TITLE: Buprenorphine/Naloxone Versus Methadone for the Treatment of Opioid Dependence: A Review of Comparative Clinical Effectiveness, Cost-Effectiveness and Guidelines

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CONTEXT AND POLICY ISSUES

Opioid use disorder (also known as opioid dependence or drug addiction) is defined as maladaptive and persistent strong desires, cravings, and urges to use an opioid, difficulty in controlling its use, the presence of a physiological withdrawal state when its use is tapered quickly or stopped, tolerance to the physiological and behavioural effects of the drug, neglect of alternative pleasures and interests, and persistent use of the drug despite harm to oneself and others.[1] It is a complex disease involving physiological, psychological, genetic, behavioral, and environmental factors.[2] It was estimated in 2012 that there were 15.6 million illicit opioid users worldwide, with 11 million who primarily used heroin.[3] In Canada, it was estimated that there were more than 80,000 regular illegal opioid users in 2003.[4] Opioid use disorder is not only related to the use of illegal opioid drugs, but also prescription drugs, such as codeine, hydromorphone, oxycodone, morphine, fentanyl, and others.[5] In Canadians aged 15 years and older, 16.9% reported using opioid pain relievers in the past year in 2012. Of these, 5.2% (243,000 Canadians or 0.9% of the total population) reported abusing them.[6] More recently, there has been an increase in deaths due to fentanyl misuse; the Canadian Centre on Substance Abuse reported that between 2009 and 2014, there were 655 deaths in Canada where fentanyl was determined to be a cause or a contributing cause.[7]

Opioid use disorder can be treated with pharmacologically active prescription opioids that help relieve opioid withdrawal symptoms including cravings, and promote function in everyday living.[8] The treatment process involves stabilizing the patient through treatments that minimize the effects of drug use on motivation and mental state, or detoxification to minimize withdrawal symptoms. Most importantly, chronic treatment helps prevent relapse.[1,9] In Canada, there are two medications approved for the treatment of opioid use disorder: methadone and buprenorphine/naloxone. When taken as prescribed, these medications lack euphoric effect, alleviate opioid withdrawal symptoms, and diminish opioid cravings.[10,11]

Methadone is a full μ-opioid receptor agonist. It is indicated for opioid withdrawal (detoxification) or for maintenance treatment in adults diagnosed with a moderate to severe opioid use disorder.[12] Detoxification using methadone is done by gradual decreases in dose over a period of 180 days or less.[13] A treatment longer than 180 days is considered maintenance treatment. Methadone is also indicated as an analgesic for the treatment of cancer pain (acute and palliative care) or chronic pain.[12]

Methadone is available as an oral solution or as a concentrated oral solution (Methadose, Metadol, Metadol-D) which must be administered in a vehicle that does not lend itself to injection (for example orange-flavored crystal drinks).[13-15] An oral tablet (Metadol) is also available and is indicated for analgesia.[15] For all indications, methadone may be prescribed by a physician who has received an exemption under section 56 of the Controlled Drugs and Substances Act from the Federal Minister of Health through the Office of Controlled Substances at Health Canada.[12]

Buprenorphine/naloxone (brand name: Suboxone), a sublingual tablet, is a fixed combination of buprenorphine (a partial μ-opioid receptor agonist) and naloxone (a full opioid antagonist) in a 4:1 ratio.[16] Naloxone was added to prevent the intravenous abuse of buprenorphine. When taken sublingually, the absorption of naloxone is minimal; however when injected, it can rapidly precipitate opioid withdrawal.[17,18]

Suboxone was approved by Health Canada in 2007 "for substitution treatment in adults with problematic opioid drug dependence."[10] Physicians do not require an exemption under the Federal Act to prescribe Suboxone; however it is recommended that Suboxone be prescribed by physicians with experience in the treatment of opioid use disorder and who have completed a recognized Suboxone Education Program.[10] Buprenorphine alone (not combined with naloxone) is not marketed for the treatment of opioid use disorder in Canada.

In 2013, Suboxone (buprenorphine/naloxone) became available as a generic and its direct cost, and cost differential with methadone, decreased. Buprenorphine/naloxone has several advantages compared with methadone. Methadone is a full agonist; there is no ceiling to respiratory depression or sedation effects and an overdose can be fatal.[18] Buprenorphine also has a long half-life but because it is a partial agonist, it has a ceiling effect (effect plateaus at higher doses) and thus the risk of overdose is decreased.[18,19] Other advantages of buprenorphine/naloxone include its long duration of action which allows for every second day dosing if needed; its administration as a sublingual tablet; its lack of requirements of an exemption to be prescribed; and its formulation with less potential for abuse.

Given the foregoing, an assessment is required to assist decision-makers and prescribers in selecting between the two treatments. Hence, the purpose of this review is to provide evidence on the comparative clinical effectiveness and cost-effectiveness of buprenorphine/naloxone compared with methadone, for the treatment of patients with opioid use disorder. Clinical practice guidelines will also be examined.

This report was reviewed by experts in substance use and addiction treatment.

RESEARCH QUESTIONS

1. What is the clinical effectiveness of buprenorphine/naloxone compared with methadone for the treatment of patients with opioid dependence?

2. What is the cost-effectiveness of buprenorphine/naloxone compared with methadone for the treatment of patients with opioid dependence?

3. What are the evidence-based guidelines associated with the use of buprenorphine/naloxone for the treatment of patients with opioid dependence?

KEY FINDINGS

The comparative clinical effectiveness of maintenance treatment with buprenorphine/naloxone and methadone for the treatment of opioid use disorder was assessed in five randomized controlled trials and five non-randomized studies.

It was shown that more methadone patients were retained in treatment compared with buprenorphine/naloxone. Patients who stopped treatment did so for a variety of reasons including loss to follow-up and non-compliance with medication. Patients on buprenorphine/naloxone were more likely than patients on methadone to abstain from opioid use when measured quantitatively through urine testing. Of note, patients may have been under-dosed in the studies and hence, the true effectiveness of buprenorphine/naloxone and methadone may actually be greater than what was reported in the studies. Specifically, in one study buprenorphine/naloxone showed a linear dose-response relationship. Higher doses of methadone and of buprenorphine/naloxone were more effective than lower doses.

