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SUMMARY WITH CRITICAL APPRAISAL

Buprenorphine-Naloxone Tablet Versus Methadone for the Treatment of Patients with Opioid Use Disorder: A Review of Clinical Effectiveness, 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

AE	adverse events
AGREE II	Appraisal of Guidelines for Research Evaluation 2
AMSTAR 2	A Measurement Tool to Assess Systematic Reviews 2
BC	British Columbia
BCCSU	British Columbia Centre on Substance Use
BUP-NAL	the combination product of buprenorphine with naloxone, as a single preparation in a tablet formulation
CADTH	Canadian Agency for Drugs and Technologies in Health
CENTRAL	Cochrane Central Register of Controlled Trials
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CRD	University of York Centre for Reviews and Dissemination
CRISM	Canadian Research Initiative in Substance Misuse
DSM	Diagnostic and Statistical Manual of Mental Disorders
EMBASE	Excerpta Medica database
GRADE	Grading of Recommendations, Assessment, Development, and Evaluation
HIV	human immunodeficiency virus
HTA	health technology assessment
ISI	Institute for Scientific Information
MA	meta-analysis
MEDLINE	Medical Literature Analysis and Retrieval System Online
MeSH	medical subject headings
NEED	National Health Service Economic Evaluation Database
NR	not reported
NRS	non-randomized study
OAT	opioid agonist treatment
OUD	opioid use disorder
PEER	Canadian Family Physician's Patients, Experience, Evidence Research group
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	International prospective register of systematic reviews
PsycINFO	psychological information database
PubMED	Public MEDLINE
RCT	randomized controlled trial
SD	standard deviation
SOGC	Society of Obstetricians and Gynaecologists of Canada
SR	systematic review

Context and Policy Issues

The *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition* (DSM-5), 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] Of note, Canadian’s consumption of prescription narcotics has increased substantially in recent years, passing from an average 8,713 daily doses per million Canadians in 2000-2002,[4] to 26,029 in 2015-2017.[5] In 2017, the prevalence of opioid use disorder was estimated to be 1.01% in the Canadian population.[6] Because younger Canadians (typically those less than 30 years of age) are disproportionately affected, this results in increased premature morbidity and mortality, with 51,139 years of life lost (for all ages) in 2017.[7] In 2018, there were 4,460 opioid-related deaths in Canada, 94% of which were unintentional (i.e., accidental).[8] Furthermore, based on 2014 data, males seem unequally burdened with a 1.6-fold prevalence, and a 2.3-fold death rate, that of females.[9]

The clinical management of OUD depends on the desired treatment intensity, ranging from withdrawal management (i.e., detoxification) in low intensity cases, opioid substitution therapy, 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 (e.g., with buprenorphine or methadone), is commonly used since these agents work to relieve opioid withdrawal symptoms and reduce cravings.[10]

In Canada, several formulations of buprenorphine are available for the treatment of OUD; however, the combination product of buprenorphine with naloxone (BUP-NAL) in a tablet formulation will be the focus of this review. Buprenorphine tightly binds to, and partially agonizes, the mu-opioid receptors in the central nervous system and elsewhere in the body.[10] The presence of naloxone, in this combination product, is to deter the misuse of the drug through crushing and injecting, since the naloxone component would cause opioid withdrawal symptoms.[10] Likewise, methadone binds to, but fully agonizes, mu-opioid receptors.[10] Depending on the therapy of choice and 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.[11]

CADTH has previously reviewed the evidence for the use of buprenorphine and methadone for the treatment of OUD.[12-17] One report focused on the various formulations of buprenorphine,[15] one was limited to pregnant populations,[13] one was a qualitative review of patient preferences and perspectives,[12] one was a review of various treatment programs for OUD,[16] one was summary of abstracts based on evidence available in 2017,[14] and another was a summary of abstracts on the efficacy of various methadone formulations.[17] The objective of the current report is to evaluate the comparative clinical effectiveness, cost-effectiveness, and evidence-based guidelines regarding BUP-NAL and methadone for the treatment of OUD.

Research Questions

1. What is the clinical effectiveness of buprenorphine-naloxone tablets compared with methadone for the treatment of patients with opioid use disorder?
2. What is the cost-effectiveness of buprenorphine-naloxone tablets compared with methadone for the treatment of patients with opioid use disorder?
3. What are the evidence-based guidelines associated with the use of buprenorphine-naloxone for the treatment of patients with opioid use disorder?
4. What are the evidence-based guidelines associated with the use of methadone for the treatment of patients with opioid use disorder?

Key Findings

Four relevant systematic reviews, one randomized controlled trial, and one non-randomized study were identified regarding the clinical effectiveness of buprenorphine-naloxone (BUP-NAL) as compared to methadone for the treatment of opioid use disorder (OUD). No relevant economic evaluations were identified.

No clear patterns emerged regarding the comparative effectiveness of BUP-NAL and methadone. It remains uncertain whether the findings of the reviewed literature are generalizable to the Canadian population as many of the included studies were conducted outside of Canada.

Six reports,[3,18-22] representing four guidelines were identified regarding the use of BUP-NAL or methadone for the treatment of OUD. Four guidelines provide strong recommendations for the use of BUP-NAL as treatment initiation or maintenance. Two guidelines are specific to pregnant people and offer conflicting recommendations.

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

Methods

Literature Search Methods

This report makes use of a literature search conducted for a previous CADTH report. The original literature search was conducted in June 2016 on key resources including Medline, EMBASE, 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. No filters were applied to limit retrieval by study type. Where possible, retrieval was limited to the human population. The initial search was also limited to English language documents published between January 1, 2011 and June 21, 2016. For the current report, database searches were rerun on July 4, 2019 to capture any articles published since the initial search date. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Methadone and Suboxone. No search filters were applied to limit retrieval by study type for questions 1 and 2. Search filters were applied to limit retrieval to guidelines only for questions 3 and 4. The search of major health technology agencies, as well as a focused Internet search was also updated to include documents published since June 2016.

Selection Criteria and Methods

Two reviewers screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. 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 were extracted by one reviewer.

Table 1: Selection Criteria

Population	Patients with opioid use disorder (i.e., Opioid Use Disorder [DSM-5], Opioid Abuse [DSM-IV], Opioid Dependence [DSM-IV]), in all settings.
Interventions	Q1-3: Buprenorphine-naloxone tablet formulation Q4: Methadone
Comparators	Q1-2: Methadone [any formulation; including but not limited to methadone powder, Methadose (commercial product), and Metadol D (commercial product)] Q3-4: No comparator necessary
Outcomes	Q1: Clinical effectiveness (e.g., mortality, opioid use, HIV and hepatitis infection rate, criminal activity) Q2: Cost-effectiveness outcomes (e.g., incremental cost per quality adjusted life year or health benefit) Q3-4: Guidelines
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; HIV = human immunodeficiency virus

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 2016, or were included in the previous 2016 CADTH report.[23] SRs[24-26] that had relevant included studies fully captured in other, more recent and comprehensive SRs were excluded. SRs 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 SR entirely. Primary studies retrieved by the search were excluded if they were captured in one or more included SR. Finally, guidelines with unclear methodology were also excluded.

Critical Appraisal of Individual Studies

The included SRs were critically appraised by one reviewer using AMSTAR 2,[27] the randomized control trial (RCT) and non-randomized study (NRS) were critically appraised using the Downs and Black checklist,[28] and guidelines were assessed with the AGREE II instrument.[29] 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 184 citations were identified in the literature search. Following screening of titles and abstracts, 153 citations were excluded and 31 potentially relevant reports from the

electronic search were retrieved for full-text review. In addition, nine potentially relevant publications were retrieved from the grey literature search for full-text review. Of these 40 potentially relevant articles, 28 publications were excluded for various reasons, while 12 publications met the inclusion criteria and were included in this report. These comprised four systematic reviews (SRs)[30-33] (one with meta-analysis),[31] one randomized controlled trial (RCT),[34] one non-randomized study (NRS)[35] and six reports,[3,18-22] representing four guidelines. Two of the reports were supplements[19,20] to one of the included guideline.[3] Appendix 1 presents the PRISMA[36] flowchart of the study selection. Note that because 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.

Appendix 6 includes 11 additional references that did not meet the inclusion criteria of this report but may be of interest. These include a SR,[37] two RCTs,[38,39] four NRSs,[40-43] one clinical practice guideline,[44] and three review articles.[45-47]

Summary of Study Characteristics

Four SRs[30-33] (one with meta-analysis),[31] one RCT,[34] one NRS,[35] and six reports,[3,18-22] representing four guidelines were identified and included in this review. Two of the SRs[32,33] met the inclusion criteria for this report; however, none of the primary studies included in the SRs met the eligibility criteria for this report; therefore, no summary can be provided. No relevant health technology assessments, or economic evaluations were identified. Detailed characteristics are available in Appendix 2, Table 2, Table 3, and Table 4

Study Design

The four included SRs[30-33] (one with meta-analysis),[31] had objectives and inclusion criteria that were broader than for the present report (i.e., were wider in scope). Authors of one SR,[30] published in 2019, included literature searches for relevant published RCTs. The second review[31], also published in 2019 included relevant published RCTs or quasi-experimental studies. The first systematic review[30] included six citations[48-53] of three relevant primary studies,[48,49,51] while the second review[31] included one relevant RCT,[54] for a total of four unique primary studies. The remaining two SRs,[32,33] both published in 2017, met the inclusion criteria for this report; however, they contained no primary studies that answered our research questions. As shown in Appendix 5 Table 11, there was no primary study overlap among the included SRs.

Two primary studies regarding the clinical effectiveness and safety of BUP-NAL and methadone for the treatment of patients with OUD were identified. The first, a 2019 RCT[34] was a secondary analysis of a prospective follow-up study[55] of a phase four RCT trial on liver safety.[51] This latter study[51] was included in one of the SRs[30] where only outcomes on gender differences were reported; however, the current primary study[34] describes additional outcomes not discussed in the SR. The second primary study is a 2016 , prospective cohort, mixed-methods study that utilised quantitative methods to determine treatment outcomes and patient characteristics, as well as qualitative methods to evaluate patient's perceptions of their treatment.[35]

Six reports,[3,18-22] representing four guidelines were identified regarding the treatment of OUD that contained recommendations for the use of BUP-NAL or methadone,[3,18-22] which includes two supplements[19,20] to a main guideline.[3] The first guideline, published in 2019 from the Canadian Family Physician's Patients, Experience, Evidence, Research (PEER) group, is the product of 17 SRs on selected clinical questions.[18] The second 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 (BCCSU)/Ministry of Health Guideline for the Clinical Management of Opioid Use Disorder, released in February 2017".[21] They further updated the literature in 2016 and included meta-analyses of randomized clinical trials, quasi-experimental studies, observational reports, and expert opinion.[21] The third guideline, published in 2017 by the Society of Obstetricians and Gynaecologists of Canada (SOGC),[22] was the results of a literature search for SRs, RCTs, and NRSs from 1996 to 2016. The three subsequent guidelines are published by the British Columbia Centre on Substance Use (BCCSU), and include a main guideline published in 2017,[3] a pregnancy supplement published in 2018,[19] and a youth supplement also published in 2018.[20] The supplements lacked detail on the search methods; while the main guideline stated that authors conducted a structured literature review where studies were independently assessed for inclusion by staff.

As indicated in Table 4, authors of three guidelines used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool to evaluate the quality of evidence and strength of recommendations.[3,18,21] One guideline,[22] used the ranking of the Canadian Task Force on Preventive Health Care, while details were lacking on evidence quality assessment for the two supplements.[19,20] Recommendations were consensus-based and were developed with consideration of feedback from internal and external stakeholders and experts in three guidelines.[3,18,21] While details on the development of recommendations and guideline validation were lacking in the remaining three guidelines.[19,20,22]

Country of Origin

The included SRs were by authors in Canada,[30] the United States of America,[31] the United Kingdom,[32] and Australia.[33] Relevant primary studies in the SRs were conducted in the United States of America and the Republic of Georgia, between 2008 and 2013.

