcomes were clearly described • Population characteristics were clearly described and inclusion/exclusion criteria given • The major findings of the study were described in a way that allows verification of analyses and conclusions • Estimates of random variability were reported • • Data analyses were planned at the outset • Length of follow up was consistent between the intervention and comparator groups • Compliance with the intervention seemed reliable • The main outcome measures used were valid and reliable (e.g., OOWS and SOWS) • Analyses were based on intention to treat • Loss to follow-up was taken into account • Sources of funding were disclosed and were unlikely to have influenced the findings of the study	• Although treatment-emergent AEs, AEs, and serious AEs were reported and scored in the results, there was no attempt at providing a comprehensive list of possible AEs a priori • Despite that the patient characteristics were described, there is no demonstration that the distribution of main confounding factors was similar to the source population • This was an open-label study with no blinding of study participants or outcome assessors • Six participants (three in each group) withdrew prior to completion, yet there was no apparent adjustment to the analyses for the different lengths of follow-up. Furthermore, patient characteristics for these withdrawals were not provided • There was no information concerning the source of participants included in the study • The time period over which patients were recruited was not specified • Although patients were randomized to the intervention or comparator, details on the methodology used to randomize were lacking and absence of predictability cannot be assessed • No power calculation performed, low numbers in intervention groups, so unlikely to have had enough power to detect a statistically meaningful difference for several outcomes of interest • The authors disclosed conflicts of interest which may have influenced the findings of the study, including that the principle author has patents on various novel naloxone formulations
Gunderson, 2016[23]	
• The study's objective, intervention, and main outcomes were clearly described • Population characteristics were clearly described and eligibility criteria given • The major findings of the study were described in a way that allows verification of analyses and conclusions • Estimates of random variability were reported • Study participants appear to be representative of the population of interest • Data analyses were planned at the outset • Length of follow up was consistent between the intervention and comparator groups • The main outcome measures used were valid and reliable (e.g., COWS and SOWS) • The time period over which patients were recruited was	• Although AEs were reported there was no attempt at providing a comprehensive list of possible AEs a priori • There was no apparent adjustment to the analyses for the different lengths of follow-up due to participant withdrawal and lost to follow-up. Furthermore, patient characteristics for these withdrawals were not provided • Despite that the patient characteristics were described, there was no demonstration that the distribution of main confounding factors were validated as similar to the source population • This was an open-label study with no blinding of study participants or outcome assessors • There was no information concerning the source of participants included in the study • Although patients were randomized to the intervention or

Table 7: Strengths and Limitations of Clinical Studies using the Downs and Black Checklist[18]

Strengths	Limitations
specified	comparator, details on the methodology used to randomize are lacking and absence of predictability cannot be assessed • The analyses were based on treatment results rather than intention to treat • No power calculation performed • Sources of funding were disclosed and may have influenced the findings of the study • The authors disclosed conflicts of interest which may have influenced the findings of the study, including that some authors have received funding from the manufacturer
Webster, 2016[24]	
• The study's objective, intervention, and main outcomes were clearly described • Population characteristics were clearly described and eligibility criteria given • The major findings of the study were described in a way that allows verification of analyses and conclusions • Estimates of random variability were reported • Actual probability values (*P*-values) were reported • Study participants appear to be representative of the population of interest • Data analyses were planned at the outset • The time period over which patients were recruited was specified • It appears that compliance with the allocated treatment was reliable • The main outcome measures used were valid and reliable (e.g., COWS and SOWS) • Patients were randomized to the intervention or comparator using a non-stratified, block randomization system, that employed an external service for generating the random allocation sequences • Length of follow up was consistent between the intervention and comparator groups • A power calculation was performed, determining that 150 participants were required per group (300 total) for analysis of the primary outcome	• Although AEs were reported there was no attempt at providing a comprehensive list of possible AEs a priori • There was no apparent adjustment to the analyses for the different lengths of follow-up due to participant withdrawal and lost to follow-up. Furthermore, patient characteristics for these withdrawals were not provided • Despite the blinding during the induction phase, the maintenance phase was an open-label study with no blinding of study participants or outcome assessors • There was no information concerning the source of participants included in the study • The analyses were based on the per-protocol sample rather than intention to treat • Despite that the patient characteristics were described, there was no demonstration that the distribution of main confounding factors were validated as similar to the source population • Sources of funding were disclosed and may have influenced the findings of the study • The authors did not disclosed conflicts of interest
Gunderson, 2015[25]	
• The study's objective, intervention, and main outcomes were clearly described • Population characteristics were clearly described and eligibility criteria given • The major findings of the study were described in a way that allows verification of analyses and conclusions • Estimates of random variability were reported • Study participants appear to be representative of the population of interest	• Although AEs were reported there was no attempt at providing a comprehensive list of possible AEs a priori • Patient characteristics for withdrawals and lost to follow-up were not provided • There was no information concerning the source of participants included in the study • The analyses were based on the per-protocol population rather than intention to treat. • Sources of funding were disclosed and may have influenced

Table 7: Strengths and Limitations of Clinical Studies using the Downs and Black Checklist[18]

Strengths	Limitations
• Data analyses were planned at the outset • Length of follow up was consistent between the intervention and comparator groups • The main outcome measures used were valid and reliable (e.g., COWS and SOWS) • The time period over which patients were recruited was specified • Sensitivity analyses were conducted on data from the entire study cohort. • Survival analyses were conducted for the primary outcomes • Study participants and outcome assessors were blinded to the treatment assignment during the induction • Patients were randomized to the intervention or comparator, using an interactive technology allocation service • A power calculation was performed, determining that 708 participants were required for analysis of the primary outcome	the findings of the study, including that the study received funding from the manufacturer • The authors disclosed conflicts of interest which may have influenced the findings of the study, including that some authors have received funding from the manufacturer
Non-Randomized Studies	
Kelty, 2018[26]	
• The study's aim, intervention, and main outcomes were clearly described • Population characteristics were clearly described and eligibility criteria given • Estimates of random variability were reported • Study participants appear to be representative of the population of interest • Data analyses were planned at the outset • Survival analyses were conducted for the primary outcomes to adjust for the different lengths of follow-up in the intervention and comparator groups • AEs were reported and a comprehensive list of possible AEs was provided a priori • The main outcome measures used were valid and reliable • The time period over which patients were recruited was specified • Participants data was recruited through a jurisdictional prescription monitoring program which would be representative of the source population • If patients had more than one series of treatment, only the first treatment was considered. • Sources of funding were disclosed and were unlikely to have influenced the findings of the study • The authors disclosed no conflicts of interest	• Simple outcome data for the major findings of the study were not presented in a way that allows verification of analyses and conclusions (presented as rates) • A power calculation was not reported to determine if the sample was of an adequate size
Hoffman, 2017[27]	
• The study's objective, intervention, and main outcomes were clearly described • Population characteristics were clearly described and	• 373 of 668 participants dropped out. Patient characteristics for withdrawals and lost to follow-up were not provided • Although AEs were reported there was no attempt at

Table 7: Strengths and Limitations of Clinical Studies using the Downs and Black Checklist[18]