There was no statistically significant difference between buprenorphine/naloxone and methadone in the number of patients experiencing harms, including mortality.

The results of four economic evaluations showed that treatment with buprenorphine/naloxone was more effective but more costly than treatment with methadone; however the incremental cost effectiveness ratios were small. In some scenarios, buprenorphine/naloxone was dominant (more effective and less costly). Applicability of these results to the Canadian setting is unclear.

One Canadian clinical practice guideline specific to buprenorphine/naloxone and dated 2011 recommends that the choice of treatment be guided by the individual clinical circumstances and patient preference.

Overall, buprenorphine/naloxone appears to be a safe, effective, and cost-effective choice for treating opioid use disorder compared with methadone.

METHODS

Literature Search Methods

A limited literature search was conducted on key resources including Ovid Medline, Ovid Embase, PubMed, 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 used to limit retrieval by publication type for research questions 1 and 2. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses and guidelines for question 3. Where possible, retrieval was limited to the human population. The search was also limited to English language documents. Questions 1 and 2 used information from a previous CADTH Rapid Response entitled: "Suboxone versus Methadone for the Treatment of Opioid Dependence: A Review of the Clinical and Cost-effectiveness" (dated November 14, 2013) which addressed the same questions on clinical and cost-effectiveness as the present Rapid Response. The search used in the previous Rapid Response spanned January 1, 2003 to October 15, 2013. This search was updated to June 21, 2016. For question 3, the search was limited to articles published between January 1, 2011 and June 21, 2016.

Rapid Response reports are organized so that the evidence for each research question is presented separately.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Patients of any age with opioid dependence
Intervention	Buprenorphine/naloxone (e.g. Suboxone)
Comparator	Methadone [any formulation; including but not limited to methadone powder, Methadose (commercial product), and Metadol D (commercial product)]
Outcomes	· Clinical effectiveness (e.g. retention in treatment, heroin use, use of other drugs of abuse [including opioids]) and safety (e.g. harms, harms reduction, mortality) · Cost-effectiveness · Guidelines
Study Designs	Health Technology Assessment/ Systematic Reviews/ Meta-analysis, Randomized Controlled Trials, Non-randomized Studies, Economic Evaluations, Guidelines

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1 or were published prior to the search dates outlined in the Methods section. Studies on buprenorphine alone were excluded because it is not marketed in Canada for the treatment of opioid use disorder.

The following articles were also excluded:

- Reports which did not clearly state whether the formulation of buprenorphine included naloxone or when the study results for buprenorphine/naloxone were aggregated with those of buprenorphine alone
- Systematic reviews and guidelines with incomplete reporting of methods

- Studies that were deemed to have incomplete reporting of outcomes (such as not reporting numerical values for outcomes)
- Qualitative studies and surveys on patients' experiences and preferences
- Economic evaluations that were not cost-effectiveness or cost-utility analyses

Critical Appraisal of Individual Studies

The included randomized controlled trials and non-randomized studies were critically appraised using the Downs and Black checklist,[20] economic studies were assessed using the Drummond checklist,[21] and guidelines were assessed with the AGREE II instrument.[22] 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 188 citations were identified in the literature search. Following screening of titles and abstracts, 141 citations were excluded and 47 potentially relevant reports from the electronic search were retrieved for full-text review. An additional 16 potentially relevant publications were retrieved from the grey literature search (nine of which came from examining systematic reviews, see Table 2). Of these 63 potentially relevant articles, 42 publications were excluded for various reasons, while 16 reports (10 studies, four economic evaluations, and two clinical practice guidelines) in 21 publications met the inclusion criteria and were included in this report. Appendix 1 describes the PRISMA flowchart of the study selection.

Of note, four systematic reviews initially met the inclusion criteria[23-26] but will not be reviewed in favour of their included trials. The number of included trials within each systematic review ranged from 14 trials to 55 trials (total 138 trials). Upon closer examination nine trials of the 138 trials appeared to compare the combination product buprenorphine/naloxone to methadone. These nine trials were retrieved and scrutinized further (Table 2). A total of six trials met the selection criteria and were reviewed as part of the included trials; the other three trials were excluded because they did not include buprenorphine/naloxone as an intervention.

Table 2: Systematic Reviews

Timki, 2015[24] (55 trials)		**Perry, 2015**[23] (14 trials)		**Mattick, 2014**[25] (31 trials)		**Gowing, 2011**[26] (38 trials)	
Trials included in the systematic reviews and potentially relevant							
Saxon, 2013[27]	Include	Brown, 2013[28]	Not relevant (intervention)	Kakko, 2007[29]	Not relevant (intervention)	Lott, 2006[30]	Not relevant (intervention)
Woody, 2014[31]	Include: Secondary analyses of Saxon[27]			Kamien, 2008[32]	Include		
Potter, 2013[33]				Magura, 2009[34]	Include		
Otiashvili, 2013[35]	Include						

Additional references of potential interest are provided in Appendix 6. The results of previous CADTH reports on opioid dependence and related topics are listed in Appendix 7.

Summary of Study Characteristics

1. Clinical Studies

Five randomized controlled trials (RCTs)[27,32,34-36] and five non-randomized studies[37-41] met the inclusion criteria. Secondary publications were available for two randomized controlled trials: Otiashvili et al., 2013,[35] (one additional publication)[42] and Saxon et al., 2013,[27] (four additional publications).[31,33,43,44] All were secondary analyses that contained findings on additional outcomes; one publication also included long-term follow-up data (mean of 60 months).[44] Detailed tables on the study characteristics are available in Appendix 2, Tables A1 and A2.