The RCT was conducted in the United States of America.[34] The NRS was conducted in Spain.[35] The guidelines are all developed in Canada.[3,18-22]

Patient Population

One SR[30] included studies that enrolled adult participants with OUD in various treatment settings. The primary studies relevant to this report had sample sizes of 80,[49] 268,[48] and 1,267 participants.[51] The second review[31] examined people on medication assisted treatment incarcerated in correctional facilities (i.e., prisons and jails) and following their release. The primary study relevant to this report had 81 participants.[54]

The RCT focused on 303 opioid-dependant adults recruited from three California clinics.[34]

The NRS evaluated 135 participants enrolled in the opiate derivatives treatment programme at sixteen drug addiction health care units in Spain.[35]

The target population of the Canadian Family Physician PEER guidelines are patients with OUD, except pregnant people or patients less than 18 years of age,[18] while the intended users are clinicians and patients to assist with shared informed decisions making.[18] The target populations for the CRISM guidelines are adolescents, young adults, and adults with uncomplicated OUD and also included specific considerations for special populations.[21] The intended users are Canadian physicians, nursing and allied healthcare providers,

medical educators, clinical care case managers, policymakers, healthcare administrators.[21] The intended users of the BCCSU main guideline and its two supplements are British Columbia health care professionals involved in the treatment of individuals with OUD.[3,19,20] The target population of the BCCSU main guidelines are individuals with OUD,[3] the BCCSU Youth Supplement targets youth (adolescents 12 to 17 years old and young adults 18 to 25 years old) with OUD, while the BCCSU Pregnancy Supplement targets pregnant people with OUD.[19] Similarly, the guidelines of the SOGC targets pregnant people who have substance use disorders and are intended for health care providers caring for pregnant people.[22]

Interventions and Comparators

In one SR,[30] buprenorphine-based interventions (including BUP-NAL) were compared to non-buprenorphine treatments, a taper schedule, or placebo. The second SR[31] investigated buprenorphine (including BUP-NAL), methadone, or naltrexone treatment compared to any comparator (including administrative comparison groups).

The RCT evaluated BUP-NAL compared to methadone.[34]

The NRS followed participants initially on a methadone maintenance programme who were switched to BUP-NAL compared to participants who remained in a methadone maintenance programme.[35]

The guidelines considered various OUD treatments, including: pharmacotherapies,[3,18-22] psychosocial management,[3,18,20-22] residential treatment,[3,18-21] withdrawal management strategies,[3,19-22] harm reduction,[3,19,22] and brief interventions.[22]

Outcomes

The outcomes considered in the SRs were treatment engagement,[31] treatment retention,[30] opioid use,[30,31] other drug use,[30] sexual risk behaviour,[30] health risk behaviour,[31] quality of life,[30] legal involvement,[30] recidivism,[31] mental health,[30] and physical health.[30]

In the RCT, the outcomes of interest were arrests, incarcerations, treatment participation, and death.[34]

In the NRS, the outcomes of interest were quality of life.[35]

The outcomes of interest in the guidelines included OUD adherence with treatment,[3,18-21] recidivism,[18,21] morbidity,[3,19-22] mortality,[3,19-22] side effects,[18,21] adverse events (AEs),[21] cravings,[21] substance consumption (e.g., alcohol, opioid),[3,18-21] quality of life,[21] and obstetrical outcomes.[19,22]

Summary of Critical Appraisal

Additional details regarding the strengths and limitations of the included publications are provided in Appendix 3, Table 5, Table 6, and Table 7.

Systematic Reviews

Strengths of all SRs[30-33] (one with meta-analysis)[31] included: clear objectives and inclusion criteria, reporting of key search terms and search strategies, provision of a list of included studies and summary of their characteristics, and a quality assessment of included studies using an appropriate tool. In addition, three SRs considered risk of bias when interpreting and discussing the results of individual studies.[30,31,33] Authors of one SR[30] registered their

protocol to an online database of systematic review protocols on health-related topics (PROSPERO) prior to the conduct of the review, while another was a Cochrane review with an a priori protocol.[33] These strengths of reporting increase confidence in the findings and the reproducibility of the SRs. In all reviews, multiple databases were used to identify relevant literature; however, two did not indicate performing a search for grey literature which increases the risk of missing relevant, non-indexed studies.[30,31] Study selection was performed in duplicate and described in detail for all but one SR.[30] The possibility of publication bias was only investigated in one SR.[33] One SR[30] contained primary studies conducted outside of Canada and their findings may not be generalizable to the Canadian setting.

RCT

The RCT[34] had several strengths, 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 the major findings were described in a way that allowed verification of analyses and conclusions. Estimates of random variability were reported, and the data analyses were planned at the outset. Limitations of the study included: lack of characterisation of the participants who withdrew or were lost to follow-up and being an open-label study with no blinding of study participants or outcome assessors. Furthermore, this study[34] was a secondary analysis of an initial RCT designed to evaluate the effects of BUP-NAL and methadone on liver function. As such, its design may not have been sufficiently powered to detect the outcomes of interest in the secondary analysis. Moreover, in the initial RCT, one of the exit pathways was via a taper schedule of less than or equal to eight weeks, which is not representative of routine clinical care. It was unclear if both groups were affected equally; thus, results should be interpreted with caution since we were unable to assess if a differential treatment bias was introduced in the follow up studies.[34] The randomization methodology of the original RCT was not reported, other than to indicate that it was changed partway from a 1:1 allocation, to the buprenorphine and methadone groups, to a 2:1 allocation because of higher dropout rates in the buprenorphine group. This may have introduced a bias and it is not clear if there were differences in important baseline characteristics among the participants who enrolled before or after this change. Furthermore, it was not reported if the data were analysed separately, before and after the allocation change. Lastly, participants were compensated after their assessment ($50 gift card) and after providing a urine sample ($10), which may have introduced a participation bias.[34]

NRS

The NRS had several strengths, 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., Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form).[35] The study did not report conducting an a priori power calculation .[35] Although authors did provide a statement on conflicts of interest (two authors are employees of a company that receives funding from the drug manufacturer), they did not discuss how these conflicts were managed.[35] The main outcomes measures used were questionnaire assessments at the beginning and end of the experiment and are hence subject to response bias. Participants were transferred to the BUP-NAL group consecutively, “upon meeting the criteria for treatment transfer and after signing the informed consent document”[35] (*p30)*, and there was no characterisation of the participants who withdrew or were lost to follow-up, as such an assessment of selection bias cannot be conducted.[35]

Evidence-Based Guidelines

In the six reports, representing four guidelines[3,18-22] the scope and purpose were well described. While all were developed in Canada, only two[18,21] sought the views and preferences of the target population. All but one[22] provided an explicit link between the recommendations and the evidence. Two guidelines, the Canadian Family Physician's PEER and the SOGC, employed systematic methods to search for evidence.[18,22] The criteria for selecting the evidence were poorly described in the Canadian Family Physician's PEER guideline as well as the two BCCSU supplements.[19,20,22] These same reports did not describe the strengths and limitations of the evidence, nor did they describe the methods for formulating their recommendations.[19,20,22] The CRISM and BCCSU main guideline described a procedure for updating their documents.[3,21] The Canadian Family Physician's PEER guidelines did provide "practice pearls" as advice and tools for putting the recommendations into practice.[18]

Summary of Findings

A detailed summary of findings and recommendations is provided in Appendix 4, Table 8, Table 9, and Table 10.

Clinical Effectiveness of Buprenorphine-Naloxone Tablet Compared With Methadone for the Treatment of Patients With Opioid Use Disorder

Treatment retention

Information regarding the comparative effectiveness of BUP-NAL and methadone for retention in treatment was available from two SRs[30,31], the RCT,[34] and the NRS.[35]

Authors of one SR[31] reported that, post-release from incarceration, a greater number of BUP-NAL participants reported to a community-based substance use treatment centre (P-value not reported),[31] and self-reported being engaged in the treatment at three-months (P-value not reported).[31] The second SR[30] reported that females in the BUP-NAL group were less likely to be retained in treatment compared to males ($p < 0.01$),[30] whereas the opposite was found in the methadone group, females were more likely to be retained in treatment compared to males ($p < 0.01$).[30]

The RCT reported on the time spent in any OUD treatment over the five-years of follow-up and reported that those initially randomized to BUP-NAL spent less time in any OUD treatment ($P = 0.02$).[34]

The NRS reported that three months after treatment assignment 7.6% of BUP-NAL participants had discontinued their treatment, compared to 14.3% of methadone participants (reported as not significant; P-value not reported).[35]

Illicit Use of Opioids

Evidence regarding the comparative effectiveness of BUP-NAL and methadone for reducing the illicit use of opioids was available from one SR,[31] and the NRS.[35]

The authors of the SR reported on one primary study[54] that did not observe a difference, between the BUP-NAL and methadone groups, in self-reported opioid use at three months of follow up post-release from incarceration.[31]

In the NRS, a statistically significant difference in abstinence behaviour was seen at three months of follow-up, where 75.9% of participants in the BUP-NAL group remained abstinent compared to 53.1% in the methadone group (P = 0.012).[35]

Recidivism

Evidence regarding the comparative effectiveness of BUP-NAL and methadone for recidivism was available from one SR[31] and the RCT.[34]

The authors of the SR reported on one primary study[54] that did not observe a difference (P-value not reported), between the BUP-NAL and methadone groups, in self-reported re-arrest or re-incarceration at three months of follow up post-release from incarceration.[31]

The RCT reported no differences in arrests or incarcerations, (P-value not reported for either outcome) between the BUP-NAL and methadone groups during five years of follow-up.[34]

Quality of Life

Evidence regarding the comparative effectiveness of BUP-NAL and methadone for quality of life was available from the NRS.[35]

The NRS reported no significant change (P-value not reported) in quality of life score from baseline at three-months of follow-up in the quantitative analysis.[35] Using the Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form, the overall score for the BUP-NAL group increased from 46.97 at baseline to 49.74 at three-months, while the overall score for the methadone group decreased from 45.02 to 44.76.[35] This seems to be in contradiction with the author's conclusions that "Based on the analysis of some variables, patients treated with [BUP-NAL] had a higher quality of life than patients treated with methadone, particularly considering the greater ease experienced by the former in normalizing their lifestyle." (*p.40*)[35]

Mortality

Evidence regarding the safety of BUP-NAL and methadone with respect to mortality was available from one SR[31] and the RCT.[34]

No overdoses or mortality were observed in the relevant primary study of the SR.[31]

The RCT described deaths over five-years of follow-up and reported one in the BUP-NAL group and one in the methadone group (P-value not reported).[34]

Side Effects

Evidence regarding the safety of BUP-NAL and methadone with respect to side effects was available from the NRS.[35]

The authors of the NRS reported that 63.3% of participants in the methadone group indicated the presence of side-effects from the treatment. The most common side effects included: constipation (49.0%), sweating (28.6%), decreased libido (28.6%).[35] In comparison, 20.3% of the BUP-NAL participants experienced side effects, with the most common being: weight loss (5.1%), and nausea (3.8%).[35]

Sexual Risk

Evidence regarding the safety of BUP-NAL and methadone with respect to risky sexual behaviour was available from one SR.[30]

The relevant primary study in the SR noted that males in the methadone group had a decreasing risk over time, compared with males in the BUP-NAL group (p = 0.03).[30] Whereas, risky sexual behaviour among females generally decreased over time, with no difference between BUP-NAL and methadone groups (p = 0.02).[30]

Cost-Effectiveness of Buprenorphine-Naloxone Tablet Compared With Methadone for the Treatment of Patients with Opioid Use Disorder

No relevant evidence regarding BUP-NAL compared with methadone for OUD was identified; therefore, no summary can be provided.