Strengths	Limitations
eligibility criteria given • Estimates of random variability were reported • Study participants appear to be representative of the population of interest • Data analyses were planned at the outset • It appears that compliance with the allocated treatment was reliable • The main outcome measures used were valid and reliable • The time period over which patients were recruited was specified	providing a comprehensive list of possible AEs a priori • Actual probability values (*P*-values) were not reported • This was an open-label study with no blinding of study participants or outcome assessors • There was no apparent adjustment to the analyses for the different lengths of follow-up due to participant withdrawal and lost to follow-up. Furthermore, patient characteristics for these withdrawals were not provided • There was no information concerning the source of participants included in the study • While participants were randomized in the source studies, the method of randomization is not specified • The analyses were based on the treatment rather than intention to treat • Simple outcome data for the major findings of the study were not presented in a way that allows verification of analyses and conclusions • A power calculation was not reported to determine if the sample was of an adequate size • Sources of funding were disclosed and may have influenced the findings of the study, including that the study received funding from the manufacturer • The authors disclosed conflicts of interest which may have influenced the findings of the study, including that some authors have received funding from the manufacturer
Sullivan, 2015[28]	
• The study's purpose, intervention, and main outcomes were clearly described • Population characteristics were clearly described and eligibility criteria given • A comprehensive attempt was made to measure AEs • Study participants appear to be representative of the population of interest • Data analyses were planned at the outset • It appears that compliance with the allocated treatment was reliable • The main outcome measures used were valid and reliable (e.g., COWS) • The time period over which patients were recruited was specified • Simple outcome data for the major findings of the study were presented in a way that allows verification of analyses and conclusions	• Patient characteristics for withdrawals and lost to follow-up were not provided • Actual probability values (*P*-values) were not reported • This was an open-label study with no blinding of study participants or outcome assessors • There was no apparent adjustment to the analyses for the different lengths of follow-up due to participant withdrawal and lost to follow-up. Furthermore, patient characteristics for these withdrawals were not provided • There was no information concerning the source of participants included in the study • A power calculation was not reported to determine if the sample was of an adequate size • Sources of funding were disclosed and may have influenced the findings of the study, including that the study received funding from the manufacturer • The authors disclosed conflicts of interest which may have influenced the findings of the study, including that some authors have received funding from the manufacturer
Clay, 2014[29]	
• The study's objective, intervention, and main outcomes were clearly described	• AEs were not reported • Patient characteristics for lost to follow-up were not

Table 7: Strengths and Limitations of Clinical Studies using the Downs and Black Checklist[18]

Strengths	Limitations
• Population characteristics were clearly described and inclusion exclusion criteria given • Study participants appear to be representative of the population of interest • Data analyses were planned at the outset • The main outcome measures used were valid and reliable • The time period over which patients were recruited was specified • Simple outcome data for the major findings of the study were presented in a way that allows verification of analyses and conclusions • Actual probability values (*P*-values) were reported	provided • A power calculation was not reported to determine if the sample was of an adequate size • Sources of funding were disclosed and may have influenced the findings of the study, including that the study received funding from the manufacturer • The authors disclosed conflicts of interest which may have influenced the findings of the study, including that some authors have received funding from the manufacturer
Proctor, 2014[30]	
• The study's objective, intervention, and main outcomes were clearly described • Population characteristics were clearly described and inclusion exclusion criteria given • Study participants appear to be representative of the population of interest • Data analyses were planned at the outset • The main outcome measures used were valid and reliable • The time period over which patients were recruited was specified • Simple outcome data for the major findings of the study were presented in a way that allows verification of analyses and conclusions • This was a multi-centre study which increases the generalisability of the results. • Since this was a retrospective study, the source of participants comprised the entire population under study and would be representative • Sources of funding were disclosed and were unlikely to have influenced the findings of the study • The authors disclosed conflicts of interest which were unlikely to have influenced the findings of the study	• AEs were not reported • Simple outcome data for the major findings of the study were not presented in a way that allows verification of analyses and conclusions • Patient characteristics for lost to follow-up were not provided • Actual probability values (*P*-values) were not reported • A power calculation was not reported to determine if the sample was of an adequate size
Soyka, 2014[31]	
• The study's objective, intervention, and main outcomes were clearly described • Population characteristics were clearly described • Study participants appeared to be representative of the population of interest • Data analyses were planned at the outset • The main outcome measures used were valid and reliable • Simple outcome data for the major findings of the study were presented in a way that allows verification of analyses and conclusions •	• Population inclusion and exclusion criteria were not reported • The time period over which patients were recruited was not specified • Although AEs were reported there was no attempt at providing a comprehensive list of possible AEs a priori • Patient characteristics for lost to follow-up were not provided • A power calculation was not reported to determine if the sample was of an adequate size • Sources of funding were not disclosed

Table 7: Strengths and Limitations of Clinical Studies using the Downs and Black Checklist[18]

Strengths	Limitations
	• The authors disclosed conflicts of interest which may have influenced the findings of the study, including that some authors have received funding from the manufacturer

AE = adverse event; COWS = Clinical Opiate Withdrawal Scale; OOWS = Objective Opiate Withdrawal Scale; SOWS = Subjective Opiate Withdrawal Scale.

Table 8: Strengths and Limitations of Economic Studies using the Drummond Checklist[17]

Strengths	Limitations
Institute for Clinical and Economic Review, 2018[20]	
Study design • The research questions, economic importance of the research question, viewpoints of the analysis, and rationale for choosing alternative interventions compared were clearly stated • The treatment strategies being compared were clearly described • Justification was provided for including both US health care sector and societal perspectives in the analysis • The form of economic evaluation used was stated (5-state Markov model) • The choice of form of economic evaluation was justified in relation to the questions addressed **Data collection** • The sources of effectiveness estimates and drug costs were provided and described in detail • The primary outcome measures for the economic evaluation were clearly stated • Methods to value benefits were stated • Details of the subjects from whom valuations were obtained were given • Productivity loss was considered in a scenario analysis that took a modified societal perspective • Drug prices per dose were provided • Details of currency were given (all costs were inflated to 2018 US dollars) • The structure of the Markov model was clearly described **Analysis and interpretation of results** • Time horizon of costs and benefits was stated (5 years in the base-case) • The discount rate for costs and outcomes was stated (3% per year) • The approach to sensitivity analysis was given • The choice of variables for sensitivity analysis were justified • The answer to the study question was given • Incremental analysis was reported • Conclusions follow from the data reported **Conflicts of interest and source of funding** • The authors and expert reviewers stated that they had no conflicts of interest related to this analysis • Sources of funding were disclosed (government grants and non-profit foundations) and were unlikely to have influenced the findings of the analysis	• Justification for selecting a 3% discount rate was not provided • The findings of this US-based study may not be generalizable to the Canadian health system

Table 8: Strengths and Limitations of Economic Studies using the Drummond Checklist[17]

Strengths	Limitations
Carter, 2017[32]	
Study design • The research questions, economic importance of the research question, viewpoints of the analysis, and rationale for choosing alternative interventions compared were clearly stated • The treatment strategies being compared were clearly described • The form of economic evaluation used was stated (4-state Markov model) • The choice of form of economic evaluation was justified in relation to the questions addressed **Data collection** • The sources of effectiveness estimates and drug costs were provided and described in detail • The primary outcome measures for the economic evaluation were clearly stated • Methods to value benefits were stated • Details of the subjects from whom valuations were obtained were given • Productivity loss were reported separately from other clinical and economic outcomes • Details of currency were given (all costs were adjusted to 2016 US dollars) • The structure of the Markov model was clearly described **Analysis and interpretation of results** • Time horizon of costs and benefits was stated (12 months) • The discount rate was stated (0%) • The approach to sensitivity analysis was given • The choice of variables for sensitivity analysis were justified • The answer to the study question is given • Incremental analysis was reported • Conclusions follow from the data reported	• The choice of using a US societal perspective was not justified by the authors • A one year time-horizon may not accurately reflect the economics of the chronic condition investigated (OUD) • The model did not consider the possibility of patients transitioning to an off treatment, not relapsed state • Both treatment cohorts received monthly psychosocial counselling if they were retained in treatment, an assumption that may not accurately reflect adherence rates to these sorts of therapies • The study was funded by Braeburn Pharmaceutical, a pharmaceutical company that holds the US rights to [the buprenorphine implant] (the treatment that was estimated as being cost-effective in the analysis) • The authors of the study declared a series of ties to industry, including former or current employment to Braeburn Pharmaceuticals and EPI-Q Inc. • The findings of this US-based study may not be generalizable to the Canadian health system

OUD = opioid use disorder.