The RCTs were open-labeled trials except for one trial that used a double-blind, double dummy study design.[32] One trial was conducted in Georgia[35] and the other four trials were conducted in the US. The number of recruited patients in the included trials ranged from 54 patients to 1,269 patients. The diagnosis of opioid use disorder was confirmed based on the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria in three RCTs.[27,32,36] One trial was conducted in incarcerated men with sentences of 10 days to 90 days and with a dependence to heroin and other non-prescribed opioids.[34] Patients in the other trials had addictions to heroin or prescription opioids with a duration of drug use of 6 years[35,36] and nine to 12 years.[32] In Magura et al.[34] and in Saxon et al.[27] (and its secondary analyses), the mean duration of the addiction was not reported. All five RCTs' goal was to evaluate maintenance treatment and two trials offered medication tapering over 8 weeks[43] or 12 weeks at the end of the trials.[35]The incarcerated men in Magura et al. received treatment for 23 days and 32 days with buprenorphine/naloxone and methadone respectively, while in jail.[34] Duration of treatment post-release was not stated although outcomes were assessed at 3 months. In the other trials, the patients were treated for 3 months to 6 months, and one trial[27] had long-term data with a follow-up duration of 2 years to 8 years post-randomization (mean of approximately 60 months).[44] One trial reported using methadone tablets.[36] Three trials reported mean daily doses of 8.5 mg, 14.9 mg, and 22.1 mg of buprenorphine (as part of the buprenorphine/naloxone mix), and 20.9 mg,39 mg and 93.2 mg of methadone.[27,35,36] The other two trials had daily doses of up to 16 mg and 32 mg of buprenorphine (buprenorphine/naloxone mix) and 70 mg to 90 mg of methadone; mean daily doses were not reported in these two trials.[32,34] The outcomes measured in the trials included: treatment retention (measured as the number of weeks patients remained in treatment or measured as number of patients remaining in treatment), opioid or heroin use (measured from urine samples or from self-reports), and harms. One trial used instruments (Timeline Followback, Addiction Severity Index, and Risk Assessment Battery) to measure drug use and behaviours related to needle-sharing and sexual activities.[35] Magura et al. also measured the frequency of re-arrest and re-incarceration.[34]

The non-randomized studies were observational and originated from Finland, the United Kingdom, Italy, and the US (2 studies). Four studies enrolled opioid dependent patients undergoing opioid maintenance treatment.[37,39-41] Diagnosis of opioid use disorder was confirmed with DSM criteria in one study.[37] One of these four studies enrolled men only.[41] One retrospective cohort study was conducted in mothers and their newborn babies.[38] The non-randomized studies selected data obtained over 6 months to a year in study periods ranging from one year to two years. The number of patients enrolled in these non-randomized studies ranged from 62 patients to 3,812 patients. The buprenorphine mean daily doses (as part of the buprenorphine/naloxone mix) ranged from 9.75 mg to 14.8 mg. Four studies reported methadone mean daily doses of 64.6 mg to 79.3 mg; one study did not report the methadone dose.[41] The outcomes measured included treatment retention, opioid use (measured from urine

samples or from self-reports), improvements in social life and education level, and presence of neonatal abstinence syndrome.

2. Economic Evaluations

Four economic evaluations were identified from the literature search[45-48] All four economic evaluations were cost-effectiveness analyses comparing buprenorphine/naloxone to methadone.[45-48] One economic evaluation also included a cost-utility analysis.[45] Countries of origin were Portugal, the United Kingdom, Greece, and Australia. Time horizons of 6 months in two evaluations[46,48] and of one year in the other two evaluations[45,47] were chosen. None of the evaluations reported a discount rate. Key assumptions and other characteristics are outlined in Appendix 2, Table A3.

Gouveia et al. used data reported in the literature.[45] A "social" perspective was chosen, although the perspective was really that of the public payer since indirect costs were not included. The measures of clinical effectiveness used were heroin-free days (based on negative urine test; data from the literature) and quality adjusted life years (QALYs). The cost data included medication cost (including cost of compounding the methadone), physician visits, psychotherapy, nursing labour costs, social worker visits, toxicology drug tests, and administrative/ general costs. Resource unit costs (in euros) were obtained from the Portuguese legislation.[45] The costs of crime were included in a sensitivity analysis with data obtained from an economic analysis dated 2011.[49]

Maas et al. used data obtained from patients recruited from one rural and two urban community drug service clinics in the UK (n=361).[46] Effectiveness was defined as the ability to retain patients in the programme for 6 months; and facilitate cessation of illicit opiate use. All analyses were performed using intention to treat. Costs, which were estimated from the perspective of the drug treatment clinic, included the cost of medications, dispensing and supervision fees, and clinic costs such as urine tests. All costs were estimated in UK sterling at 2010-2011 financial year.[46]

In Geitona et al., the data used were retrospectively retrieved from the local health authority databases.[47] The perspective was not explicitly stated but is that of the public payer as the expenses included personnel, drugs/ consumables, medical consultations/ diagnostic investigations, maintenance of equipment and buildings, and overheads. Prices (in euros) were those of the Greek National Health System in 2008. The clinical effectiveness was assessed using the completion of treatment (voluntary discharge of participants as a results of achieving abstinence from illicit opioids and completing a stabilization period of 2 years) and the number of deaths that were related to the use or overdose of illicit opioid drugs.[47]

In Doran et al., a treatment provider perspective was adopted with a reference year of 1998 to 1999.[48] Resources use was identified at both the patient and facility level, which included staff time, diagnostics, medications, supplies, equipment, and ancillary services. The summation of patient and facility resource use provided an estimate of total cost of each patient's treatment episode. The primary measure of clinical effectiveness was the change in number of heroin-free days between the month prior to treatment and the 6th month.[48]

3. Guidelines

Two clinical practice guidelines met the selection criteria (Appendix 2, Table A4).[50,51] The two guidelines selected for review were developed in 2011, one by the Centre for Addiction and Mental Health (CAMH) in Canada[50] and the other by the World Federation of Societies of

Biological Psychiatry (WFSBP).[51] They provided recommendations for the treatment of opioid use disorder; one guideline was specific to buprenorphine/naloxone[50] and the other was more general and included all medications used in the treatment and management of opioid use disorder.[51] Searches of electronic databases were performed from 1980 to 2009 in the Canadian guideline and up to January 2010 in the other guideline.