Evidence-Based Guidelines Associated With the use of Buprenorphine-Naloxone for the Treatment of Patients with Opioid Use Disorder

Six reports,[3,18-22] representing four guidelines were identified regarding recommendations for the use of BUP-NAL for the treatment of patients with OUD. Two of the reports were supplements[19,20] to one of the included guideline.[3]

The first from the Canadian Family Physician's PEER group, recommend that clinicians engage their patients in a discussion on treatment options.[18] They continue by pointing out that BUP-NAL "might be easier to implement in practice owing to fewer prescribing restrictions and considerations" (*p322*).[18] This is a strong recommendation, based on moderate-quality evidence.[18] They also strongly recommend against (based on low-quality evidence) short-term treatment duration, reminding clinicians that "optimal duration is unknown and might be indefinite" (*p322*).[18] They weakly recommend (based on very low-quality evidence) the judicious use of take-home doses when patient needs and patient stability warrant it.[18]

Both the CRISM and BCCSU main guidelines,[3,21] recommend initiating treatment with BUP-NAL whenever feasible to reduce the risk of toxicity,[3,21] morbidity and mortality,[21] as well as to facilitate safer take-home dosing.[3,21] This is a strong recommendation, based on high quality evidence.[3,21] Furthermore, both guidelines strongly recommend (based on moderate quality evidence) considering switching methadone patients, who feel the treatment may be complex, to BUP-NAL.[3,21] The BCCSU main guideline also strongly recommends, based on moderate quality evidence, that a switch to BUP-NAL be considered in patients who are not responding optimally on methadone.[3] Additionally, this guideline strongly recommends, based on moderate quality evidence, that a slow taper (e.g., over 1 year) be considered in individuals who wish to discontinue therapy after a sustained response.[3]

The BCCSU Youth Supplement, makes recommendations for adolescents 12 to 17 years old and young adults 18 to 25 years old.[20] They recommend that "the full range of available treatment should be considered for youth with OUD […]" (*p*10) and point to BUP-NAL as first-line therapy in cases where pharmacotherapy is indicated "due to safety advantages and improved flexibility (e.g., take-home doses)" (*p*10).[20] The BCCSU Youth Supplement does not report the strength of their recommendations nor the quality of evidence upon which these are founded.

The BCCSU Pregnancy Supplement, as well as the SOGC guideline, both make recommendations for pregnant people.[19,22] BCCSU recommends BUP-NAL as an

alternative to methadone for first line therapy citing that "[recent] studies have found this medication to be as safe and effective as methadone and buprenorphine monotherapy […]" (*p10*).[19] While the SOGC indicates that there is good evidence (obtained from at least one properly randomized controlled trial) to recommend that "[the] standard of care for the management of opioid use disorders during pregnancy is opioid agonist treatment with methadone or buprenorphine" (*p923*) forgoing the designation of a preferred first-line therapy.[22]

The SOGC further recommends, based on good evidence from well-designed controlled trials without randomization, that "[women] who become pregnant while on buprenorphine/naloxone should be switched to buprenorphine monoproduct" (*p923*).[22] Also, they further specify that "[women] taking buprenorphine should only switch to methadone if the buprenorphine monoproduct is not accessible and/or the woman feels that she is not responding to the current treatment" (*p932*).[22] This contrasts with the BCCSU Pregnancy Supplement which does not recommend switching therapies in pregnant patients or during the postpartum period if the patient is stable on an OAT, further specifying that patients already stabilised on BUP-NAL before becoming pregnant do not need to be switched to the buprenorphine monotherapy during pregnancy.[19] The BCCSU Pregnancy Supplement does not report the strength of their recommendations nor the quality of evidence upon which these are founded.

Evidence-Based Guidelines Associated With the use of Methadone for the Treatment of Patients with Opioid Use Disorder

Six evidence-based guidelines[3,18-22] were identified regarding recommendations for the use of methadone for the treatment of patients with OUD.

The first from the Canadian Family Physician's PEER group, recommend that clinicians engage their patients in a discussion on treatment options.[18] They continue by pointing out that methadone "might be superior for retention in treatment" (*p322*).[18] This is a strong recommendation, based on moderate-quality evidence.[18] They also strongly recommend (based on low-quality evidence) against short-term treatment duration, reminding clinicians that "optimal duration is unknown and might be indefinite" (*p322*).[18] They weakly recommend (based on very low-quality evidence) the judicious use of take-home doses when patient needs and patient stability warrant it.[18]

Both the CRISM and BCCSU main guidelines,[3,21] recommend switching BUP-NAL patients who are not responding optimally to methadone. Moreover, they recommend that treatment can be initiated with methadone in cases where patients circumstances (e.g., challenging induction) render it preferential to BUP-NAL.[3,21] Both of these are strong recommendations, based on high quality evidence.[3,21] Furthermore, the CRISM and BCCSU main guidelines strongly recommend (based on moderate quality evidence) considering switching methadone patients, who feel the treatment may be complex, to BUP-NAL.[3,21] Additionally, the BCCSU guideline strongly recommend, based on moderate quality evidence, that a slow taper (e.g., over 1 year be considered in individuals who wish to discontinue therapy after a sustained response.[3]

The BCCSU Youth Supplement, make recommendations for adolescents 12 to 17 years old and young adults 18 to 25 years old.[20] They recommend that "the full range of available treatment should be considered for youth with OUD […]" (*p*10) and further recommend that "methadone should be considered in youth who do not respond to adequately dosed [BUP-

NAL] […]" (*p10*).[20] The BCCSU Youth Supplement does not report the strength of their recommendations nor the quality of evidence upon which these are founded.

The BCCSU Pregnancy Supplement, as well as the SOGC guideline, both make recommendations for pregnant people.[19,22] BCCSU recommends methadone as the first-line option.[19] While the SOGC indicates that there is good evidence (obtained from at least one properly randomized controlled trial) to recommend that "[the] standard of care for the management of opioid use disorders during pregnancy is opioid agonist treatment with methadone or buprenorphine" (*p923*) forgoing the designation of a preferred first-line therapy.[22]

The SOGC further recommends, based on good evidence from well-designed controlled trials without randomization, that "[women] who become pregnant while on buprenorphine/naloxone should be switched to buprenorphine monoproduct" (*p923*).[22] Also, they further specify that "[women] who become pregnant while on methadone should continue on methadone maintenance therapy and should not switch to buprenorphine due to the risk of opioid withdrawal" (*p932*).[22] This contrasts with the BCCSU Pregnancy Supplement which does not recommend switching therapies in pregnant patients or during the postpartum period if the patient is stable on an OAT.[19] The BCCSU Pregnancy Supplement does not report the strength of their recommendations nor the quality of evidence upon which these are founded.

Limitations

A number of limitations were identified in the critical appraisal as shown in Appendix 3, Table 5, Table 6, and Table 7; however, additional limitations exist. The main limitations of this review are related to limited study populations and generalizability of findings.

A primary limitation that should be considered when interpreting these results is that studies were open-label, where participants and outcome assessors were not blinded to the treatment received. This should be considered when reviewing studies where outcomes were patient self-reported (e.g., self-reported opioid use, recidivism, engagement in a substance use treatment program), since these findings may be at risk of recall bias (in either direction) depending on the perceptions and expectations of participants and clinicians involved.

Three studies[31,34,35] reported results without providing some, or all, associated P-values, which may have introduced an outcome reporting bias limiting the overall reliability of their results.

Few relevant outcomes comparing the AEs or toxicity between BUP-NAL and methadone were reported in the identified comparative studies,[30,31,34,35] which prevents a comprehensive comparison of clinical safety between BUP-NAL and methadone. This suggests that additional comparative research in this area is required.

No studies contained information specific to the influence of rural or urban settings on treatment of people with OUD; therefore, the comparative clinical effectiveness of BUP-NAL and methadone in these settings is largely unknown.

The applicability of the evidence to Canadian settings is unclear as all relevant primary studies[34,35,48,49,51,54] were conducted outside of Canada. Access, both in tangible and economic terms, to opioid agonist therapy varies in other jurisdictions. For instance in one study,[35] while the methadone treatment group was fully funded, patients in the BUP-NAL

group had to accept the financial burden of co-payments, which contributed to drop-outs from the study.

Although one SR[30] examined sex differences in treatment outcomes they found scant evidence, with two of the relevant citations[52,53] reporting on this outcome. Still, it may be difficult to generalize the results in women since studies enrolled a disproportionately higher number of men.[34,35,48,49,51]

While three of the included guidelines were of thorough in their guideline development descriptions,[3,18,21] one guideline and the two supplements lacked methodological detail,[19,20,22] introducing uncertainty in their recommendations.

Conclusions and Implications for Decision or Policy Making

This report identified clinical effectiveness evidence and evidence-based guidelines regarding the use of BUP-NAL and methadone for the treatment of OUD. Four relevant SRs[30-33] (one with meta-analysis),[31] one RCT,[34] one NRS,[35] and six evidence-based guidelines were identified.[3,18-22] No relevant economic evaluations were identified.

The identified literature,[30,31,34,35] revealed mixed conclusions regarding the clinical effectiveness of BUP-NAL compared with methadone for individuals with OUD. Three included studies observed no differences in several outcomes of interest, such as female sexual risk,[30] health risk behaviours,[31] death,[30,31,34] abstinence,[31] or recidivism,[31,34] between patients treated with BUP-NAL and methadone. Treatment retention was higher in the BUP-NAL groups of two studies,[31,35] and in the male BUP-NAL participants of another study.[30] On the other hand, it was higher in the methadone group of one study,[34] and in the female methadone participants of another study.[30] The analyses of one non-randomized cohort study revealed a higher quality of life and abstinence for those on BUP-NAL.[35] No clear patterns emerged from these data which could suggest the overall superiority of one pharmacotherapy over another.

Six evidence-based guidelines were identified that provided recommendations regarding the use of BUP-NAL or methadone for OUD.[3,18-22] One guideline recommends involving the patient in a discussion of their options,[18] while two others provided a strong recommendations for the use of BUP-NAL as treatment initiation or maintenance.[3,21] This is echoed by the BCCSU Youth Supplement guideline, which recommends BUP-NAL as first-line when pharmacotherapy is indicated, and to consider switching to methadone if a poor response is observed.[20]

Two guidelines,[19,22] focused on recommendations for pregnant people. These guidelines presented conflicting recommendations regarding the use of BUP-NAL and methadone. The most recent guideline, a BCCSU Pregnancy Supplement, recommends that methadone is generally first-line during pregnancy, while BUP-NAL is a suitable alternative, and that switching therapies in stable patients is not recommended unless clinically necessary.[19] Conversely, the SOGC guidelines determined that pregnant people on BUP-NAL should be switched to the buprenorphine monoproduct or other alternatives.[22] The lack of consensus in the identified guidelines suggests that more comparative studies are required in this population.