Table 9: Strengths and Limitations of Guidelines using AGREE II[19]

Item	Guideline	
	CRISM, 2018[13]	Department of Veterans Affairs/Department of Defense, 2015[14]
Domain 1: Scope and Purpose		
1. The overall objective(s) of the guideline is (are) specifically described.	Yes	Yes
2. The health question(s) covered by the guideline is (are) specifically described.	Yes	Yes
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	Yes	Yes
Domain 2: Stakeholder Involvement		
4. The guideline development group includes individuals from all relevant professional groups.	Yes	Yes
5. The views and preferences of the target population (patients, public, etc.) have been sought.	Yes	No
6. The target users of the guideline are clearly defined.	Yes	Yes
Domain 3: Rigour of Development		
7. Systematic methods were used to search for evidence.	No	Yes
8. The criteria for selecting the evidence are clearly described.	Yes	Yes
9. The strengths and limitations of the body of evidence are clearly described.	Yes	Yes
10. The methods for formulating the recommendations are clearly described.	Yes	Yes
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.	Yes	Yes
12. There is an explicit link between the recommendations and the supporting evidence.	Yes	No
13. The guideline has been externally reviewed by experts prior to its publication.	Yes	Yes
14. A procedure for updating the guideline is provided.	Yes	No
Domain 4: Clarity of Presentation		
15. The recommendations are specific and unambiguous.	Yes	Yes
16. The different options for management of the condition or health issue are clearly presented.	Yes	Yes
17. Key recommendations are easily identifiable.	Yes	Yes
Domain 5: Applicability		
18. The guideline describes facilitators and barriers to its application.	No	No
19. The guideline provides advice and/or tools on how the	No	No

Table 9: Strengths and Limitations of Guidelines using AGREE II[19]

Item	Guideline	
recommendations can be put into practice.		
20. The potential resource implications of applying the recommendations have been considered.	No	No
21. The guideline presents monitoring and/or auditing criteria.	No	No
Domain 6: Editorial Independence		
22. The views of the funding body have not influenced the content of the guideline.	Yes	Yes
23. Competing interests of guideline development group members have been recorded and addressed.	Yes	Yes

Appendix 4: Main Study Findings and Authors' Conclusions

Table 10: Summary of Findings of Included Systematic Reviews

<table>
<tr><th>Main Study Findings</th><th>Authors' Conclusion</th></tr>
<tr><td colspan="2">Institute for Clinical and Economic Review, 2018[20]</td></tr>
<tr><td>Systematic review that investigated the effectiveness and value of new medication options (i.e., buprenorphine subcutaneous extended-release injection, buprenorphine implant, naltrexone intramuscular extended-release injection) in patients with OUD.

Relevant individual studies: The systematic review included 5 relevant primary studies on the comparative clinical effectiveness of buprenorphine or BUP-NAL formulations for the treatment of OUD.

Findings: The systematic review presented results on various relevant clinical outcomes .

Comparison of buprenorphine subcutaneous extended-release injection (BSERI) and sublingual BUP-NAL (SLBN) for the treatment of OUD with respect to several outcomes
<table>
<tr><th rowspan="3">Primary study citation (sample size)</th><th rowspan="3">Follow-up</th><th colspan="2">Mean outcome value</th><th rowspan="3">Statistical significance[a] (P-value)</th></tr>
<tr><th colspan="2">Treatment group</th></tr>
<tr><th>BSERI</th><th>SLBN</th></tr>
<tr><td colspan="5">Opioid-Negative Urine Samples (%)</td></tr>
<tr><td>Lofwall, 2018 (N = 428)</td><td>Week 1-24
Week 1-12
Week 13-24
Week 4-24</td><td>35.1 (SE: 2.5)
35.8 (SE: 2.6)
33.9 (SE: 2.6)
35.1 (SE: 2.5)</td><td>28.4 (SE: 2.5)
29.9 (SE: 2.6)
25.4 (SE: 2.6)
26.7 (SE: 2.5)</td><td>NS
NS
0.02
0.004</td></tr>
<tr><td>CPDD Injection Poster, 2018 (N = 224)</td><td>Week 4-24</td><td>30.9 (SE: 3.3)</td><td>15.4 (SE: 2.7)</td><td>< 0.001</td></tr>
<tr><td>CPDD Heroin Poster, 2018 (N = 303)</td><td>Week 4-24</td><td>29.9</td><td>12.7</td><td>< 0.001</td></tr>
<tr><td colspan="5">All-Cause Discontinuations (%)</td></tr>
<tr><td>Lofwall, 2018 (N = 428)</td><td>Any time point</td><td>41</td><td>43</td><td>NR</td></tr>
<tr><td colspan="5">Opioid Craving – VAS Scores (mean score)</td></tr>
<tr><td>Lofwall, 2018 (N = 428)</td><td>Week 1-24</td><td>17.3 (SD: 25.5)</td><td>17.3 (SD: 25.5)</td><td>NR</td></tr>
<tr><td colspan="5">Opioid Withdrawal –COWS Scores (mean change from baseline)</td></tr>
<tr><td>Lofwall, 2018 (N = 428)</td><td>Week 24</td><td>3.3 (SD: 3.5)</td><td>2.7 (SD: 4.0)</td><td>NR</td></tr>
<tr><td colspan="5">Serious Adverse Events (%)</td></tr>
<tr><td>Lofwall, 2018 (N = 428)</td><td>Any time point</td><td>2.3</td><td>6</td><td>NR</td></tr>
<tr><td>CPDD</td><td>Any time point</td><td>1.8</td><td>14.5</td><td>NR</td></tr>
</table>
</td><td>"Evidence for [subcutaneous buprenorphine] is comprised of one 24-week Phase III trial in comparison to buprenorphine/naloxone. Data was limited on clinical outcomes due to the limed number of trials available for synthesis. Results found [subcutaneous buprenorphine] to be non-inferior to buprenorphine, but not significantly different in abstinence, opioid craving, and opioid withdrawal. Similarly, while discontinuation rates were high, they did not differ between the active arms, and safety profiles were also comparable. For participants with OUD being considered for MAT, we have moderate certainty that [subcutaneous buprenorphine] provides a small, or substantial net health benefit given the increased convenience and provider interaction associated with subcutaneous injections, but high certainty that it is at least comparable as it is a buprenorphine-containing treatment. Therefore, we consider the evidence on [subcutaneous buprenorphine] to be comparable or better."[20] (p49)

"Evidence for [buprenorphine implant] compared to buprenorphine/ naloxone comprises two 24-week Phase III trials, although only one was considered key. Due to the inclusion criteria and trial design, the</td></tr>
</table>