Grading of recommendations and levels of evidence

The guidelines developed their recommendations by a consensus process from expert committee based on the systematically reviewed evidence. The strength of their recommendations was graded and was directly linked to the quality level of the supporting evidence. Two systems for rating the quality level of evidence and recommendation strength were used in the included guidelines. Evidence from well designed and conducted systematic review or RCT was considered high quality level and the recommendation based on high quality evidence was graded as grade A or grade1. The detailed rating system on the quality level of the evidence and the strength grade of the recommendation used in each guideline are presented in Appendix 4.

Summary of Critical Appraisal

The strengths and limitations of the included reports are summarized in Appendix 3.

1. Clinical studies

The objectives and selection criteria were stated in all clinical studies. Patient characteristics, interventions, and outcomes were well described in eight of the clinical studies. Two non-randomized studies did not clearly describe the patients.[37,41] The interventions and the outcomes were not well described in one non-randomized study.[41] The RCTs had computer generated randomizations and all were open-label with the exception of one RCT that used a double-blind, double dummy study design.[32] Intention to treat analyses were performed in the RCTs by Otiashvili et al and in Saxon et al.[27,35] Saxon et al. provided justification on its choice of sample size.[27] One study would have results that would be generalizable to patients with opioid use disorder because it sampled 34 treatment facilities.[39] Three studies had findings which were generalizable to specific populations such as men,[41] incarcerated men,[34] or newborns.[38]

2. Economic Evaluations

In the economic evaluation reports, the research questions were well defined and the analysis methods were clearly stated. The key parameters on which the analyses were based were justified, except in Maas et al. which did not appropriately describe the dosages used.[46] The time horizons were clearly specified in all reports: All economic evaluations used a time horizon of at least 6 months which should be sufficient to determine whether or not a patient benefited from treatment. However, one evaluation included premature death, yet the time horizon of the analysis was limited to one year.[45] Sensitivity analyses were not performed in Mass et al.[46] In Gouveia et al., the range or distribution of values were not clearly described for conducting their sensitivity analyses.[45] One limitation of the Australian report was that the investigators based their analyses on retrospective data (cost and efficacy data) collected more than 10 years ago.[48] Discount rates were not applied in any of the evaluations most likely due to the fact that the time horizons were 6 months and one year. The generalizability of the study results to Canada is uncertain due to the fact that none of the evaluations used North American data.

3. Guidelines

The included guidelines were developed by professional association or expert committee based on a systematic review process which was well described in one guideline.[50] The objectives, clinical questions and the population for whom guidance was intended were well described. Guideline development groups were representative of their relevant professional groups and recommendations were peer reviewed in one guideline.[50] Conflict of interest was declared. The recommendations were clearly presented and explicitly linked to supporting evidence. One limitation was the lack of clarity regarding patient involvement in guideline development. The WFSBP guideline did not clearly provide the future update plan.[51]

Summary of Findings

The overall findings are summarized below and detailed findings from the individual studies are provided in Appendix 5.

What is the clinical effectiveness of buprenorphine/naloxone compared with methadone for the treatment of patients with opioid dependence?

Treatment retention

Treatment retention was an outcome of interest in four RCTs and one non-randomized study.[27,32,35,36,39] Treatment retention was measured as number of weeks the patients remained in treatment or as number of patients who remained in treatment (Appendix 2, Table A2). As shown in Table 3, more than 80% of patients completed 12 weeks of treatment in one study (87.5% of patients with buprenorphine/naloxone compared with 82.5 % of patients with methadone, statistical significance not reported).[35] At 17 weeks, the result for methadone was numerically superior to buprenorphine/naloxone (28.9% of patients remaining in treatment with methadone vs. 24.1% with buprenorphine/naloxone, P value not reported.) At 6 months one study found no statistically significant difference between buprenorphine/naloxone and methadone[36] whereas two studies reported a statistically significant difference with more methadone patients remaining in treatment (48% with methadone vs. 30% with buprenorphine/naloxone, $P = 0.001$; and 74% with methadone vs. 46% with buprenorphine/naloxone, $P < 0.01$).[27,39] Patients who stopped treatment did so for a variety of reasons including being lost to follow-up and non-compliance with medication. The reasons for treatment discontinuation for each RCT are outlined in Appendix 5, Table A9.

When the number of weeks on treatment was considered, both methadone and buprenorphine/naloxone patients remained in treatment for a mean of 12 weeks in one study.[32] Two other studies showed statistically significant differences of 17 weeks to 18 weeks for buprenorphine/naloxone compared with approximately 24 weeks to 26 weeks for the methadone group ($P < 0.0001$ and $P < 0.001$).[27,39]

Table 3: Treatment Retention				
Study	**Timing of Outcomes**	**buprenorphine/naloxone**	**Methadone**	**P value**
% Patients Completing Studies				
	Time of measurement			
Otiashvili[35]	at 12 weeks	87.5	82.5	NR
Kamien[32]	at 17 weeks*	24.1	28.9	NR
Saxon[27]	at 6 months	46.1	74.1	<0.01
Neumann[36]	at 6 months	50.0	46.4	NS
Proctor[39]	at 6 months	30.3	48.3	0.001
		OR = 2.48 (95%CI: 1.57 to 3.92)		
# Weeks on Treatment, mean (SD or SE)				
	Duration of Study			
Kamien[32]	17 weeks*	12.5 (SE 0.2)	12.3 (SE 0.2)	NR
Saxon[27]	24 weeks, FU 32 weeks	18.5 (SD 12.7)	25.8 (SD 10.0)	<0.0001
Proctor[39]	6 months or to discharge	17.05	24.27	<0.001

CI = confidence interval; FU = follow -up; NR = not reported; NS = not significant; OR = odds ratio; SD = standard deviation; SE = standard error
*results are for the group receiving higher doses of the medications

A secondary analysis of the Saxon et al. trial[27] evaluated the dose-retention relationship of the two medications.[43] Doses of methadone greater than 60 mg showed 80% or greater retention, and doses of 120 mg or greater showed 91% retention. Buprenorphine/naloxone showed a linear relationship, with increasing dose having better retention. At doses of 30 mg to 32 mg, a treatment retention of approximately 60% was obtained.[43]

The Saxon et al. trial subsequently published a report on their long-term data.[44] At the 60-month interview, 46% of buprenorphine/naloxone patients and 37% of methadone patients were not in any treatment for opioid dependence. Also at 60 months, 48% of methadone patients were still in treatment with methadone compared with 12% of buprenorphine/naloxone patients being treated with buprenorphine/naloxone.[44] These findings are difficult to interpret because the reasons for stopping treatment were not described. Patients may no longer be in treatment because they were able to successfully stop the medication; the medication was stopped because of illicit opioid use while on treatment; or other reasons.