The limitations of the included studies 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 effectiveness of BUP-NAL and methadone,

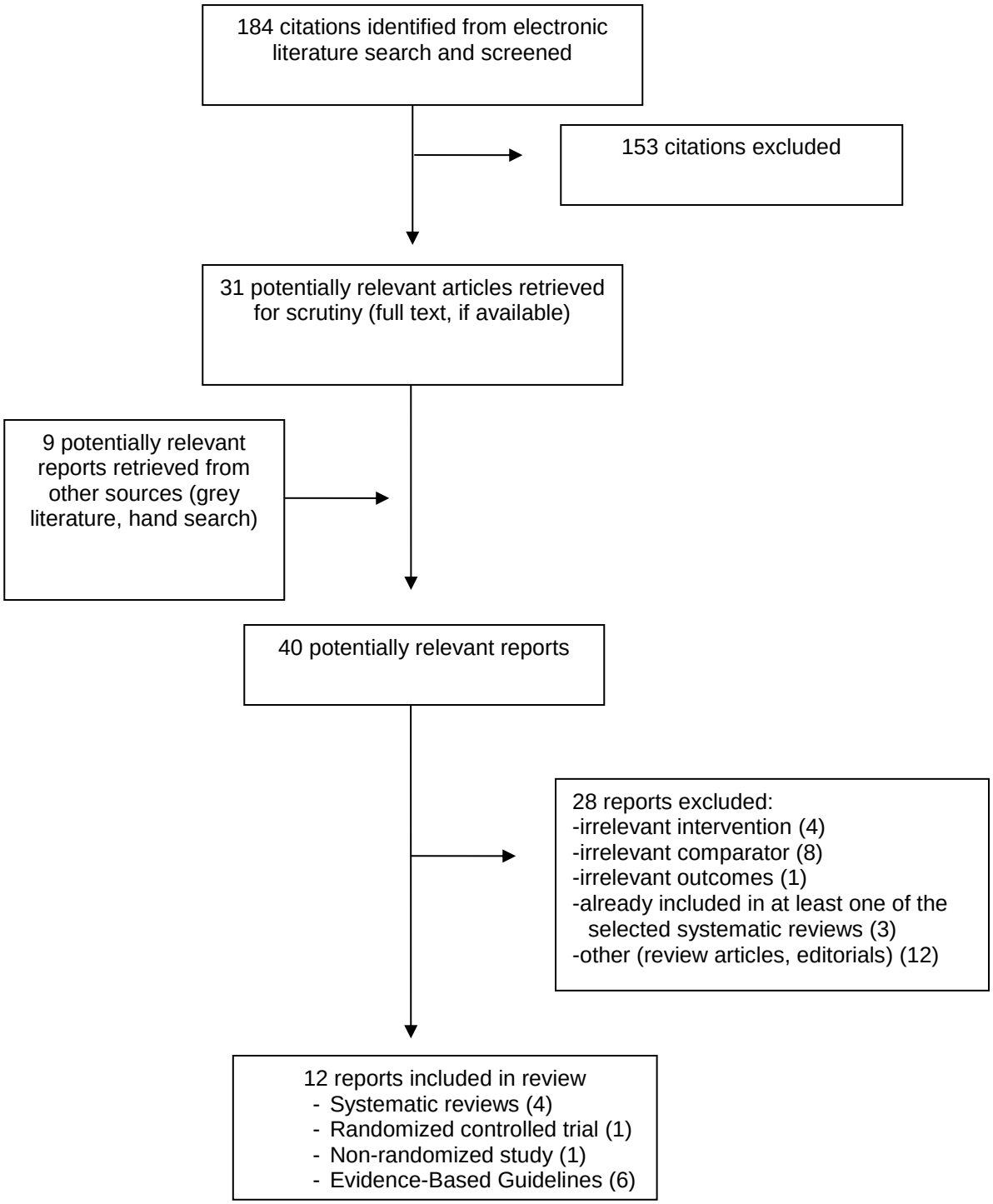
especially by way of large, methodologically-sound RCTs or well-designed meta-analyses, would help reduce this uncertainty.

References

1. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders: fifth edition (DSM-5).* Washington (DC): American Psychiatric Association; 2013.
2. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders: fourth edition, text revision (DSM-IV-TR).* Washington (DC): American Psychiatric Association; 2000.
3. British Columbia Centre on Substance Use, British Columbia Ministry of Health. A Guideline for the Clinical Management of Opioid Use Disorder. 2017: http://www.bccsu.ca/wp-content/uploads/2017/06/BC-OUD-Guidelines_June2017.pdf Accessed 27-Aug-2019.
4. International Narcotics Control Board. Narcotic drugs: estimated world requirements for 2004 - statistics for 2002. Vienna, Austria: United Nations; 2003: http://www.incb.org/documents/Narcotic-Drugs/Technical-Publications/2003/NARCOTICS2003.pdf. Accessed 2019 Jul 28.
5. International Narcotics Control Board. Narcotic drugs: estimated world requirements for 2019 - statistics for 2017. Vienna, Austria: United Nations; 2018: http://www.incb.org/documents/Narcotic-Drugs/Technical-Publications/2018/INCB-Narcotics_Drugs_Technical_Publication_2018.pdf. Accessed 2019 Jul 28.
6. Institute for Health Metrics and Evaluation. The Global Burden of Disease study data visualization hub : estimated prevalence caused by opioid use disorders, for both sexes and all ages in Canada. Seattle (WA): University of Washington; 2019: https://vizhub.healthdata.org/gbd-compare/. Accessed 2019 Jul 28.
7. Institute for Health Metrics and Evaluation. The Global Burden of Disease study data visualization hub : estimated years of life lost caused by opioid use disorders, for both sexes and all ages in Canada. Seattle (WA): University of Washington; 2019: https://vizhub.healthdata.org/gbd-compare/. Accessed 2019 Jul 28.
8. Special Advisory Committee on the Epidemic of Opioid Overdoses. National report: apparent opioid-related deaths in Canada (January 2016 to December 2018). 2019; https://health-infobase.canada.ca/datalab/national-surveillance-opioid-mortality.html, 2019 Jul 28.
9. Orpana HM, Lang JJ, Baxi M, et al. Canadian trends in opioid-related mortality and disability from opioid use disorder from 1990 to 2014 through the lens of the Global Burden of Disease Study. *Health Promot Chronic Dis Prev Can* 2018;38(6):234-243.
10. Isaac P, Janecek E, Kalvik A, Zhang M. *Opioid agonist maintenance treatment : a pharmacist's guide to methadone and buprenorphine for opioid use disorders.* Toronto (ON): Centre for Addiction and Mental Health; 2015.
11. Kampman K, Jarvis M. American Society of Addiction Medicine (ASAM) national practice guideline for the use of medications in the treatment of addiction involving opioid use. *J Addict Med.* 2015;9(5):358-367.
12. Majid U, Loshak H. Buprenorphine for opioid use disorders: a rapid qualitative review. (CADTH Rapid response report: summary with critical appraisal). Ottawa (ON): CADTH; 2019 Apr: https://cadth.ca/sites/default/files/pdf/htis/2019/RC1100%20Buprenorphine%20for%20OUD%20Final.pdf. Accessed 2019 Jul 04.
13. Edge R, Butcher R. Buprenorphine for opioid use disorders during pregnancy: a review of comparative clinical effectiveness, safety, cost-effectiveness, and guidelines. (CADTH Rapid response report: summary with critical appraisal). Ottawa (ON): CADTH; 2019 May: https://cadth.ca/sites/default/files/pdf/htis/2019/RC1111%20Buprenorphine%20for%20Opioid%20Use%20Disorder%20During%20Pregnancy%20Final.pdf. Accessed 2019 Jul 04.
14. Seal K, Argaez C. Buprenorphine formulations for the treatment of opioid use disorders: comparative clinical effectiveness, cost-effectiveness, and guidelines. (CADTH Rapid response report: summary of abstracts). Ottawa (ON): CADTH; 2018 Apr: https://cadth.ca/sites/default/files/pdf/htis/2018/RA0951%20Buprenorphine%20Formulations%20Update%20Final.pdf. Accessed 2019 Jul 04.
15. Marchand D, Young C, Loshak H. Buprenorphine for opioid use disorder: a review of comparative clinical effectiveness, safety, cost-effectiveness, and guidelines. (CADTH Rapid response report: summary with critical appraisal). Ottawa (ON): CADTH; 2019 Apr: https://cadth.ca/sites/default/files/pdf/htis/2019/RC1092%20Buprenorphine%20for%20OUD%20Final.pdf. Accessed 2019 Jul 04.
16. Gray C, Banerjee S, Argaez C. Treatment programs for opioid use disorders: a review of guidelines. (CADTH Rapid response report: summary with critical appraisal). Ottawa (ON): CADTH; 2018 Aug: https://cadth.ca/sites/default/files/pdf/htis/2018/RC1010%20Treatment%20Programs%20for%20Opioid%20Use%20Disorders%20Final.pdf. Accessed 2019 Jul 04.
17. Gray C, Visinini S. Metadol liquid, Methadose, and compounded Methadone in patients using opioid agonist therapy: comparative clinical effectiveness and guidelines. (CADTH Rapid response report: summary of abstracts). Ottawa (ON): CADTH; 2018 Apr: https://cadth.ca/sites/default/files/pdf/htis/2018/RB1208%20OAT%20Methadose%20Final.pdf. Accessed 2019 Jul 04.
18. Korownyk C, Perry D, Ton J, et al. Managing opioid use disorder in primary care. *PEER simplified guideline.* 2019;65(5):321-330.
19. British Columbia Centre on Substance Use, British Columbia Ministry of Health, British Columbia Ministry of Mental Health and Addictions, Perinatal Services British Columbia. A Guideline for the clinical management of opioid use disorder—pregnancy supplement. Vancouver (BC): British Columbia Centre on Substance Use; 2018: http://www.bccsu.ca/wp-content/uploads/2018/06/OUD-Pregnancy.pdf. Accessed 2019 Aug 27.
20. British Columbia Centre on Substance Use, British Columbia Ministry of Health, British Columbia Ministry of Mental Health and Addictions. A Guideline for the clinical management of opioid use disorder—youth supplement. Vancouver (BC): British Columbia Centre on Substance Use; 2018: http://www.bccsu.ca/wp-content/uploads/2018/06/OUD-Youth.pdf. Accessed 2019 Aug 27.
21. Canadian Research Initiative in Substance Misuse (CRISM). CRISM national guideline for the clinical management of opioid use disorder. Ottawa (ON): CRISM (Canadian Institutes of Health Research); 2018 Mar: https://crism.ca/wp-content/uploads/2018/03/CRISM_NationalGuideline_OUD-ENG.pdf. Accessed 2019 Jul 29.
22. Ordean A, Wong S, Graves L. No. 349-Substance use in pregnancy. *J Obstet Gynaecol Can,.* 2017;39(10):922-937.e922.
23. Canadian Agency for Drugs and Technologies in Health. Buprenorphine/Naloxone versus Methadone for the treatment of opioid dependence: a review of comparative clinical effectiveness, cost-effectiveness and guidelines. Ottawa (ON): CADTH; 2016 Sep: https://www.cadth.ca/sites/default/files/pdf/htis/sep-2016/RD0032_Suboxone_Final.pdf. Accessed 2019 Jul 04.
24. Bi-Mohammed Z, Wright NM, Hearty P, King N, Gavin H. Prescription opioid abuse in prison settings: A systematic review of prevalence, practice and treatment responses. *Drug Alcohol Depend.* 2017;171:122-131.
25. Ali S, Tahir B, Jabeen S, Malik M. Methadone treatment of opiate addiction: a systematic review of comparative studies. *Innov Clin Neurosci.* 2017;14(7-8):8-19.
26. Nielsen S, Larance B, Degenhardt L, Gowing L, Kehler C, Lintzeris N. Opioid agonist treatment for pharmaceutical opioid dependent people. *Cochrane Database Syst Rev.* 2016(5).
27. Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ.* 2017;358:j4008. http://www.bmj.com/content/bmj/358/bmj.j4008.full.pdf. Accessed 2019 Jul 29.
28. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Community Health.* 1998;52(6):377-384. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1756728/pdf/v052p00377.pdf. Accessed 2019 Jul 29.