Table 10: Summary of Findings of Included Systematic Reviews

Main Study Findings					Authors' Conclusion
Injection Poster, 2018 (N = 224)					populations in the trials may be different from the general population being considered for MAT. The key trial included only participants who were clinically stable and receiving buprenorphine tablets for at least 24 weeks *before* the trial. Additionally, the other trial excluded participants with severe opioid withdrawal symptoms and cravings, which may have inflated the reported benefits of [the buprenorphine implant] on abstinence outcomes in this trial. No significant differences were found for opioid craving and opioid withdrawal. Similar rates of discontinuation occurred between both active arms, along with similar proportions of serious adverse events. For participants with OUD being considered for MAT, we have moderate certainty of a comparable or small net health for the trial populations. However, we have concerns that the study population may not be reflective of the more general population being considered for MAT. Therefore, we consider the evidence on [the buprenorphine implant] in comparison to buprenorphine/naloxone to be promising but inconclusive."[20] (*p*49)
Discontinuation Due to Adverse Events (%)					
Lofwall, 2018 (N = 428)	Any time point	3.3	1.4	NR	
At Least One Opioid Overdose Event (%)					
Lofwall, 2018 (N = 428)	Any time point	0	2.3	NR	
CPDD Injection Poster, 2018 (N = 224)	Any time point	0	4.5	NR	
Fatal Overdoses (%)					
Lofwall, 2018 (N = 428)	Any time point	0	0	NR	
CPDD Injection Poster, 2018 (N = 224)	Any time point	0	0	NR	
Deaths (%)					
Lofwall, 2018 (N = 428)	Any time point	0.5	0	NR	
CPDD Injection Poster, 2018 (N = 224)	Any time point	NR	0	NR	

[a]The threshold for statistical significance was set to $P < 0.05$.
BSERI = buprenorphine subcutaneous extended-release injection; COWS = Clinical Opiate Withdrawal Scale; N = number of patients; NR = not reported; NS = non-significant; SD = standard deviation; SE = standard error; SLBN = sublingual buprenorphine-naloxone; VAS = visual analog scale.

Comparison of buprenorphine implant (BI) and sublingual BUP-NAL (SLBN) for the treatment of OUD with respect to several outcomes

Primary study citation (sample size)	Follow-up	Mean outcome value		Statistical significance[a] (*P*-value)
		Treatment group		
		BI	SLBN	
Opioid-Negative Urine Samples (%)				
Rosenthal, 2016 (N = 177)	Week 24	85.7 (SE: NR)	71.9 (SE: NR)	0.027
Rosenthal, 2013	Week 1-24 Week 1-16	31.2 (SE: NR) 39.6 (SE: NR)	33.5 (SE: NR) 37.8 (SE: NR)	NS NS

Table 10: Summary of Findings of Included Systematic Reviews

Main Study Findings					Authors' Conclusion
(N = 233)	Week 17-24	28.9 (SE: NR)	29.6 (SE: NR)	NS	
All-Cause Discontinuations (%)					
Rosenthal, 2016 (N = 177)	Any time point	7	6	NR	
Rosenthal, 2013 (N = 233)	Any time point	36	36	NR	
Opioid Craving – Mean VAS Scores					
Rosenthal, 2013 (N = 233)	Week 1-24	10.2	7.1	0.054	
Opioid Withdrawal – COWS Scores (mean change from baseline)					
Rosenthal, 2016 (N = 177)	Week 24	-0.1 (SD: 1.51)	-0.1 (SD: 1.69)	NS	
Rosenthal, 2013 (N = 233)	Week 24	2.49 (SD: NR)	1.71 (SD: NR)	0.0005	
Opioid Withdrawal – SOWS Scores (mean change from baseline)					
Rosenthal, 2016 (N = 177)	Week 24	-0.6 (SD: 4.63)	0.1 (SD: 5.26)	NS	
Rosenthal, 2013 (N = 233)	Week 24	5.3 (SD: NR)	2.83 (SD: NR)	0.0006	
Serious Adverse Events (%)					
Rosenthal, 2016 (N = 177)	Any time point	2.3	3.4	NR	
Rosenthal, 2013 (N = 233)	Any time point	5.3	5.9	NR	
Discontinuation Due to Adverse Events (%)					
Rosenthal, 2016 (N = 177)	Any time point	1.1	0	NR	
Rosenthal, 2013 (N = 233)	Any time point	0	0.8	NR	
Fatal Overdoses (%)					
Rosenthal, 2013 (N = 233)	Any time point	0	0.8	NR	
Deaths (%)					
Rosenthal, 2013 (N = 233)	Any time point	0	0.8	NR	

[a]The threshold for statistical significance was set to $P < 0.05$.
BI = buprenorphine implant; COWS = Clinical Opiate Withdrawal Scale; N = number of patients; NR = not reported; NS = non-significant; SD = standard deviation; SE = standard error; SLBN = sublingual buprenorphine-naloxone; SOWS = Subjective Opiate Withdrawal Scale; VAS = visual analog scale.

Table 10: Summary of Findings of Included Systematic Reviews

<table>
<tr><th>Main Study Findings</th><th>Authors' Conclusion</th></tr>
<tr><td colspan="2">Minozzi, 2014[21]</td></tr>
<tr><td>Systematic review that investigated the clinical effectiveness of any maintenance treatment alone or in combination with psychosocial intervention compared to no intervention, other pharmacological intervention, or psychosocial interventions for the treatment of adolescents with OUD.

Relevant individual studies: The systematic review included one relevant primary study on the comparative clinical effectiveness of BUP-NAL maintenance versus buprenorphine detoxification for the treatment of OUD.

Findings: The systematic review presented results on various clinical outcomes that could be extracted for the relevant studies.

Comparison of BUP-NAL maintenance (maintenance) versus buprenorphine detoxification (detox) for the treatment of OUD with respect to several outcomes
<table>
<tr><th rowspan="3">Primary study citation</th><th rowspan="3">Outcome</th><th colspan="2">Number of patients with an event</th><th rowspan="3">Risk ratio (95% CI)</th></tr>
<tr><th colspan="2">Treatment group</th></tr>
<tr><th>Maintenance (N = 74)</th><th>Detox (N = 78)</th></tr>
<tr><td rowspan="8">Woody, 2008 (N = 233)</td><td>Drop-outs</td><td>22</td><td>62</td><td>0.37 (0.26 to 0.54)</td></tr>
<tr><td>Positive urine test at the end of treatment</td><td>49</td><td>53</td><td>0.97 (0.78 to 1.22)</td></tr>
<tr><td>Self-reported heroin use at 12-month FU</td><td>39</td><td>56</td><td>0.73 (0.57 to 0.95)</td></tr>
<tr><td>Enrolment in addiction treatment at 12-month FU</td><td>39</td><td>31</td><td>1.33 (0.94 to 1.88)</td></tr>
<tr><td>Self-reported alcohol use</td><td>16</td><td>19</td><td>0.89 (0.49 to 1.59)</td></tr>
<tr><td>Self-reported marijuana use</td><td>12</td><td>20</td><td>0.63 (0.33 to 1.20)</td></tr>
<tr><td>Self-reported cocaine use</td><td>1</td><td>9</td><td>0.12 (0.02 to 0.90)</td></tr>
</table>
CI = confidence interval; FU = follow-up; N = number of patients.</td><td>"Maintenance treatment appeared to be more efficacious in retaining patients in treatment but not in reducing patients with a positive urine test at the end of the study. Self reported opioid use at one-year follow-up was significantly lower in the maintenance group, even though both groups reported a high level of opioid use and more patients in the maintenance group were enrolled in other addiction treatment programmes at 12-month follow-up."[21] (p15)

"There is an urgent need for further randomised controlled trials comparing maintenance treatment with detoxification treatment or psychosocial treatment alone before carrying out studies that compare different pharmacological maintenance treatments. These studies should have long follow-up and measure relapse rates after the end of treatment and social functioning (integration at school or at work, family relationships)."[21] (p16)</td></tr>
</table>

MAT = medication-assisted treatment; OUD = opioid use disorder.