Use of Opioids or Heroin

Nine of the 10 studies assessed the use of opioids during treatment and this was measured by analysing urine samples or from patients self-reports (Table 4). Four studies found that patients on buprenorphine/naloxone were better at maintaining abstinence from opioids as measured in urine samples, and of these four studies, two reported a statistically significant difference.[35,41] Buprenorphine/naloxone was better numerically in two studies but statistical significance was not reported.[37,39] Conversely, methadone showed a statistically significant difference long-term, with 43% of buprenorphine/naloxone patients who had positive urine samples compared with 31% of methadone patients, $P<0.01$.[27,44] Two studies found no statistically significant difference;[32,43] however, one study was based a small sample size of 26 patients.[36]

Table 4: Use of Opioids or Heroin				
Study	**Time of measurement**	**buprenorphine/naloxone**	**Methadone**	**P value**
% Patients with Positive Urine Samples				
Neumann[36]	at 6 months	38.5	15.4	NS
Curcio[41]	over one year	47	70	<0.001
Saxon[27,44]	up to 60 months	42.8	31.7	<0.01
% Positive Urine Samples				
Otiashvili[35]	at 12 weeks	0.2	1.5	0.03
Proctor[39]	at 6 months	11.1	17.4	NR
Heikman[37]	over 6 months	33.3	51.4	NR
% Patients with 12 Consecutive Opioid-free Urine Samples				
Kamien[32]	at week 16*	17	16	NS
% Patients self-reporting opioid use				
Neumann[36]	at 6 months	38.3	0	0.039
Self-reported Days of Opioid Use in Last 30 Days, mean (SD or SE)				
Magura[34]	3-month post-release	13.7 (SD 14.3)	14.4 (SD 13.4)	NS
Kamien[32]	at week 16*	3.1 (SE 1.7)	4.3 (SE 1.6)	NR
Self-reported Days of Heroin Use in Past 90 days, mean (SD)				
McKeganey[40]	at 6 months	38.64 (31.05)	37.40 (38.66)	NR
	at 14 months	8.5 (12.52)	24.15 (33.27)	NR

NR = not reported; NS = not significant; SD = standard deviation; SE = standard error
*results are for the group receiving higher doses of the medications

When patients self-reported opioid use, one study reported no statistically significant differences between the two groups (approximately 14 days of opioid use in the last month).[34] Two studies had similar results (approximately 3 days to 4 days of opioid use in the last month in one study, and approximately 37 days to 38 days of heroin use in the last 3 months in the other study).[32,40] One study found a statistically significant difference; however this was based on the results for 26 patients, with 5 of 13 buprenorphine/naloxone patients reporting opioid use compared with no patients of the 13 methadone patients.[36] Longer-term, patients reported less days of heroin use with buprenorphine/naloxone (8.5 days in the last 3 months) compared with methadone (24 days in the last 3 months).[40]

Harms

Harms of buprenorphine/naloxone and methadone were reported in five studies (Table 5).[27,32,34-36] There were no statistically significant differences in the number of patients experiencing harms, including death; however one study reported more adverse events with buprenorphine/naloxone compared with methadone (108 events vs. 80 events, $P = 0.003$).[35] Examples of adverse events reported included insomnia, constipation, and depression.[35] Serious adverse events were reported in two studies and included persistent headache, non-cardiac chest pain, bradycardia, spontaneous abortion, suicidal ideation or threat, change in mental status, cholecystitis, gastric ulcer, benzodiazepine overdose, and hospitalization for abscess due to heroin injection, high blood pressure, lung mass with shoulder infection, intoxication or vomiting.[27,32] In one trial, one overdose with methadone was reported.[27] Withdrawals due to adverse events were reported in one study, with one patient withdrawing due to headaches, and another due to the presence of tic (reported as "nodding all the time",

page 8).[34] This same study reported that six patients in the buprenorphine/naloxone groups had to withdraw from treatment due to suspected diversion, compared with one methadone patient.[34]

Table 5: Harms

Study	buprenorphine/naloxone	Methadone	P value
Death, n/N (%)			
Saxon[27,44]	23/630 (3.6)	26/450 (5.8)	NS
Adverse events, n (%)			
Neumann[36]	8 patients (61.5)	9 patients (69.2)	NS
Otiashvili[35]	108 events	80 events	0.003
Serious adverse events, n (%)			
Kamien[32]	1 event	4 events	NR
Saxon[27]	38 patients (5.2), 50 events	45 patients (8.7), 59 events	NS
Withdrawals due to adverse events			
Magura[34]	1 patient (1.7)	1 patient (1.8)	NS
Withdrawals due to suspected diversion, n (%)			
Magura[34]	6 patients (10)	1 patient (1.8)	NR

Two studies reported reductions in HIV risk behaviours (for example less needle sharing) and in sexual risk behaviours, with no statistically significant difference between groups.[27,31,35]

Other Outcomes

In Magura et al., there was no difference in the number of patients arrested or re-incarcerated after release from jail. No deaths were reported between study intake and the post-release three month follow-up.[34]

Curcio et al. reported a statistically significant improvement in social life status (patients reported as being married or co-habiting) and in educational level (patients with a high school diploma) with buprenorphine/naloxone compared with methadone (P<0.001).[41]

One study considered both neonatal and maternal outcomes in women giving birth and treated for opioid dependence.[38] Wiegand et al. reported no statistically significant differences in maternal outcomes (e.g., mode of delivery, weight gain, prenatal care visits) and no statistically significant differences in babies with respect to head circumference, birth weight, length, NICU admission, being born prematurely, and Apgar scores at one and five minutes. However, more babies from mothers who took methadone were treated for neonatal abstinence syndrome (25.1% with buprenorphine/naloxone vs. 51.6% with methadone, Odds Ratio 2.55, 95% Confidence Interval 1.31 to 4.98, *P* = 0.01) and more babies had severe withdrawal symptoms (*P* = 0.02). Finally, length of hospitalization was longer in babies whose mother took methadone (5.6 days with buprenorphine/naloxone vs. 9.8 days with methadone, *P* = 0.02).[38]

What is the cost-effectiveness of buprenorphine/ naloxone compared with methadone for the treatment of patients with opioid dependence?