29. Agree Next Steps Consortium. The AGREE II Instrument. [Hamilton, ON]: AGREE Enterprise; 2017: https://www.agreetrust.org/wp-content/uploads/2017/12/AGREE-II-Users-Manual-and-23-item-Instrument-2009-Update-2017.pdf. Accessed 2019 Jul 29.
30. Ling S, Mangaoil R, Cleverley K, Sproule B, Puts M. A systematic review of sex differences in treatment outcomes among people with opioid use disorder receiving buprenorphine maintenance versus other treatment conditions. *Drug Alcohol Depend.* 2019;197:168-182.
31. Moore KE, Roberts W, Reid HH, Smith KMZ, Oberleitner LMS, McKee SA. Effectiveness of medication assisted treatment for opioid use in prison and jail settings: A meta-analysis and systematic review. *J Subst Abuse Treat.* 2019;99:32-43.
32. Chetty M, Kenworthy JJ, Langham S, Walker A, Dunlop WCN. A systematic review of health economic models of opioid agonist therapies in maintenance treatment of non-prescription opioid dependence. *Addict Sci Clin Pract.* 2017;12(1):6-6.
33. Gowing L, Ali R, White JM, Mbewe D. Buprenorphine for managing opioid withdrawal. *Cochrane Database Syst Rev.* 2017(2).
34. Evans EA, Zhu Y, Yoo C, Huang D, Hser YI. Criminal justice outcomes over 5 years after randomization to buprenorphine-naloxone or methadone treatment for opioid use disorder. *Addiction.* 2019;27:27.
35. Carrera I, Sanchez L, Sabater E, et al. Study on users' perception of agonist opioid treatment in the galician network of drug addiction. *Heroin Addict Relat Clin Probl.* 2016;18(3):5-8.
36. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol.* 2009;62(10):e1-e34.
37. Saulle R, Vecchi S, Gowing L. Supervised dosing with a long-acting opioid medication in the management of opioid dependence. *Cochrane Database Syst Rev.* 2017;4:CD011983.
38. Law FD, Diaper AM, Melichar JK, Coulton S, Nutt DJ, Myles JS. Buprenorphine/naloxone versus methadone and lofexidine in community stabilisation and detoxification: A randomised controlled trial of low dose short-term opiate-dependent individuals. *J Psychopharmacol.* 2017;31(8):1046-1055.
39. Hser YI, Huang D, Saxon AJ, et al. Distinctive trajectories of opioid use over an extended follow-up of patients in a multisite trial on Buprenorphine + Naloxone and Methadone. *J Addict Med.* 2017;11(1):63-69.
40. Mittal ML, Jain S, Sun S, et al. Opioid agonist treatment and the process of injection drug use initiation. *Drug Alcohol Depend.* 2019;197:354-360.
41. Bozinoff N, DeBeck K, Milloy MJ, et al. Utilization of opioid agonist therapy among incarcerated persons with opioid use disorder in Vancouver, Canada. *Drug Alcohol Depend.* 2018;193:42-47.
42. Braback M, Ekstrom L, Troberg K, et al. Malmo treatment referral and intervention study-high 12-month retention rates in patients referred from syringe exchange to Methadone or Buprenorphine/Naloxone treatment. *Front Psychiatry.* 2017 Aug;8:161.
43. Heikman PK, Muhonen LH, Ojanpera IA. Polydrug abuse among opioid maintenance treatment patients is related to inadequate dose of maintenance treatment medicine. *BMC Psychiatry.* 2017;17(1):245.
44. Gaur N, Gautam M, Singh S, Venkatesh Raju V, Sarkar S. Clinical practice guidelines on assessment and management of substance abuse disorder in children and adolescents. *Indian J Psychiatry.* 2019;61(8 Supplement 2):S333-S349.
45. Peeler M, Fiscella K, Terplan M, Sufrin C. Best practices for pregnant incarcerated women with opioid use disorder. *J Correct Health Care.* 2019 Jan;25(1):4-14.
46. Srivastava A, Kahan M, Nader M. Primary care management of opioid use disorders: Abstinence, methadone, or buprenorphine-naloxone? *Can Fam Physician.* 2017;63(3):200-205.
47. Monheit B, Pietrzak D, Hocking S. Prescription drug abuse - A timely update. *Aust Fam Physician.* 2016;45(12):862-866.
48. Kamien JB, Branstetter SA, Amass L. Buprenorphine-naloxone versus methadone maintenance therapy: A randomised double-blind trial with opioid-dependent patients. *Heroin Addict Relat Clin Probl.* 2008;10(4):5-18.
49. Otiashvili D, Piralishvili G, Sikharulidze Z, Kamkamidze G, Poole S, Woody GE. Methadone and buprenorphine-naloxone are effective in reducing illicit buprenorphine and other opioid use, and reducing HIV risk behavior—outcomes of a randomized trial. *Drug Alcohol Depend.* 2013;133(2):376-382.
50. Piralishvili G, Otiashvili D, Sikharulidze Z, Kamkamidze G, Poole S, Woody GE. Opioid addicted Buprenorphine injectors: drug use during and after 12-weeks of Buprenorphine–Naloxone or Methadone in the Republic of Georgia. *J Subst Abuse Treat.* 2015 Mar;50:32-37.
51. Saxon AJ, Ling W, Hillhouse M, et al. Buprenorphine/Naloxone and methadone effects on laboratory indices of liver health: A randomized trial. *Drug Alcohol Depend.* 2013;128(1):71-76.
52. Woody GE, Bruce D, Korthuis PT, et al. HIV risk reduction with buprenorphine-naloxone or methadone: findings from a randomized trial. *J Acquir Immune Defic Syndr.* 2014;66(3):288-293.
53. Hser Y-I, Saxon AJ, Huang D, et al. Treatment retention among patients randomized to buprenorphine/naloxone compared to methadone in a multi-site trial. *Addiction.* 2014;109(1):79-87.
54. Magura S, Lee JD, Hershberger J, et al. Buprenorphine and methadone maintenance in jail and post-release: a randomized clinical trial. *Drug Alcohol Depend.* 2009;99(1):222-230.
55. Hser YI, Evans E, Huang D, et al. Long-term outcomes after randomization to buprenorphine/naloxone versus methadone in a multi-site trial. *Addiction.* 2016;111(4):695-705.
56. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ.* 2008;336(7650):924-926.

Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Systematic Reviews and Meta-Analyses

First Author, Publication Year, Country	Study Designs, Search Strategy, Numbers of Studies Included, Quality Assessment Tool, and Objective	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Ling, 2019[30] Canada	**Study design**: SR of relevant published RCTs. **Literature search strategy**: Authors performed literature searches in CINAHL, PsycINFO, MEDLINE, EMBASE, CENTRAL up to February 24, 2018. These searches were supplemented by a manual search of the reference lists of included trials. A grey literature search was not performed. **Number of studies included**: In total, 33 citations, representing 25 studies were included. Six citations of three studies, were relevant for this review. **Quality assessment tool**: Conducted using the Cochrane Risk of Bias assessment **Objective**: To determine the presence of sex differences in treatment outcomes and whether these differences were related to the type of treatment.	Adult participants with OUD The studies relevant to this report had sample sizes of 80,[49] 268,[48] and 1,267 participants.[51]	**Interventions**: A buprenorphine maintenance intervention of any formulation, including BUP-NAL combination products. **Comparators**: Non-buprenorphine maintenance treatment; buprenorphine taper; placebo. Studies relevant to the present report compared of BUP-NAL to methadone.	**Relevant Outcomes:** - Treatment retention - Opioid use - Other drug use - Sexual risk behaviour - Quality of life, - Legal involvement - Mental health, - Physical health **Follow-up:** minimum of four weeks
Moore, 2019[31] United States of America	**Study design**: SR of relevant published RCTs or quasi-experimental studies with an administrative	People incarcerated in correctional facilities (i.e., prisons and jails).	**Interventions**: Induction or maintenance on methadone,	**Relevant Outcomes:** - Treatment engagement - Opioid use

Table 2: Characteristics of Included Systematic Reviews and Meta-Analyses

First Author, Publication Year, Country	Study Designs, Search Strategy, Numbers of Studies Included, Quality Assessment Tool, and Objective	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
	comparison group. A meta-analysis was performed on the RCTs. **Literature search strategy**: Authors performed literature searches in PsycINFO, PubMed up to December 2017. **Number of studies included**: In total, 24 studies were included, with one relevant RCT for this review. **Quality assessment tool**: NR **Objective**: To examine the effectiveness of medication assisted treatment delivered in prisons and jails on post-release outcomes.	The study relevant to this report had 81 participants.[54]	buprenorphine, or naltrexone **Comparators**: any comparator	- Recidivism (i.e., re-arrest, re-incarceration) - Health risk behaviours **Follow-up:** NR
Chetty, 2017[32] United Kingdom	**Study design**: SR of health economic studies. **Literature search strategy**: Authors performed literature searches in eight databases, including: MEDLINE, EMBASE, Cochrane Library, NEED up to March 18, 2015. This was supplemented by a search of publications by HTA agencies. Bibliographies of included articles were also searched.	People dependant on non-prescription opioids and receiving associated pharmacotherapy.	**Interventions**: A variety of pharmacotherapies, including BUP-NAL and methadone. **Comparators**: any pharmacotherapy used for maintenance; no therapy; placebo.	**Relevant Outcomes:** - Health economic models of any type. **Follow-up:** Not applicable

Table 2: Characteristics of Included Systematic Reviews and Meta-Analyses

First Author, Publication Year, Country	Study Designs, Search Strategy, Numbers of Studies Included, Quality Assessment Tool, and Objective	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
	Number of studies included: In total, 18 were relevant to other questions in the review. No primary studies were relevant to this report. **Quality assessment tool**: An adapted form of the checklist for economic evaluations developed by the University of Glasgow. **Objective**: To identify methods for modelling opioid agonists therapy as well as costs and outcomes considered in opioid dependence.			
Gowing, 2017[33] Australia	**Study design**: SR of RCTs **Literature search strategy**: Authors searched CENTRAL, MEDLINE, EMBASE, PsycINFO, and Web of Science to December 22, 2016. This was supplemented by hand searching the reference lists of relevant papers, ongoing trial registers, and conference proceedings. **Number of studies included**: In total, 27 studies in 49 publications were relevant to other questions in the review. No primary studies	Opioid dependent participants going through managed withdrawal.	**Interventions**: Buprenorphine, alone or in combination with naloxone. **Comparators**: A variety of pharmacotherapies, including tapered doses of methadone.	**Relevant Outcomes:** - Intensity of withdrawal - Duration of treatment - Adverse effects - Completion of treatment **Follow-up:** NR

Table 2: Characteristics of Included Systematic Reviews and Meta-Analyses

First Author, Publication Year, Country	Study Designs, Search Strategy, Numbers of Studies Included, Quality Assessment Tool, and Objective	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
	were relevant to this report. **Quality assessment tool**: the Cochrane Risk of Bias assessment tool. **Objective**: To assess the effects of buprenorphine-based therapy versus other pharmacotherapies for managing opioid withdrawal.			

BUP-NAL = buprenorphine-naloxone tablet; CENTRAL = Cochrane Central Register of Controlled Trials; CINAHL = Cumulative Index to Nursing and Allied Health Literature; EMBASE = Excerpta Medica database; HTA = Health Technology Assessment; MEDLINE = Medical Literature Analysis and Retrieval System Online; NEED = National Health Service Economic Evaluation Database; NR = not reported; OUD = opioid use disorder; PsycINFO = psychological information database; PubMED = Public MEDLINE; 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	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Randomized Controlled Trial				
Evans, 2019[34] United States of America	**Study design**: a secondary analysis of a prospective follow-up study[55] of a phase IV RCT trial on liver safety.[51] **Setting**: federally licensed opioid dependence treatment programs located in California, Oregon, Washington, Pennsylvania, and Connecticut. **Objective**: evaluation of criminal justice	The analytical sample included opioid-dependant participants recruited from three California clinics and who completed a follow-up interview. **Number of patients in analytical sample**: 303 participants (179 BUP-NAL and 124 methadone). **Mean age (SD) of analytical sample**: 37.9 (11.3); P < 0.001.	**Intervention**: BUP-NAL **Comparator**: Methadone	**Outcomes**: - Arrests - Incarceration - Treatment participation - Death **Follow-up**: Five years post-randomization. Whereas, the initial RCT followed participants for 24 weeks of treatment, then a taper over ≤ 8 weeks or a referral for ongoing clinical treatment.