Table 11: Summary of Findings of Included Primary Clinical Studies

Main Study Findings	Authors' Conclusion
Randomized Controlled Trials	
Strang, 2017[22]	

A randomized open-label study to test the safety of buprenorphine oral lyophilisate wafer versus the sublingual formulation.
 	
Retention in treatment:
• BUP-NAL rapid dissolving sublingual tablet
  ○ End of titration period (day 7): 96%.
  ○ End of maintenance period (day 14): 91%.
• BUP-NAL sublingual film
  ○ End of titration period (day 7): 85%
  ○ End of maintenance period (day 14): 85%.
 	
OOWS and SOWS:
• "No significant between-group differences were detected"[22] (*p*64)
 	
Adverse events:
• BUP-NAL rapid dissolving sublingual tablet
  ○ Deaths = 0; serious AE = 0; severe AE = 0; moderate AE = 4; mild AE = 13; number of subjects withdrawal due to TEAEs = 0
• BUP-NAL sublingual film
  ○ Deaths = 0; serious AE = 0; severe AE = 0; moderate AE = 3; mild AE = 1; number of subjects withdrawal due to TEAEs = 0
 	
Laboratory tests, physical examination, and ECG recordings:
"No clinically significant differences were observed between groups […]"[22] (*p*65)
	" No increased respiratory depression was found and clinically no difference between medications was observed. […] In supervised dosing contexts, rapidly disintegrating formulations may enable wider buprenorphine prescribing."[22] (*p*61)

Gunderson, 2016[23]	

A secondary analysis of a blinded, randomized trial examining the effect of switching treatments between a BUP-NAL rapid dissolving sublingual tablet and a BUP-NAL film formulation.
 	
Mean (SD) COWS scores:
• Intervention group
  ○ Day 15, tablet: 4.1 (±3.5)
  ○ Day 22, after switch to film: 3.3 (±3.4)
• Comparator group
  ○ Day 15, film: 3.7 (±3.4)
  ○ Day 22, after switch to tablet: 3.4 (±3.3)
 	
Mean (SD) SOWS scores:
• Intervention group
  ○ Day 15, tablet: 7.2 (±7.7)
  ○ Day 22, after switch to film: 7.3 (±9.2)
• Comparator group
  ○ Day 15, film: 6.7 (±8.1)
  ○ Day 22, after switch to tablet: 6.8 (±7.9)
 	
Mean (SD) VAS craving scores:
• Intervention group
  ○ Day 15, tablet: 21.6 (±23.9)
	"These data indicate that among opioid-dependent patients receiving BNX maintenance treatment, transition between BNX film and BNX-RDT may be undertaken with comparable efficacy and safety. Patient discontinuation rates during the treatment switch phase were similar for each group, and the transition between both products was associated with continued withdrawal suppression, craving reduction, and similar safety profiles. Thus, there is no apparent clinical rationale from the findings indicating limitations when switching patients between the film and tablet products tested in the study. Most patients

Table 11: Summary of Findings of Included Primary Clinical Studies

Main Study Findings	Authors' Conclusion
○ Day 22, after switch to film: 20.9 (±23.8) • Comparator group ○ Day 15, film: 19.1 (±23.4) ○ Day 22, after switch to tablet: 20.2 (±22.9) **Treatment-related AEs** • During entire open-label phase: ○ BUP-NAL rapid dissolving sublingual tablet: 53 out of 635. ○ BUP-NAL sublingual film: 47 out of 630 **Serious AE**: "However, after the day 15 switch, 1 patient in the BNX film group experienced a serious AE of increased transaminase levels deemed unrelated to study medication."[23] (*p*126)	preferred BNX-RDT over BNX film; however, further study is required regarding the clinical implications of patient preference."[23] (*p*128)
Webster, 2016[24]	
A prospective randomized, multi-centre blinded (induction), open-label (maintenance), parallel-group, active-controlled, noninferiority trial to evaluate whether BUP-NAL rapid dissolving sublingual tablet was noninferior to generic buprenorphine during the induction phase of treatment. **Retention in treatment**: • BUP-NAL rapid dissolving sublingual tablet: ○ Day 3: 132 out of 155 • Generic buprenorphine sublingual tablets: ○ Day 3: 147 out of 155 • Between-group statistical significance: *P* = 0.040 **Mean (SD) COWS improvements from baseline**: • Intervention group ○ Day 4: −9.4 (±5.8) ○ Day 29: −12.5 (±5.2) • Comparator group ○ Day 4: −8.5 (±5.7) ○ Day 29: −11.4 (±5.4) **Mean (SD) SOWS improvements from baseline**: • Intervention group ○ Day 4: −24.7 (±16.0) ○ Day 29: −30.4 (±16.0) • Comparator group ○ Day 4: −18.9 (±13.8) ○ Day 29: −24.3 (±14.2) **Mean (SD) VAS craving scores**: • Intervention group ○ Day 4: −40.1 (±28.6) ○ Day 29: −52.7 (±29.1) • Comparator group ○ Day 4: −34.2 (±29.4) ○ Day 29: −45.1 (±29.8) **Adverse events**: • Intervention group (n = 155): AE = 45; TEAE = 32; Severe AE = 3; Severe TEAE = 2; Serious	"Overall, the results from these analyses demonstrate that BNX-RDT and generic buprenorphine are both effective for induction treatment of adults with opioid dependence. Although non-inferiority of BNX-RDT to generic buprenorphine in treatment retention at day 3 was not established in the present study, retention was comparable in the pooled analysis that included a larger sample size. Both BNX-RDT and generic buprenorphine treatments were well-tolerated and demonstrated comparable efficacy in reducing withdrawal symptoms and cravings. Improvements in withdrawal symptoms, cravings, and opioid use were sustained during stabilization and maintenance treatment with BNX-RDT. Taken together, these findings suggest that BNX-RDT is a well-tolerated and effective treatment for both induction and maintenance of adult patients with opioid dependence."[24] (*p*336)