Treatment with buprenorphine/naloxone was more costly and more effective in the 2015 Portuguese economic evaluation.[45] The total costs for one year were 2,079.3 euros and 1,965.0

euros for buprenorphine/naloxone and methadone, respectively. The buprenorphine/naloxone group reported 284 heroin-free days whereas the methadone group reported 247 heroin-free days. The incremental cost per heroin-free days was 3.06 euros. Total QALYs were estimated to be 0.5901 and 0.5707 with buprenorphine/naloxone and methadone, respectively, for an incremental cost per QALY gained of 5,914.1 euros. When premature death attributable to treatment was no longer considered in a sensitivity analysis (in the base case analysis, a mortality rate of 0.02 per 1,000 patients with buprenorphine/naloxone and of 2.75 per 1,000 patients with methadone was assumed), the incremental cost-utility ratio increased to 16,604. In another sensitivity analysis, buprenorphine/naloxone became dominant (lower cost, higher QALY) when the costs of crime were considered.[45]

The 2013 UK cost-effectiveness analysis reported greater effectiveness with methadone compared to buprenorphine/naloxone, as buprenorphine/naloxone was 19.4% less effective at retaining patients at 6 months.[46] Yet, 7% more patients stopped using illicit opiates with buprenorphine/naloxone. The differential cost was £63, with buprenorphine/naloxone having higher costs. Considering treatment retention, buprenorphine/naloxone was dominated by methadone. An incremental cost-effectiveness ratio (ICER) of £903 was reported for patients who stopped illicit opiate use.[46]

In the 2012 Greek cost-effectiveness analysis, the estimated patient total costs for one year were 2,876 euros for treatment with buprenorphine/naloxone and 5,626 euros for treatment with methadone.[47] In terms of the clinical effectiveness, buprenorphine/naloxone increased the percentage of treatment completion by approximately 1.5-fold. The percentage of deaths in the buprenorphine/naloxone group was 2.5-fold less than that reported with methadone. As a result, the cost-effectiveness analysis demonstrated that buprenorphine/naloxone therapy was dominating methadone. The ICER for buprenorphine/naloxone versus methadone was -795.03 with respect to treatment completion, and was -1,410.7 with respect to percentage of avoided deaths. Variations in the different cost parameters, measured in sensitivity analyses, did not reverse the findings of the evaluation and in fact buprenorphine/naloxone became dominant for some scenarios.[47]

In the 2005 Australian economic evaluation, the mean treatment costs over a 6-month period were AUD$1,593 for buprenorphine/naloxone, and AUD$1,415 for methadone.[48] The changes in the number of heroin-free days between the month prior to treatment (baseline) and the sixth month were 7.34 days for buprenorphine/naloxone and 6.84 days for methadone. Therefore, the ICER for the comparison between buprenorphine/naloxone and methadone was AUD$357 (confidence interval: -1,520 to 2,367), suggesting that buprenorphine/naloxone was more expensive but more effective than methadone. Variations in the different cost parameters, measured in sensitivity analyses, did not reverse the findings of the evaluation.[48]

Table 6 summarizes the findings of the economic evaluations.

Table 6: Summary of Economic Evaluations				
Study, cost measures	**Effectiveness**	**Costs**	**ICER/ ICUR**	**Sensitivity analyses**
Gouveia[45] 2011, euros	-SUB better for heroin-free days -SUB higher QALYs	SUB higher	-ICER: 3.06 -ICUR: 5,914	1: excluding data on mortality, ICUR 16,604 2: including cost of crimes, SUB dominant
Maas[46] 2010-2011 UK sterling	-MET better for treatment retention -SUB better for stopping illicit drug use	SUB higher	-MET dominant for treatment retention -ICER: 903 per patient for stopping illicit drug use	NA
Geitona[47] 2008 euros	-SUB better for treatment completion and for mortality	MET higher	-SEB dominant for both outcomes	-does not change the results
Doran[48] 1998-1999 AUD	-SUB better for heroin-free days	SUB higher	-ICER: AUD357	-does not change the results

AUD = Australian dollars; ICER = incremental cost effectiveness ratio; ICUR = incremental cost utility ratio; MET = methadone; NA = not applicable; UK = United Kingdom; SUB = Suboxone

What are the evidence-based guidelines associated with the use of buprenorphine/ naloxone for the treatment of patients with opioid dependence?

The CAMH guideline recommends that clinicians consider prescribing buprenorphine/naloxone or methadone for patients diagnosed with opioid dependence.[50] Care can be given in a primary care setting or in a specialized addiction treatment setting. The choice of buprenorphine/naloxone or methadone should be guided by the individual clinical circumstances and patient preference. Maintenance treatment with buprenorphine/naloxone should be initiated at a maintenance dose titrated as rapidly as possible to achieve stabilization while avoiding over-sedation or precipitated withdrawal. Once maintenance is achieved, non-daily dosing of buprenorphine/naloxone is as effective as daily dosing. All of these recommendations received the highest rating. Recommendations are given with respect to when buprenorphine/naloxone is preferred over methadone, for example in case of presence of prolonged QT interval, history of adverse events with methadone, significant respiratory illness, history of opioid use disorder is less than one year, and being elderly, adolescent or young adult.[50]

The WFSBP guideline has only one recommendation with respect to buprenorphine/naloxone. It stated that buprenorphine/naloxone is a standard treatment for the treatment of opioid use disorder (recommendation not graded).[51]

Limitations

Searching for studies which compared buprenorphine/naloxone to methadone was challenging given that some authors used the terms buprenorphine and buprenorphine/naloxone

interchangeably. Studies that did not specify Suboxone or buprenorphine/naloxone in the abstracts during article selection were excluded. Hence, studies comparing buprenorphine/naloxone to methadone may have been missed.