Table 3: Characteristics of Included Primary Clinical Studies

First Author, Publication Year, Country	Study Design, Setting, and Objective	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
	outcomes in people who are opioid-dependent randomized to receive BUP-NAL or methadone.	**Sex of analytical sample**: 33.3% female		
Non-Randomized Study				
Carrera, 2016[35] Spain	**Study design**: a prospective cohort, mixed-methods study. **Setting**: patients enrolled in the opiate derivatives treatment programme at sixteen drug addiction health care units of the Galician Network of Addictive Disorders. **Objective**: to assess the quality of life and the perceived satisfaction of participants.	Participants were over 18 years old, receiving methadone maintenance therapy of less than or equal to 30 mg daily. **Number of patients**: 135 total, with 83 in the intervention group. **Mean age**: for the intervention group was 39.87 years, while the comparator group was 39.40 years. **Sex**: intervention group was 84.8% male, while the comparator group was 85.7% male.	**Intervention**: participants initially on a methadone maintenance programme were switched to BUP-NAL. **Comparator**: patients remained in a methadone maintenance programme.	**Relevant outcomes**: - Quality of Life Enjoyment and Satisfaction Questionnaire, short form **Follow-up**: Three months

BUP-NAL = buprenorphine-naloxone tablet; RCT = randomized controlled trial; SD = standard deviation.

Table 4: 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
Canadian Family Physician: Patients, Experience, Evidence, Research (PEER) group, 2019[18]						
Intended users: Clinicians and patients to assist with shared informed	Various OUD treatments, including: Pharmacotherapy (BUP-NAL, methadone, naltrexone, and	Various outcomes, including: treatment retention, abstinence, sedation, re-	Seventeen SRs were completed to answer clinical questions from the guideline committee. The	**GRADE quality of evidence:** • High • Moderate • Low • Very low	The guideline committee, composed of 13 clinicians, used the results of all systematic reviews to draft the	Peer review involving 52 health professionals and five people with

Table 4: 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
decisions making. **Target population**: Patients with OUD, except pregnant people or patients less than 18 years of age.	cannabinoids), psychosocial management, residential treatment.	incarceration, illicit drug use.	resources used were MEDLINE, Cochrane Library, Google, published guidelines on OUD, and reference lists of the included SRs, up to June 2018.	**GRADE strength of recommendation**:[56] • Strong ("we recommend") • Weak ("could consider")	guidelines. The recommendations were decided based on consensus of the committee.	lived experience.
British Columbia Centre on Substance Use (BCCSU) - Pregnancy Supplement, 2018[19]						
Intended users: Health care professionals involved in the treatment of individuals with OUD. **Target population**: As a supplement to the BSSCU 2017 guideline,[3] the focus is on pregnant people with an OUD.	Various OUD treatments including: detoxification, residential treatment, pharmacotherapies, and harm reduction.	Various outcomes, including: treatment retention, abstinence, morbidity, mortality, and obstetrical outcomes.	NR	NR	NR	NR
British Columbia Centre on Substance Use (BCCSU) - Youth Supplement, 2018[20]						
Intended users: Health care professionals involved in the treatment of individuals with OUD. **Target population**:	Various OUD treatments including: withdrawal management, pharmacotherapies, and non-pharmacological treatments.	Various outcomes, including: treatment retention, abstinence, morbidity, and mortality.	NR	NR	NR	NR

Table 4: 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
As a supplement to the BSSCU 2017 guideline,[3] the focus is on youth (adolescents 12 to 17 years old and young adults 18 to 25 years old) with OUD.						
Canadian Research Initiative in Substance Misuse (CRISM), 2018[21]						
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	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" (*p90*)[21] Updated literature searches were	**GRADE quality of evidence:** • High • Moderate • Low • Very low **GRADE strength of recommendation**[56] • 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 4: 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
pregnant people.			performed in 2016 in PubMed, ISI Web of Science, and the Cochrane Library.			
British Columbia Centre on Substance Use (BCCSU), 2017[3]						
Intended users: BC physicians, nursing, and allied health professionals and other care providers involved in the treatment of individuals with OUD, as well as policy makers and administrators. **Target population**: Individuals with OUD.	Various OUD treatments including: detoxification, residential treatment, pharmacotherapies, psychosocial interventions, and harm reduction.	Various outcomes, including: treatment retention, abstinence, morbidity and mortality.	Authors conducted a review of the literature, retaining SRs, MAs, RCTs, NRSs, and expert opinion.	**GRADE quality of evidence:** • High • Moderate • Low • Very low **GRADE strength of recommendation**[56]: • Strong • Weak	Consensus of committee members through group communication and meetings.	Internal review and external review comprised of experts and stakeholders.
Society of Obstetricians and Gynaecologists of Canada (SOGC), 2017[22]						
Intended users: Health care providers caring for pregnant people. **Target population**: Pregnant people who have	Various OUD treatments including: withdrawal management, brief interventions, pharmacotherapies, psychosocial interventions, and harm reduction.	Various outcomes, including: treatment retention, antenatal complications, morbidity, mortality, and obstetrical outcomes.	Authors conducted a search for SRs, RCTs, and NRSs, in MEDLINE, PubMed, and the Cochrane Library from 1996 to 2016. This was supplemented with hand	Quality of evidence assessed using the ranking of the Canadian Task Force on Preventive Health Care:[22] • I: at least one proper RCT • II-1: well designed trial	NR	NR

Table 4: 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
substance use disorders.			searching of reference lists.	without randomization • II-2: well-designed cohort or case-control study • II-3: comparisons between times or places with or without the intervention. • III: expert opinions. Classification of recommendations: • A: good evidence to recommend • B: fair evidence to recommend • C: conflicting evidence • D: fair evidence to recommend against • E: good evidence to recommend against • I: insufficient evidence (in quantity or quality)		

BC = British Columbia; BCCSU = British Columbia Centre on Substance Use; BUP-NAL = buprenorphine-naloxone tablet; GRADE = Grading of Recommendations Assessment, Development and Evaluation; HIV = human immunodeficiency virus; ISI = Institute for Scientific Information; MA = meta-analysis; MEDLINE = Medical Literature Analysis and Retrieval System Online; NR = not reported; NRS = non-randomized study; OUD = opioid use disorder; PubMED = Public MEDLINE; SR = systematic review; RCT = randomized controlled trial.

Appendix 3: Critical Appraisal of Included Publications

Table 5: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR 2[27]

Strengths	Limitations
Ling, 2019[30]	
• The objectives and inclusion/exclusion criteria were clearly stated and included components of population, intervention, comparator, and outcomes • Multiple databases were searched (CINAHL, PsycINFO, EMBASE, MEDLINE, CENTRAL). In addition, a manual search of references from identified literature was performed • Search terms and dates were provided (February 24, 2018) • A detailed protocol of the methods was registered on Prospero (CRD42018098777) prior to the conduct of the review • Study selection and data extraction were completed in duplicate and described in detail • A list of included studies was provided, and the characteristics of included studies were described in detail • Quality was assessed using the Cochrane Risk of Bias tool. • 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 (none) and were unlikely to have influenced the findings of the review	• Grey literature searching was not performed, and no justification provided • The choice of included study designs was not justified • The possibility of publication bias was not investigated • Review authors did not report on source of funding for the included studies • 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 relevant primary studies were conducted outside of Canada (i.e., the United States of America and the Republic of Georgia), and their findings may not be generalizable to the Canadian setting.
Moore, 2019[31]	
• The objectives and inclusion/exclusion criteria were clearly stated and included components of population, intervention, comparator, and outcomes • Two databases were searched (PubMed and PsycINFO) • Search terms and dates were provided (December 2017) • A list of included studies was provided, and the characteristics of included studies were described in detail • Bias was assessed using the Cochrane Risk of Bias tool • Quality was assessed using the Cochrane Risk of Bias tool. • Review authors considered risk of bias in individual studies when interpreting and discussing the results • Sources of funding were disclosed (National Institute on Drug Abuse and State of Connecticut Department of Mental Health and Addiction Services) and were unlikely to have influenced the findings of the review	• A manual search of references from identified literature and a grey literature search were not performed, and no justification provided • An a priori protocol was not reported for the review. • Study selection and data extraction were not reported as completed in duplicate • Although the methodological quality of studies is discussed in broad terms, there was no report of a formal assessment of the quality of included studies. • There was no statement on the author's conflicts of interest related to this review • The choice of included study designs was not justified • The possibility of publication bias was not investigated • Review authors did not report on source of funding for the included studies • 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

Table 5: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR 2[27]

Strengths	Limitations
	• The relevant primary study was conducted in a large urban jail of the United States of America, and the findings may not be generalizable to the Canadian incarceration or general population settings.
Chetty, 2017[32]	
• The objectives and inclusion/exclusion criteria were clearly stated and included components of population, intervention, comparator, and outcomes • Several databases were searched (EMBASE, MEDLINE, Cochrane, Database of Abstracts of Reviews of Effects, and NEED) • Search terms and dates were provided (March 2015) • A list of included studies was provided and the characteristics of included studies were described in detail • Quality of the economic evaluation was assessed using an adapted form of the checklist for economic evaluations developed by the University of Glasgow • Study selection was completed in duplicate • A list of excluded studies was provided along with the reasons for exclusion	• An a priori protocol was not reported for the review • Risk of bias was not assessed, nor did review authors consider risk of bias in individual studies when interpreting and discussing the results • Source of funding was disclosed (Mundipharma International) and may have influenced the findings of the review. In addition, the funder was involved in analysis and interpretation of data, writing of the manuscript, and decision to publish the manuscript • Data extraction was not reported as completed in duplicate • Although authors did provide a statement on conflicts of interest (two authors are employees of the funder Mundipharma International), they did not discuss how these conflicts were managed • The possibility of publication bias was not investigated • Review authors did not report on source of funding for the included studies
Gowing, 2017[33]	
• The objectives and inclusion/exclusion criteria were clearly stated and included components of population, intervention, comparator, and outcomes • An a priori protocol was reported for the review along with differences between the protocol and the published review • Several databases were searched (CENTRAL, MEDLINE, EMBASE, PsycINFO) • Search terms and dates were provided (December 2016) • A list of included studies was provided, and the characteristics of included studies were described in detail • Quality of the included studies was assessed using the approach recommended by Cochrane • Study selection was completed in duplicate • A list of excluded studies was provided along with the reasons for exclusion • The possibility of publication bias was investigated • Risk of bias was assessed, and review authors did consider risk of bias in individual studies when interpreting and discussing the results • Review authors reported on source of funding for the included studies • Sources of funding were disclosed (Drug and Alcohol Services South Australia, Commonwealth Department of Health and Ageing) and were unlikely to have influenced the findings of the review	• Data extraction was not reported as completed in duplicate

Table 5: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR 2[27]

Strengths	Limitations
• Authors provided a statement on conflicts of interest (none known)	

CENTRAL = Cochrane Central Register of Controlled Trials; CINAHL = Cumulative Index to Nursing and Allied Health Literature; EMBASE = Excerpta Medica database; MEDLINE = Medical Literature Analysis and Retrieval System Online; NEED = National Health Service Economic Evaluation Database; PsycINFO = psychological information database; PubMED = Public MEDLINE.