Table 11: Summary of Findings of Included Primary Clinical Studies

Main Study Findings	Authors' Conclusion
AE = 1; Serious TEAE = 0; AE leading to discontinuation = 2 ○ Nausea = 12; headache = 11; vomiting = 8; insomnia = 6; constipation = 6 • Comparator group (n = 155): AE = 46; TEAE = 38; Severe AE = 1; Severe TEAE = 1; Serious AE = 0; Serious TEAE = 0; AE leading to discontinuation = 1 ○ Nausea = 13; headache = 11; vomiting = 8; insomnia = 11; constipation = 9 • "Two patients (0.7%) experienced two SAEs of attempted suicide and bacteremia secondary to pyelonephritis; both were determined unrelated to study medication. A total of three patients (1.1%) experienced four AEs that resulted in study discontinuation. No deaths occurred during either phase of the study."[24] (*p*334)	
Gunderson, 2015[25]	
A blinded, randomized, parallel-group, multi-centre, noninferiority trial assessing the efficacy of a BUP-NAL sublingual tablet, generic buprenorphine, and a BUP-NAL film formulation. **Retention rate**: • Day 3: ○ BUP-NAL sublingual tablet: 309 of 329 participants. ○ Generic buprenorphine: 302 of 326 participants • Day 15: ○ BUP-NAL sublingual tablet: 273 of 329 participants. ○ BUP-NAL film (switched from generic buprenorphine): 269 of 326 participants **Least squares mean AUC values of COWS for days 1 to 15**: • BUP-NAL sublingual tablet = 5.43 • Generic buprenorphine switched to BUP-NAL film = 5.53 **Least squares mean AUC values of SOWS for days 1 to 15**: • BUP-NAL sublingual tablet = 11.17 • Generic buprenorphine switched to BUP-NAL film = 11.25 **Least squares mean AUC values of VAS for cravings for days 1 to 15**: • BUP-NAL sublingual tablet = 30.76 • Generic buprenorphine switched to BUP-NAL film: = 30.07 **Treatment-related adverse events reported in greater than 1% of patients**: • BUP-NAL sublingual tablet ○ Double-blind period (days 1 and 2): Any = 61; headache = 20; vomiting = 12; nausea = 8; dry mouth = 8; somnolence = 6; insomnia = 5; constipation = 4. ▪ Two discontinuations ○ Open-label period (days 3 to 15): Any = 42; constipation = 10; headache = 5; nausea = 5; somnolence = 5; vomiting = 4 ▪ Two discontinuations • Generic buprenorphine switched to BUP-NAL film ○ Double-blind period (days 1 and 2): Any = 55; headache = 19; vomiting = 11; nausea = 15; dry mouth = 2; somnolence = 2; insomnia = 4; constipation = 3. ▪ Two discontinuations ○ Open-label period (days 3 to 15): Any = 37; constipation = 12; headache = 7; nausea = 1; somnolence = 1; vomiting = 2	"Non-inferiority was established between the higher-bioavailability sublingual BNX tablet formulation and the generic buprenorphine tablet formulation during the induction phase and between the higher-bioavailability BNX tablet and BNX film during the early stabilization phase of treatment among these patients dependent on short- or long-acting opioids. Treatment-retention rates on day 3 (after induction) and on day 15 (after stabilization) were similar between treatment groups, as were the decreases in withdrawal symptoms and opioid cravings. Comparable efficacy between treatments was achieved despite the administration of less buprenorphine in the BNX sublingual tablet compared with generic buprenorphine or BNX film, which is consistent with the enhanced trans-mucosal absorption of active ingredients from the BNX sublingual tablet formulation. The findings from this study suggest that the higher-bioavailability BNX sublingual tablet formulation is an efficacious and well-tolerated option for induction and early stabilization treatment of opioid

Table 11: Summary of Findings of Included Primary Clinical Studies

Main Study Findings	Authors' Conclusion
	dependence. Overall, the findings from this study provide important information for guiding informed treatment decisions by prescribers and patients during the induction and maintenance phases of treatment, as well as potentially to lessen the public health epidemic of opioid dependence."[25] (*p*2253)
Non-Randomized Studies	
Kelty, 2018[26]	
A retrospective cohort study examining and comparing rates of morbidity and mortality in opioid dependent patients treated with buprenorphine and BUP-NAL. **Mortality**: • Rates of all-cause mortalities did not statistically differ between participants in the BUP-NAL group (9.6 per 1000 patient years) compared with the buprenorphine group (7.0 per 1000 patient years) (*P* = 0.055) **Hospital admissions**: • Rates of all-cause hospital admissions were significantly higher in participants in the BUP-NAL group (592.1 per 1000 patient years) compared with the buprenorphine group (428.8 per 1000 patient years) (*P* < 0.001) **Emergency department admissions**: • Rates of all-cause emergency department admissions were significantly higher in participants in the BUP-NAL group (1133.7 per 1000 patient years) compared with the buprenorphine group (938.2 per 1000 patient years) (*P* < 0.001)	"The addition of NLX to the sublingual BUP preparation was not associated with improved health outcomes, with the exception of reduced incidence of hospital and ED admissions associated with skin and subcutaneous conditions. In contrast, elevated rates of mortality and morbidity were observed in BUP-NLX patients following the cessation of treatment, potentially associated with upregulation of the opioid receptors as a result of prolonged exposure to NLX. Further prospective research is required to compare the safety profile of BUP and BUP-NLX and their posttreatment health outcomes."[26] (*p*351)
Hoffman, 2017[27]	

A multi-centre, open-label, uncontrolled extension study assessing the safety of rapidly dissolving BUP-NAL sublingual tablets in participants with opioid dependency.
 	
Safety:
• Treatment-emergent adverse events (N = 258 patients, 557 events), most frequent:
  ○ Headache = 21 patients; constipation = 20 patients
• Severe treatment-emergent adverse events:
  ○ Constipation = 2 patients; depression = 1 patients; drug withdrawal syndrome = 1 patient
• 14 discontinuations, of which: abnormal laboratory values = 3; vomiting = 1; depression = 1; constipation = 1
	"Administration of BNX-RDT over 6 months after stabilization on buprenorphine-based therapy was well-tolerated with no new safety signals identified. Whereas efficacy was not the primary objective of the current study, improvements were observed in opioid

Table 11: Summary of Findings of Included Primary Clinical Studies

Main Study Findings	Authors' Conclusion
• Nine treatment-emergent SAEs, severe depression = 1; • Two patients experienced SAEs that resulted in death, toxic effects of heroin =1; cardiovascular disease =1. • Laboratory abnormalities in 29 patients, three discontinued. • Seven patients experienced vital sign abnormalities, considered TEAEs.	cravings, addiction severity, QOL, and HEOs in patients with opioid dependence. In the real-world clinical setting, treatment with BNX-RDT may help individuals who misuse opioids advance in their recovery, as those who continue an effective treatment regimen can expect improvements in social, emotional, and physical functioning, and also increased presence and productivity in the workplace."[27] (*p*223)
Sullivan, 2015[28]	

A multi-centre, open-label, prospective cohort study assessing the safety, tolerability, symptom control, and patient acceptance of BUP-NAL buccal film.
 	
Safety:
• TEAE = 192 participants (77.1%); drug related AE = 130 participants (52.2%); deaths = 0 (0%); Serious AE = 2 (0.8%**)**; Withdrawal due to an AE = 11 (4.0%; of which 5 experiencing withdrawal symptoms).
  ○ TEAE occurring in greater than 5% of participants:
  ▪ Lethargy = 22; Headache = 20; Nasopharyngitis = 14
• "There were no clinically significant changes in vital signs and no changes in mean ECG parameters across the study period."**[28]** (*p*1068)
• Three participants had mucosal redness that was considered drug related.
• Treatment-emergent constipation = 7 out of 249
• Patients with treatment-emergent drug withdrawal syndrome
  ○ Severe = 0
  ○ Moderate
  ▪ Requiring 0 dose adjustment = 5
  ▪ Requiring 1 dose adjustment = 5
  ▪ Requiring 2 dose adjustments = 3
  ○ Mild
  ▪ Requiring 0 dose adjustment = 16
  ▪ Requiring 1 dose adjustment = 44
  ▪ Requiring 2 dose adjustments = 16
  ○ Absent
  ▪ Requiring 0 dose adjustment = 136
  ▪ Requiring 1 dose adjustment = 20
  ▪ Requiring 2 dose adjustments = 4
	"While these results should be considered preliminary due to the open-label design, BBN was overall safe and well tolerated, and it appeared to provide adequate symptom control, in the treatment of opioid-dependent subjects previously controlled on SLBN for a minimum of 30 days. There was good adherence to study medication and favorable patient acceptance of the buccal formulation. The SLBN-BBN buprenorphine conversion ratio was 2:1."[28] (*p*1074)