Patients received treatment for 6 months or less which may not be long enough to fully measure the effectiveness of the interventions.

The studies were carried out in adult patients (approximate mean age of 30 years to 40 years). The results may not be applicable to youths, young adults, and older patients.

The use of self-reports to measure abstinence from opioid or heroin use may lead to under-reporting if the patient is worried about being asked to leave the treatment program because of non-compliance. Analyzing urine samples may be a more objective measure of effectiveness when urine testing is conducted under observation. Five of the seven studies reported conducting supervised urine testing (Appendix 2, Table A2).

The product monograph for Suboxone recommends a maintenance dose of 12 mg to 16 mg of buprenorphine once daily whereas the product monograph for methadone recommends a maintenance dose of 80 mg to 120 mg administered daily.[10,13-15] In several studies, patients were under-dosed: patients received doses of buprenorphine of less than 12 mg[35,39] and methadone doses of less than 80 mg.[34-40] Furthermore, it has recently been reported that the effectiveness of buprenorphine is proportional to its dose and that doses of up to 32 mg daily may be required to improve retention into treatment.[43,52] Only two studies used high doses (>24 mg) of buprenorphine.[27,34]

Recent guidelines (within the last two years) were not identified. The two sets of guidelines that met the selection criteria were dated 2011, and recommendations were made based on evidence published before 2010.

All economic evaluations used a public payer perspective. Given the negative societal impact of heroin and other opioid use, this may not accurately reflect the true cost-effectiveness of buprenorphine/naloxone and methadone.

None of the studies or economic evaluations was conducted in Canada and applicability of the findings to the Canadian setting is unclear.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

When Suboxone (buprenorphine/naloxone) was first marketed in Canada, the direct cost of the medication was greater than that of methadone.[53] The relative cost-effectiveness of Suboxone to methadone was unclear. Recently, a new formulation of methadone became available at a higher cost (methadone powder which required compounding was replaced by ready-made solutions), and Suboxone became available as a generic; the price differential between the two medications decreased. Buprenorphine/naloxone is an interesting treatment choice for several reasons. With buprenorphine/naloxone, the risk of overdose is lower due to buprenorphine's partial agonist properties. Furthermore, buprenorphine/naloxone has the advantage of having a long half-life and hence a long duration of action which facilitates every second day administration if needed. Buprenorphine/naloxone does not require an exemption from the Federal Minister of Health to be prescribed. Buprenorphine/naloxone is available as a sublingual tablet and thus easier to dispense and administer. The inclusion of naloxone in the formulation

theoretically also reduces the chances of injection. Given the foregoing, an assessment of the comparative effectiveness and cost-effectiveness was required to assist decision-makers and prescribers in selecting between the two treatments.

A total of 10 studies met the selection criteria, five RCTs and five non-randomized studies. The most common outcomes of interest were treatment retention, use of opioids while on treatment, and harms. In the short-term (3 months), more than 80% of patients were retained into treatment with either buprenorphine/naloxone or methadone. At 6 months, statistically significantly more methadone patients were retained in treatment compared with buprenorphine/naloxone patients in two studies whereas the results of one study showed no statistically significant difference between the two medications. Patients who stopped treatment did so for a variety of reasons including loss to follow-up and non-compliance with medication. Similarly, the number of weeks retained into treatment was statistically significantly higher with methadone. When interpreting the results of the studies, the doses of the medications must be considered as treatment retention has been shown to be greater at higher doses. Several of the studies identified under-dosed the patients, and hence, the true effectiveness of buprenorphine/naloxone and methadone may actually be greater than what is reported in the studies.

Abstinence from opioid use was quantified using patient self-reports and the more objective measure of urine testing. Buprenorphine/naloxone was better than methadone at maintaining abstinence from opioids when measured by urine testing.

Buprenorphine/naloxone was reported to statistically significantly improve social life status and educational level compared with methadone in one study.

There was no statistically significant difference in the number of patients experiencing harms; however one study reported a higher frequency of adverse events with buprenorphine/naloxone.

Reductions in HIV risk behaviours (for example less needle sharing) and in sexual risk behaviours were reported with both buprenorphine/naloxone and methadone in two studies, with no statistically significant differences between the groups.

One study conducted in incarcerated men whose treatment was initiated in jail and continued after release reported no difference in the number of patients arrested or re-incarcerated after release from jail.

Babies born to mothers who took methadone were more likely to be treated for neonatal abstinence syndrome, had severe withdrawal symptoms, and longer length of hospitalization compared with babies born to mothers who took buprenorphine/naloxone.

Four economic evaluations were identified. Buprenorphine/naloxone treatment dominated methadone treatment in one cost-effectiveness analysis, with better treatment completion and less premature deaths, at lower costs. In another cost-effectiveness analysis, methadone dominated buprenorphine/naloxone when considering the outcome of treatment retention. In three cost-effectiveness analyses, buprenorphine/naloxone was more effective at reducing opioid use but at higher costs than methadone; the incremental cost effectiveness ratios were small. When the cost of crime was included in one of these cost-effectiveness analyses, buprenorphine/naloxone became dominant. This economic evaluation also reported higher quality-adjusted life years with buprenorphine/naloxone. The applicability of these results to the

Canadian setting is unclear as none of the economic evaluations were conducted using Canadian data.

One Canadian clinical practice guideline recommended that the choice of buprenorphine/naloxone or methadone be decided based on the individual clinical circumstances and patient preference.

Overall, buprenorphine/naloxone appears to be a safe, effective, and cost-effective choice for treating opioid dependence.