Table 6: Strengths and Limitations of Clinical Studies using the Downs and Black Checklist[28]

Strengths	Limitations
Randomized Controlled Trial	
Evans, 2019[34]	
• 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 • Data analyses were planned at the outset • The time period over which patients were recruited was specified • Analyses were based on intention to treat • Length of follow up was consistent between the intervention and comparator groups • The source of participants included in the study was well described • Sources of funding were disclosed (National Institute on Drug Abuse) and was unlikely to have influenced the findings of the study • The authors disclosed no conflicts of interest	• Actual probability values (*P*-values) were not systematically reported • The main outcomes measures used (except death) were patient self-reported and subject to recall bias • The randomization methodology of the original RCT was not reported, other than to indicate that it was changed partway from a 1:1 allocation, to the buprenorphine and methadone groups, to a 2:1 allocation because of higher dropout rates in the buprenorphine group. This may have introduced a bias and it is not clear if the participants enrolled before and after this change differed in important characteristics. Furthermore, it was not reported if the data were analyses separately, before and after the allocation change. • There was no characterisation of the participants who withdrew or were lost to follow-up • This was an open-label study with no blinding of study participants or outcome assessors • Although patient characteristics were described, the distribution of demographics and main confounding factors in this study's analytical sample were sometimes different to those of the source population in the initial RCT, introducing selection and attrition biases • Participants were compensated after their assessment ($50 gift card) and after providing a urine sample ($10), which may have introduced a participation bias. • This study was a secondary analysis of an initial study designed to evaluate the effects of BUP-NAL and methadone on liver function. As such, its design may not have been sufficiently powered to detect the outcomes of interest in the secondary analysis. • In the initial RCT, one of the exit pathways was via a taper schedule of less than or equal to eight weeks, which is not representative of routine clinical care. It was unclear if both groups were affected equally; thus, results should be

Table 6: Strengths and Limitations of Clinical Studies using the Downs and Black Checklist[28]

Strengths	Limitations
	interpreted with caution since we were unable to assess if a differential treatment bias was introduced in the follow up studies.
Non-Randomized Studies	
Carrera, 2016[35]	
• 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 • Data analyses were planned at the outset • The time period over which patients were recruited was specified (April 2012 to December 2013) • Length of follow up was consistent between the intervention and comparator groups (three months) • The source of participants included in the study was well described	• Sources of funding were disclosed (Reckitt Benckiser Pharmaceuticals) and it is unclear if this influenced the findings of the study • Although authors did provide a statement on conflicts of interest (two authors are employees of a company that receives funding from Reckitt Benckiser), they did not discuss how these conflicts were managed • The main outcomes measures used were questionnaire assessments at the beginning and end of the experiment and are hence subject to response bias • Participants were assigned to the BUP-NAL group consecutively, upon meeting the eligibility criteria. This may have introduced a selection bias. • There was no characterisation of the participants who withdrew or were lost to follow-up. • This was an open-label study with no blinding of study participants or outcome assessors. • Although, many results have probability values (P-values), they were not systematically reported. • While the methadone treatment group was fully funded, patients in the BUP-NAL group had to accept the financial burden of co-payments which contributed to drop-outs in that group, possibly introducing a selection bias.

BUP-NAL = buprenorphine-naloxone tablet; RCT = randomized controlled trial.

Table 7: Strengths and Limitations of Guidelines using AGREE II[29]

Item	Guidelines					
	Canadian Family Physician: Patients, Experience, Evidence, Research (PEER) group, 2019[18]	British Columbia Centre on Substance Use (BCCSU) - Pregnancy Supplement, 2018[19]	British Columbia Centre on Substance Use (BCCSU) - Youth Supplement, 2018[20]	Canadian Research Initiative in Substance Misuse (CRISM), 2018[21]	British Columbia Centre on Substance Use (BCCSU), 2017[3]	Society of Obstetricians and Gynaecologists of Canada (SOGC), 2017[22]
Domain 1: Scope and Purpose						

Table 7: Strengths and Limitations of Guidelines using AGREE II[29]

Item	Guidelines					
	Canadian Family Physician: Patients, Experience, Evidence, Research (PEER) group, 2019[18]	British Columbia Centre on Substance Use (BCCSU) - Pregnancy Supplement, 2018[19]	British Columbia Centre on Substance Use (BCCSU) - Youth Supplement, 2018[20]	Canadian Research Initiative in Substance Misuse (CRISM), 2018[21]	British Columbia Centre on Substance Use (BCCSU), 2017[3]	Society of Obstetricians and Gynaecologists of Canada (SOGC), 2017[22]
1. The overall objective(s) of the guideline is (are) specifically described.	Yes	Yes	Yes	Yes	Yes	Yes
2. The health question(s) covered by the guideline is (are) specifically described.	Yes	No	No	Yes	No	No
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	Yes	Yes	Yes	Yes	Yes	Yes
Domain 2: Stakeholder Involvement						
4. The guideline development group includes individuals from all relevant professional groups.	Yes	Yes	Yes	Yes	Yes	No
5. The views and preferences of the target population (patients, public, etc.) have been sought.	Yes	Unclear	Unclear	Yes	No	No
6. The target users of the guideline are clearly defined.	Yes	Yes	Yes	Yes	Yes	Yes
Domain 3: Rigour of Development						

Table 7: Strengths and Limitations of Guidelines using AGREE II[29]

Item	Guidelines					
	Canadian Family Physician: Patients, Experience, Evidence, Research (PEER) group, 2019[18]	British Columbia Centre on Substance Use (BCCSU) - Pregnancy Supplement, 2018[19]	British Columbia Centre on Substance Use (BCCSU) - Youth Supplement, 2018[20]	Canadian Research Initiative in Substance Misuse (CRISM), 2018[21]	British Columbia Centre on Substance Use (BCCSU), 2017[3]	Society of Obstetricians and Gynaecologists of Canada (SOGC), 2017[22]
7. Systematic methods were used to search for evidence.	Yes	No	No	No	No	Yes
8. The criteria for selecting the evidence are clearly described.	Yes	No	No	Yes	No	No
9. The strengths and limitations of the body of evidence are clearly described.	Yes	No	No	Yes	Yes	No
10. The methods for formulating the recommendations are clearly described.	Yes	No	No	Yes	Yes	No
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.	Yes	Yes	Yes	Yes	Yes	Yes
12. There is an explicit link between the recommendations and the supporting evidence.	Yes	Yes	Yes	Yes	Yes	No
13. The guideline has been externally reviewed by experts prior to its publication.	Yes	Yes	Yes	Yes	Yes	No

Table 7: Strengths and Limitations of Guidelines using AGREE II[29]

Item	Guidelines					
	Canadian Family Physician: Patients, Experience, Evidence, Research (PEER) group, 2019[18]	British Columbia Centre on Substance Use (BCCSU) - Pregnancy Supplement, 2018[19]	British Columbia Centre on Substance Use (BCCSU) - Youth Supplement, 2018[20]	Canadian Research Initiative in Substance Misuse (CRISM), 2018[21]	British Columbia Centre on Substance Use (BCCSU), 2017[3]	Society of Obstetricians and Gynaecologists of Canada (SOGC), 2017[22]
14. A procedure for updating the guideline is provided.	No	Unclear	Unclear	Yes	Yes	No
Domain 4: Clarity of Presentation						
15. The recommendations are specific and unambiguous.	Yes	Yes	Yes	Yes	Yes	Yes
16. The different options for management of the condition or health issue are clearly presented.	Yes	Yes	Yes	Yes	Yes	Yes
17. Key recommendations are easily identifiable.	Yes	Yes	Yes	Yes	Yes	Yes
Domain 5: Applicability						
18. The guideline describes facilitators and barriers to its application.	No	Yes	Yes	No	Yes	No
19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	Yes	Yes	Yes	No	Yes	No

Table 7: Strengths and Limitations of Guidelines using AGREE II[29]

Item	Guidelines					
	Canadian Family Physician: Patients, Experience, Evidence, Research (PEER) group, 2019[18]	British Columbia Centre on Substance Use (BCCSU) - Pregnancy Supplement, 2018[19]	British Columbia Centre on Substance Use (BCCSU) - Youth Supplement, 2018[20]	Canadian Research Initiative in Substance Misuse (CRISM), 2018[21]	British Columbia Centre on Substance Use (BCCSU), 2017[3]	Society of Obstetricians and Gynaecologists of Canada (SOGC), 2017[22]
20. The potential resource implications of applying the recommendations have been considered.	No	Yes	Yes	No	Yes	No
21. The guideline presents monitoring and/or auditing criteria.	No	No	No	No	No	No
Domain 6: Editorial Independence						
22. The views of the funding body have not influenced the content of the guideline.	Yes	Unclear	Unclear	Yes	Yes	Unclear
23. Competing interests of guideline development group members have been recorded and addressed.	Yes	No	No	Yes	Yes	Unclear

Appendix 4: Main Study Findings and Authors' Conclusions

Table 8: Summary of Findings Included Systematic Reviews and Meta-Analyses

Main Study Findings	Authors' Conclusion
Ling, 2019[30]	
Relevant individual studies: The systematic review included six citations of three relevant primary studies on the clinical effectiveness of BUP-NAL compared with methadone for the treatment of patients with OUD. **Primary study citation:** • Kamien, 2008, United States of America[48] • Otiashvili, 2013, Republic of Georgia[49] Secondary analysis: ○ Piralishvili, 2015[50] • Saxon, 2013, United States of America[51] Secondary analyses: ○ Woody, 2014[52] ○ Hser, 2014[53] Of the above, only Woody[52] and Hser[53] discussed or reported on the SR's examining sex differences in treatment outcomes among people being treatment with BUP-NAL. **Findings:** • *Treatment retention:* ○ BUP-NAL: females were less likely to be retained in treatment compared to males ($p < 0.01$) ○ Methadone: females were more likely to be retained in treatment compared to males ($p < 0.01$) • *Sexual risk:* ○ Males: risk decreased over time in the methadone group compared with the BUP-NAL group ($p = 0.03$) ○ Females: risk decreased over time, with no differences between methadone and BUP-NAL group ($p = 0.02$)	"Several studies examined sex differences for the outcomes of treatment retention, opioid use, other substance use and sexual risk behaviours. However, due to inconsistent findings, small sample sizes, and inability to conduct meta-analyses, the findings of this review were inconclusive."[30] (*p179*)
Moore, 2019[31]	
Relevant individual studies: The systematic review included one relevant primary study on the clinical effectiveness of BUP-NAL compared with methadone for the treatment of patients with OUD. **Primary study citation:** Magura, 2009, United States of America[54] **Findings**: • *Report to a community-based post-release substance use treatment:* ○ BUP-NAL: 48% ○ Methadone: 14%; (P-value not reported) • *Engagement in a substance use treatment at three months post-release (self-report):* ○ BUP-NAL: 48% ○ Methadone: 23%; (P-value not reported) • *Opioid Use at three months post-release (self-report):* ○ BUP-NAL: 53%	"This meta-analysis and systematic review shows strong support for the utility of [medication assisted treatment] in increasing community-based substance-use treatment engagement post-incarceration in prison and jail, and strong support for the use of methadone in reducing illicit opioid use and injection drug use post-incarceration. Additional evaluations of naltrexone and buprenorphine are needed. To date, there is equivocal support for the use of [medication assisted treatments] for reducing

Table 8: Summary of Findings Included Systematic Reviews and Meta-Analyses

Main Study Findings	Authors' Conclusion
○ Methadone: 66%; SR authors reported as no difference, (P-value not reported) • *Recidivism (i.e., re-arrest or re-incarceration) at three months post-release (self-report):* ○ BUP-NAL: 40% ○ Methadone: 50%; SR authors reported as no difference, (P-value not reported). • *Health risk behaviours:* ○ No overdoses or mortality observed	recidivism post-release, as reengagement in community-based [medication assisted treatment] after incarceration is often not considered in the prediction of recidivism."[31] (*p42*)
Chetty, 2017[32]	
No relevant primary studies were included in the SR	
Gowing, 2017[33]	
No relevant primary studies were included in the SR	

BUP-NAL = buprenorphine-naloxone tablet; OUD = opioid use disorder; SR = systematic review.

Table 9: Summary of Findings of Included Primary Clinical Studies

Main Study Findings	Authors' Conclusion
Randomized Controlled Trial	
Evans, 2019[34]	
Arrests, incarcerations, and treatment during five years of follow-up • *Arrested* ○ BUP-NAL: 55.3% ○ Methadone: 54.0%; authors reported as no difference, (P-value not reported). • *Incarceration* ○ BUP-NAL: 40.9% ○ Methadone: 47.3%; authors reported as no difference, (P-value not reported). • *Time in any OUD treatment (irrespective of initial randomization)* ○ BUP-NAL: 48.7% ○ Methadone: 57.1%; (P = 0.02) **Death during five years of follow-up** ○ BUP-NAL: 1 ○ Methadone: 1	"This study shows that continued treatment for opioid use disorder with either buprenorphine or methadone is associated with a reduction in arrests (relative to no treatment), with changes to methadone yielding similar outcomes to no pharmacotherapy among buprenorphine-randomized individuals." [34](*p7*)
Non-Randomized Study	
Carrera, 2016[35]	
Patients who remained abstinent at three-month follow-up • BUP-NAL: 75.9% • Methadone: 53.1%; (*P* = 0.012) **Treatment discontinuation at three-month follow-up** • BUP-NAL: 7.6%	"Based on the analysis of some variables, patients treated with [BUP-NAL] had a higher quality of life than patients treated with methadone, particularly considering the greater ease experienced by the former in normalizing their lifestyle."[35](*p40*)

Table 9: Summary of Findings of Included Primary Clinical Studies

Main Study Findings	Authors' Conclusion

• Methadone: 14.3%; (reported as not significant; P-value not reported)
 	
Overall quality of life scores at three-month follow-up
• BUP-NAL: increased from 46.97 at baseline to 49.74 (reported as non significant)
• Methadone: decreased from 45.02 at baseline to 44.76 (reported as non significant)
 	
Presence of side effects at three-month follow-up
• BUP-NAL: 20.3%
  ○ Most common: weight loss = 5.1%, nausea = 3.8%.
• Methadone: 63.3%;
  ○ Most common: constipation = 49.0%, sweating = 28.6%, decreased libido = 28.6%.	