Clay, 2014[29]	
A retrospective cohort study comparing persistence in treatment, healthcare resource utilization, and total healthcare costs between patients treated with BUP-NAL sublingual film and the sublingual tablet formulation. **Discontinuations:**	"Patients treated with the film formulation of buprenorphine/ naloxone appeared to stay longer on treatment, have lower probability to be

Table 11: Summary of Findings of Included Primary Clinical Studies

Main Study Findings	Authors' Conclusion

• BUP-NAL sublingual film formulation: 1,134 cases
• BUP-NAL sublingual tablet formulation: 821 cases
• Treatment persistence at 6 months was significantly higher in the film group (63.78%) than in the tablet group (58.13%); *P* = 0.002
 	
Switch:
"In the tablet group, 251 (16.62%) patients switched to film. Of the patients on film, 102 (3.65%) switched to tablet."[29] (*p*632)
 	
Mean (CI) resource utilization 12 months before index date:
• BUP-NAL sublingual film
  ○ Pharmacy claims = 26.76 (23.16 to 30.92)
  ○ Probability to have at least one hospitalization = 0.3 (0.26 to 0.35)
  ○ Outpatient visits = 8.93 (8.14 to 9.80)
• BUP-NAL sublingual tablet
  ○ Pharmacy claims = 28.32 (24.37 to 32.90)
  ○ Probability to have at least one hospitalization = 0.34 (0.30 to 0.39)
  ○ Outpatient visits = 8.74 (7.96 to 9.61)
 	
Mean (CI) resource utilization 12 months after index date:
• BUP-NAL sublingual film
  ○ Pharmacy claims = 32.71 (26.95 to 39.70)
  ○ Probability to have at least one hospitalization = 0.19 (0.17 to 0.22)
  ○ Outpatient visits = 9.88 (8.95 to 10.92)
• BUP-NAL sublingual tablet
  ○ Pharmacy claims = 33.61 (27.65 to 40.85)
  ○ Probability to have at least one hospitalization = 0.23 (0.20 to 0.25)
  ○ Outpatient visits = 9.51 (8.60 to10.52)
 	
Mean (CI) resource utilization costs 12 months before index date:
• BUP-NAL sublingual film
  ○ Pharmacy = $2,008 (1,582 to 2,549)
  ○ Hospitalization = $7,534 (4,562 to 10,392)
  ○ ER visits = $66 (48 to 91)
  ○ Outpatient (all claims, not just visit) = $6,478 (5,346 to 7,849)
  ○ Total healthcare costs = $17,772 (14,644 to 21,569)
• BUP-NAL sublingual tablet
  ○ Pharmacy = $2,546 (1,988 to 3,260)
  ○ Hospitalization = $9,987 (7,105 to 14,038)
  ○ ER visits = $91 (63 to 130)
  ○ Outpatient (all claims, not just visit) = $7,066 (5,799 to 8,612)
  ○ Total healthcare costs = $20,632 (16,895 to 25,195)
 	
Mean (CI) resource utilization costs 12 months after index date:
• BUP-NAL sublingual film
  ○ Pharmacy = $4,028 (2,586 to 6,275)
  ○ Hospitalization = $5,371 (3.499 to 8,245)
  ○ ER visits = $57 (28 to 112)
  ○ Outpatient (all claims, not just visit) = $5,507 (2,217 to 13,676)
  ○ Total healthcare costs = $14,431 (3,277 to 63,532)
• BUP-NAL sublingual tablet
  ○ Pharmacy = $4,467 (2,886 to 6,963)
	hospitalized, and lower healthcare costs compared to patients who received the tablet formulation. As a retrospective study, it cannot be ascertained whether there is a causal relationship between treatment formulation and the studied outcomes; however, the relationship between formulation and persistence was analyzed in multiple ways, and the results were consistent with the hypothesis that the film formulation led to an improved persistence in treatment. In addition, healthcare costs were found to be higher after treatment discontinuation than during treatment, likely due to the additional expenses related to relapse and the re-initiation of treatment, which contributed to higher total costs with tablet formulation treatment."[29] (*p*635)

Table 11: Summary of Findings of Included Primary Clinical Studies

Main Study Findings	Authors' Conclusion
○ Hospitalization = $8,198 (5,550 to 12,111) ○ ER visits = $79 (42 to 145) ○ Outpatient (all claims, not just visit) = $6,668 (2,685 to 16,558) ○ Total healthcare costs = $19,853 (4,515 to 87,291)	
Proctor, 2014[30]	
A retrospective longitudinal study comparing the effectiveness of methadone, buprenorphine, and BUP-NAL in reducing illicit drug use and retaining patients in treatment. **Retention in treatment and Positive Urinalysis Drug Screens at six months**: • Buprenorphine sublingual: ○ Retention = 20.2% ○ Urine positive for opioids = 21.4% ○ Urine positive for non-opioids = 44.6% • BUP-NAL sublingual: ○ Retention = 30.4% ○ Urine positive for opioids = 11.1% ○ Urine positive for non-opioids = 22.2%	"Comparable rates of illicit drug use at 6 months may be expected irrespective of maintenance medication, while increased retention may be expected for patients maintained on methadone relative to those maintained on Suboxone or Subutex."[30] (*p*424)
Soyka, 2014[31]	
A prospective observational study assessing liver safety of treatment with BUP-NAL in BUP-NAL participants with opioid dependency(N = 337). **Number of participants with elevated alkaline phosphatase**: • Week 12 = 1 • Month 6 = 3 • Month 12 = 3 **Number of participants with elevated glutamic-pyruvic transaminase**: • Week 12 = 7 • Month 6 = 5 • Month 12 = 5 **Number of participants with elevated glutamate oxaloacetate transaminase**: • Week 12 = 7 • Month 6 = 4 • Month 12 = 2 **Number of participants with elevated gamma-glutamyl transpeptidase**: • Week 12 = 5 • Month 6 = 6 • Month 12 = 3 **Adverse events**: • Deaths = 0 • Serious AEs = 4 ○ Liver related = 0 • Non-serious AEs = 59 ○ Liver related = 3	"In conclusion, this prospective, non-interventional study gives further evidence that buprenorphine treatment appears to be safe regarding liver injury in opioid-dependent individuals. Future studies may focus on high-risk individuals with a severe liver disorder, in particular hepatitis C infection, to further explore the possible benefits and risks of buprenorphine-naloxone in such patients."[31] (*p*568)

AE = adverse event; AUC = area under curve; BBN = buprenorphine-naloxone buccal film; BNX = buprenorphine-naloxone; BNX-RDT = buprenorphine-naloxone rapid dissolving tablet; CI = confidence interval; COWS = Clinical Opiate Withdrawal Scale; ECG = electrocardiogram; ER = emergency room; HEOs = health economic

outcomes; N = number of participants; NLX = naloxone; OOWS = Objective Opiate Withdrawal Scale; QOL = quality of life; SAE = severe adverse event; SD = standard deviation; SF-36 = Short Form Health Survey; SLBN = buprenorphine-naloxone sublingual tablet or film; SOWS = Subjective Opiate Withdrawal Scale; TEAE = treatment-emergent adverse event; VAS = visual analogue scale.

Table 12: Summary of Findings of Included Economic Evaluations

Main Study Findings	Authors' Conclusion
Institute for Clinical and Economic Review, 2018[20]	

Economic evaluation that examined the cost-effectiveness of certain drugs used for medication-assisted treatment among a cohort of patients who were considered for OUD treatment. The analysis was conducted using a Markov model from the perspective of the US health care sector.
 	