BUP-NAL = buprenorphine-naloxone tablet

Table 10: Summary of Recommendations in Included Guidelines

Recommendations	Strength of Evidence and Recommendations
Canadian Family Physician: Patients, Experience, Evidence, Research (PEER) group, 2019[18]	
Strong: 1. "We recommend clinicians discuss the use of buprenorphine-naloxone or methadone with their patients for treatment of OUD. Methadone might be superior for retention in treatment. However, buprenorphine-naloxone might be easier to implement in practice owing to fewer prescribing restrictions and considerations"[18] (*p322*) 2. "We recommend against punitive measures involving opioid agonist treatment (ie, reduction in dose or loss of carries), unless safety is a concern"[18] (*p322*) 3. "We recommend against initiation of opioid agonist treatment with the intention to discontinue in the short term. Opioid agonist treatment is intended as long-term management. Optimal duration is unknown and might be indefinite" [18] (*p322*) **Weak**: 4. "Clinicians could consider take-home doses (ie, 2-7 d) as an option when need and stability indicate"[18] (*p322*) 5. "Clinicians could consider treatment agreements (ie, contracts) in the management of OUD for some patients"[18] (*p322*)	Quality of the evidence was judged using GRADE. 1. Moderate-quality evidence 2. Moderate-quality evidence 3. Low-quality evidence 4. Very low-quality evidence 5. No RCT evidence
British Columbia Centre on Substance Use (BCCSU) - Pregnancy Supplement, 2018[19]	
Strength of Recommendations not reported	

Table 10: Summary of Recommendations in Included Guidelines

Recommendations	Strength of Evidence and Recommendations
1. "The type of OAT to be initiated should be selected based on patients' individual circumstances and with consideration of access and availability. a. Methadone is traditionally recognized as the first-line option for OAT during pregnancy. […] b. Buprenorphine/naloxone is an alternative first-line medication for this population. Recent studies have found this medication to be as safe and effective as methadone and buprenorphine monotherapy during pregnancy. […]"[19] (*p10*)	1. Not reported
2. **"**Unless clinically indicated, transitioning between methadone, buprenorphine/naloxone, and slow-release oral morphine during pregnancy and postpartum periods is not recommended for patients who are stable on one of these medications prior to becoming pregnant. […]"[19] (*p10*)	2. Not reported
3. "For patients stable on buprenorphine/naloxone prior to becoming pregnant, transition to buprenorphine monotherapy during pregnancy is not necessary."[19] (*p10*)	3. Not reported
British Columbia Centre on Substance Use (BCCSU) - Youth Supplement, 2018[20]	
Strength of Recommendations not reported	
1. "The full range of available treatments should be considered for youth with OUD, including OAT, other pharmacological treatments, non-pharmacological interventions, and recovery-oriented services, with buprenorphine/naloxone recommended as first line treatment for moderate/severe OUD. […]"[20] (*p*10)	1. Not reported
2. "When pharmacological treatment is indicated, buprenorphine/naloxone is recommended as first line treatment due to safety advantages and improved flexibility (e.g., take-home doses). […]"[20] (*p*10)	2. Not reported
3. "Transitioning to methadone should be considered in youth who do not respond to adequately dosed buprenorphine/naloxone. […]"[20] (*p*10)	3. Not reported
Canadian Research Initiative in Substance Misuse (CRISM), 2018[21]	
Strong recommendations:	Quality of the evidence was judged using GRADE.
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."[21] (*p20*)	1. High quality of evidence
2. "For individuals responding poorly to buprenorphine/naloxone, consider transition to methadone treatment."[21] (*p20*)	2. High quality of evidence
3. "Initiate OAT with methadone when treatment with buprenorphine/naloxone is not the preferred option."[21] (*p20*)	3. High quality of evidence
4. "For individuals with a successful and sustained response to methadone who express a desire for treatment simplification, consider transition to	4. Moderate quality of evidence **GRADE quality of evidence:**[21]

Table 10: Summary of Recommendations in Included Guidelines

Recommendations	Strength of Evidence and Recommendations
buprenorphine/naloxone, since its superior safety profile allows for more routine take-home dosing and less frequent medical appointments."[21] (*p20*)	• **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
British Columbia Centre on Substance Use (BCCSU), 2017[3]	
Strong recommendations: 1. "Initiate opioid agonist treatment with buprenorphine/naloxone whenever feasible to reduce toxicities and facilitate recovery through safer take-home dosing."[3] (*p12*) 2. "Initiate opioid agonist treatment with methadone when treatment with buprenorphine/naloxone is not preferable (e.g., challenging induction)."[3] (*p12*) 3. "For individuals responding poorly to buprenorphine/naloxone, consider transition to methadone."[3] (*p12*) 4. "For individuals responding poorly to methadone, or with successful and sustained response to methadone desiring treatment simplification, consider transition to buprenorphine/naloxone."[3] (*p12*) 5. "For individuals with a successful and sustained response to agonist treatment desiring medication cessation, consider slow taper (e.g., 12 months) […]."[3] (*p12*)	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 5. Moderate quality of evidence
Society of Obstetricians and Gynaecologists of Canada (SOGC), 2017[22]	
Good evidence to recommend (A): 1. "The standard of care for the management of opioid use disorders during pregnancy is opioid agonist treatment with methadone or buprenorphine. Other sustained-release opioid preparations are also an option if methadone or buprenorphine is not available (I-A)."[22] (*p923*) 2. "Women who become pregnant while on methadone should continue on methadone maintenance therapy and should not switch to buprenorphine due to the risk of opioid withdrawal (I-A)."[22] (*p923*) 3. "Women who become pregnant while on buprenorphine/naloxone should be switched to buprenorphine monoproduct. Combination product should be continued until the monoproduct becomes available. Women taking buprenorphine should only switch to methadone if the buprenorphine monoproduct is not accessible and/or the woman	Quality of the evidence was judged using the ranking of the Canadian Task Force on Preventive Health Care. 1. (I) Evidence obtained from at least one properly randomized controlled trial. 2. (I) Evidence obtained from at least one properly randomized controlled trial. 3. (II-1) Evidence from well-designed controlled trials without randomization.

Table 10: Summary of Recommendations in Included Guidelines

Recommendations	Strength of Evidence and Recommendations
feels that she is not responding to the current treatment (II-1A)."[22] (*p923*)	

GRADE = Grading of Recommendations, Assessment, Development and Evaluation; OAT = opioid agonist treatment; OUD = opioid use disorder.

Appendix 5: Overlap between Included Systematic Reviews

Table 11: Relevant Primary Study Overlap between Included Systematic Reviews

Relevant Primary Study Citation	Systematic Review Citation			
	Ling, 2019[30]	Moore, 2019[31]	Chetty, 2017[32]	Gowing, 2017[33]
Kamien, 2008[48]	X			
Otiashvili, 2013[49] **Secondary analysis**: • Piralishvili, 2015[50]	X X			
Saxon, 2013[51] **Secondary analyses**: • Woody, 2014[52] • Hser, 2014[53]	X X X			
Magura, 2009[54]		X		

Appendix 6: Additional References of Potential Interest

Systematic Review

Alternative Comparator – Supervised vs. Unsupervised Dosing

Saulle R, Vecchi S, Gowing L. Supervised dosing with a long-acting opioid medication in the management of opioid dependence. *Cochrane Database Syst Rev*. 2017 Apr 27;4:CD011983. PubMed: PM28447766

Randomized Control Trials

Alternative Intervention – Concurrent Medication

Law FD, Diaper AM, Melichar JK, Coulton S, Nutt DJ, Myles JS. Buprenorphine/naloxone versus methadone and lofexidine in community stabilisation and detoxification: a randomised controlled trial of low dose short-term opiate-dependent individuals. *J Psychopharmacol*. 2017 08;31(8):1046-1055. PubMed: PM28631527

Alternative Comparator – High Opioid Use vs. Low Opioid Use

Hser YI, Huang D, Saxon AJ, et al. Distinctive trajectories of opioid use over an extended follow-up of patients in a multisite trial on Buprenorphine + Naloxone and Methadone. *J Addict Med*. 2017 Jan/Feb;11(1):63-69. PubMed: PM27898496

Non-Randomized Studies

Alternative Outcome – Initiation of Drug Use in Bystanders

Mittal ML, Jain S, Sun S, et al. Opioid agonist treatment and the process of injection drug use initiation. *Drug Alcohol Depend*. 2019 04 01;197:354-360. PubMed: PM30922483

Results not Extractable by Drug Type

Bozinoff N, DeBeck K, Milloy MJ, et al. Utilization of opioid agonist therapy among incarcerated persons with opioid use disorder in Vancouver, Canada. *Drug Alcohol Depend*. 2018 12 01;193:42-47. PubMed: PM30340144

Braback M, Ekstrom L, Troberg K, et al. Malmo treatment referral and intervention study-high 12-month retention rates in patients referred from syringe exchange to methadone or Buprenorphine/Naloxone treatment. *Front Psychiatry*. 2017;8:161. PubMed: PM28912734

Alternative Comparator – Self-Perceived Adequate vs. Inadequate Dose

Heikman PK, Muhonen LH, Ojanpera IA. Polydrug abuse among opioid maintenance treatment patients is related to inadequate dose of maintenance treatment medicine. *BMC Psychiatry*. 2017 07 06;17(1):245. PubMed: PM28683783

Clinical Practice Guidelines

Unclear Methodology

Gaur N, Gautam M, Singh S, Venkatesh Raju V, Sarkar S. Clinical practice guidelines on assessment and management of substance abuse disorder in children and adolescents. *Indian J Psychiatry*. 2019 Jan;61(8 Suppl 2):S333-S349. PubMed: PM625955389

Review Articles

Peeler M, Fiscella K, Terplan M, Sufrin C. Best practices for pregnant incarcerated women with opioid use disorder. *J Correct Health Care*. 2019 Jan;25(1):4-14. PubMed: PM30616487

Srivastava A, Kahan M, Nader M. Primary care management of opioid use disorders: abstinence, methadone, or buprenorphine-naloxone? *Can Fam Physician*. 2017 Mar;63(3):200-205. PubMed: PM28292795

Monheit B, Pietrzak D, Hocking S. Prescription drug abuse - a timely update. *Aust Fam Physician*. 2016 Dec;45(12):862-866. PubMed: PM27903034

Correction

The original report, published July 31, 2019, referenced the "sublingual film" formulation of buprenorphine-naloxone in the following report sections: title, abbreviations, context and policy issues, research questions, and in the intervention row of "Table 1: Selection Criteria". However, the "tablet" formulation of buprenorphine-naloxone was discussed in the following report sections: key findings, summary of evidence, summary of findings, conclusions and implications for decision or policy making sections, as well as the appendices. This has been corrected in this version of the report.

Furthermore, the original report did not contain two systematic reviews[32,33], one non-randomized study[35], and four publications[3,19,20,22] of two guidelines. These have been added and relevant sections have been corrected in this version of the report to reflect this additional information.