Summary of relevant findings (all costs are in 2018 US dollars):
- Base case results for buprenorphine subcutaneous extended-release injection (BSERI) versus generic sublingual BUP-NAL (SLBN)
  ○ Drug Costs
  ▪ BSERI = Unknown
  ▪ SLBN = $54,000
  ○ Other Costs
  ▪ BSERI = $66,100
  ▪ SLBN = $64,700
  ○ Total Cost
  ▪ BSERI = Unknown
  ▪ SLBN = $70,100
  ○ Life Years
  ▪ BSERI = 4.62
  ▪ SLBN = 4.62
  ○ QALYs
  ▪ BSERI = 3.26
  ▪ SLBN = 3.20
  ○ **Conclusions**
  ▪ The incremental cost-effectiveness ratio for BSERI could not be estimated due to the lack of a list price or net price
 	
- Base case results for buprenorphine implant (BI) versus generic sublingual BUP-NAL (SLBN)
  ○ Drug Costs
  ▪ BI = $11,000
  ▪ SLBN = $8,600
  ○ Other Costs
  ▪ BI = $66,900
  ▪ SLBN = $66,500
  ○ Total Costs
  ▪ BI = $77,900
  ▪ SLBN = $75,100
  ○ Life Years
  ▪ BI = 4.62
  ▪ SLBN = 4.62
  ○ QALYs
  ▪ BI = 3.38
  ▪ SLBN = 3.37
  ○ Incremental Cost per QALY Gained
  ▪ BI = $265,000
  ▪ SLBN = reference
	"In conclusion, the findings of our analysis suggest that [subcutaneous buprenorphine], Vivitrol and [the buprenorphine implant] result in only marginal changes in QALYs relative to generic SL buprenorphine/naloxone, but universally higher costs. The incremental cost-effectiveness of these therapies versus generic SL buprenorphine/naloxone therefore falls outside commonly-cited thresholds of $50,000 to $150,000 per QALY gained. Even with assumptions extremely favorable to Sublocade, its incremental cost-effectiveness versus generic SL buprenorphine/naloxone also falls outside these commonly-cited thresholds."[20] (*p*75)

Carter, 2017[32]	
Economic evaluation that examined the cost-effectiveness of subdermal implantable buprenorphine (BSI) versus sublingual buprenorphine (SLB) for the treatment of OUD. The analysis was conducted using a Markov model from a United States societal perspective. Summary of relevant findings:	"The outcomes of this model support BSI as a pharmacoeconomically preferable treatment option

Table 12: Summary of Findings of Included Economic Evaluations

Main Study Findings	Authors' Conclusion
- Base case results for subdermal implantable buprenorphine (BSI) versus sublingual buprenorphine (SLB) ○ Rate of Complete Abstinence ▪ SBI = 75% ▪ SLB = 54% ○ Retention in Treatment ▪ SBI = 78% ▪ SLB = 58% ○ Total Costs per Patient ▪ SBI = $20,733 ▪ SLB = $25,119 ○ QALYs ▪ SBI = 0.832 ▪ SLB = 0.801 ○ **Conclusions** ▪ Treatment with BSI resulted in decreased costs to society and increased QALYs; therefore, BSI was the dominant treatment option.	for opioid dependent, clinically-stable adults. This stable patient sub-group comprises only a portion of the treated OUD population, but the benefits of BSI in this sub-group might also translate into a re-distribution of resources to more effectively treat other sub-groups (e.g. less stable, new entrants to treatment). While no health-economic model should circumvent clinical judgment, providers, payors, and policy-makers should be aware that BSI offers an opportunity to improve outcomes and reduce costs."[32] (*p*898)

BI = buprenorphine implant; BSI = subdermal implantable buprenorphine; OUD = opioid use disorder; QALY = quality-adjusted life year; SLB = sublingual buprenorphine; SLBN = sublingual buprenorphine-naloxone.

Table 13: Summary of Recommendations in Included Guidelines

Recommendations and Strength of Recommendations	Quality of Evidence
CRISM, 2018[13]	
Strong: 1. "Initiate opioid agonist treatment (OAT) with buprenorphine/naloxone whenever feasible to reduce the risk of toxicity, morbidity and mortality, as well as to facilitate safer take-home dosing."[13] (*p*20) 2. "For individuals responding poorly to buprenorphine/naloxone, consider transition to methadone treatment."[13] (*p*20) 3. "Initiate OAT with methadone when treatment with buprenorphine/naloxone is not the preferred option."[13] (*p*20) 4. "For individuals with a successful and sustained response to methadone who express a desire for treatment simplification, consider transition to buprenorphine/naloxone, since its superior safety profile allows for more routine take-home dosing and less frequent medical appointments."[13] (*p*20)	Quality of the evidence was judged using GRADE. 1. High quality of evidence 2. High quality of evidence 3. High quality of evidence 4. Moderate quality of evidence **GRADE quality of evidence:**[13] • **High**= very confident the true effect lies close to that of the estimate of the effect • **Moderate** = moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different • **Low** = confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect • **Very low** = very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect
Department of Veterans Affairs/Department of Defense, 2015[14]	
Strong For: "For patients with [OUD], we recommend offering one of the following medications considering patient preferences: • Buprenorphine/naloxone • Methadone in an Opioid Treatment Program"[14] (*p*38) "For patients with [OUD] for whom buprenorphine is indicated, we recommend individualizing choice of appropriate treatment setting (i.e., Opioid Treatment Program or office-based) considering patient preferences."[14] (*p*38) "For patients with [OUD] for whom opioid agonist treatment is contraindicated, unacceptable, unavailable, or discontinued and who have established abstinence for a sufficient period of time (see narrative), we recommend offering: • Extended-release injectable naltrexone"[14] (*p*38) "At initiation of office-based buprenorphine, we recommend	There is no explicit link between quality of the evidence and recommendations, but rather it is discussed for each intervention in text. **GRADE strength of recommendation**: • **Strong** = "[…] indicates that the Work Group is highly confident that desirable outcomes outweigh undesirable outcomes"[14] • **Weak** = "If the Work Group is less confident of the balance between desirable and undesirable outcomes, they present a weak recommendation"[14]

Table 13: Summary of Recommendations in Included Guidelines

Recommendations and Strength of Recommendations	Quality of Evidence
addiction-focused Medical Management (see narrative) alone or in conjunction with another psychosocial intervention."[14] (*p*38) **Weak For**: "In pregnant women with [OUD] for whom buprenorphine is selected, we suggest offering buprenorphine alone (i.e., without naloxone) considering patient preferences."[14] (*p*38)	

GRADE = Grading of Recommendations, Assessment, Development and Evaluation.

Appendix 5: Additional References of Potential Interest

Randomized Controlled Trials

Alternative Population - Extended-Release Buprenorphine versus Placebo

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Guidelines and Recommendations

Guidelines Informed by Expert Consensus

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Clinical Practice Guidelines – Unclear Methodology

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Zoorob R, Kowalchuk A, Mejia de Grubb M. Buprenorphine therapy for opioid use disorder. *Am Fam Physician*. 2018;97(5):313-320.
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American Society of Addiction Medicine. National practice guideline for the use of medications in the treatment of addiction involving opioid use; 2015: https://www.asam.org/docs/default-source/practice-support/guidelines-and-consensus-docs/asam-national-practice-guideline-supplement.pdf. Accessed 2019 Apr 23.

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