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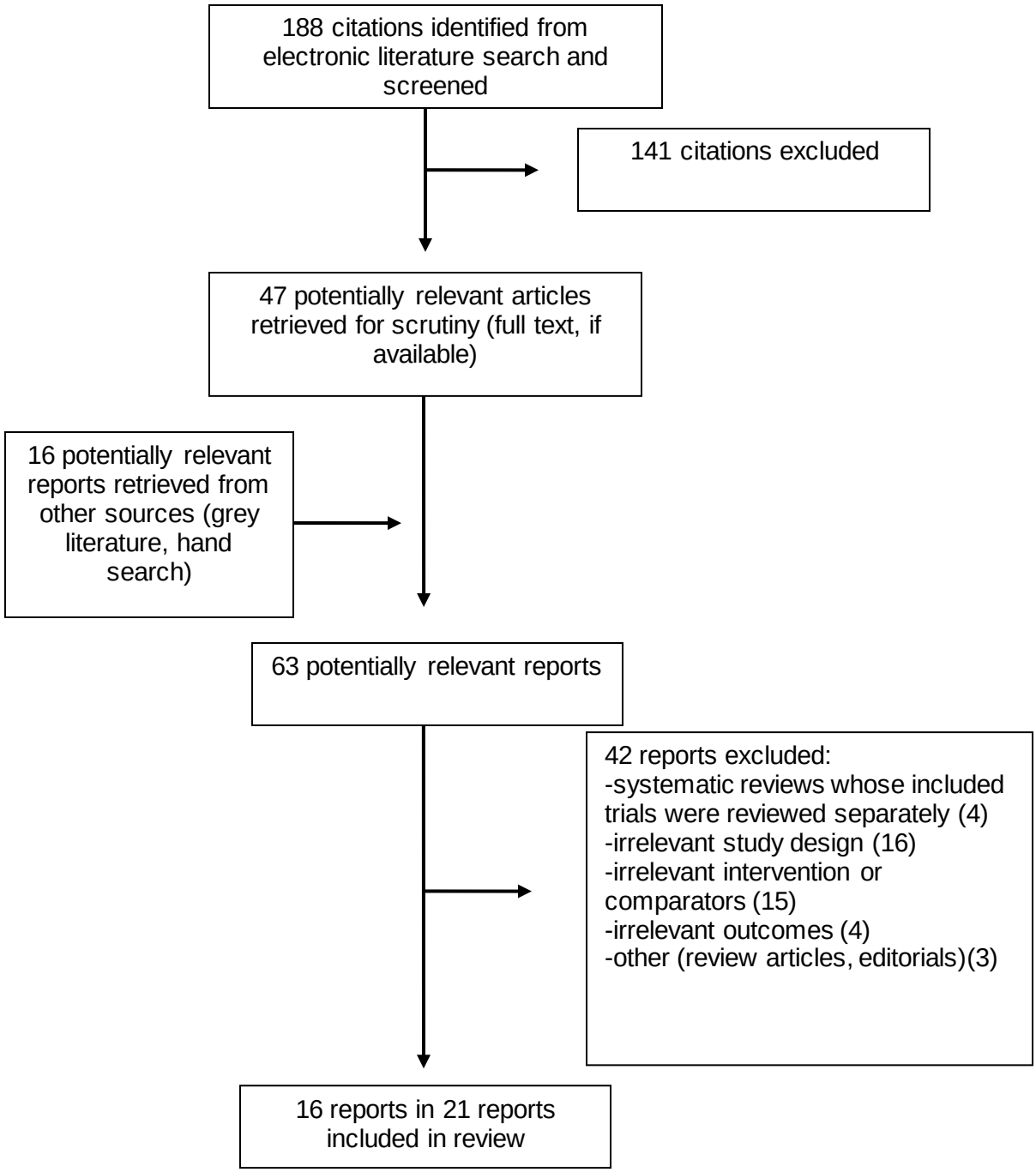
APPENDIX 1: Selection of Included Studies



APPENDIX 2: Characteristics of Included Publications

Table A1: Characteristics of Included Clinical Studies

First Author, Publication Year, Country	Study Design, Length of Follow-up	Patient Characteristics, Study Sample Size	Intervention(s)	Comparator(s)	Main Clinical Outcomes
RCTs					
Neumann, 2013[36] US	Open-label RCT Treatment duration: 6 months of maintenance treatment	Patients with chronic pain and coexistent opioid addiction to prescription opioids (not specified), duration of drug use: ~6 years N = 54	SUB (buprenorphine 4 to16 mg and naloxone 1 to 4 mg), average daily dose: 14.93/3.73 mg n=26	MET tablets 10 to 60 mg/day, average daily dose: 29.09 mg n=28	Treatment retention, opioid use, adverse events
Otiashvili, 2013[35] Georgia Secondary analysis: · Piralishvili, 2015[42]	Open-label RCT Treatment duration: 12 weeks followed by a dose taper and follow-up at week 20 week. ITT analysis	Patients with addiction to heroin, Subutex, other opioids, stimulants, benzodiazepines and marijuana; duration of drug use: ~6 years N = 80	SUB, mean dose 8.5 mg n = 40	MET, mean dose 39 mg n = 40	Treatment retention, TLFB[a], ASI[b], RAB[c], adverse events
Saxon, 2013[27] US Three secondary analyses: · Potter, 2013[33] · Hser, 2014[43]	Open-label RCT Treatment duration: 24 weeks then medication tapered over eight weeks or	Patients with opioid dependence to injection drugs (heroin, cocaine, non-heroin opioids and amphetamines), and AST/ALT no	SUB, mean maximum daily dose 22.1 mg (median 24 mg) n = 740 (340 evaluable)	MET, mean maximum daily dose 93.2 mg (median 90 mg) n = 529 (391 evaluable)	Treatment retention, treatment completion, SAEs In Woody, 2014:[31] RBS[d] In Hser, 2015:[44]

[a] Timeline Follow back (TLFB) is a method used to obtain quantitative estimates of marijuana, cigarette, and other drug use. It can be administered by an interviewer, self-administered, or administered by computer. The clients retrospectively estimate their drug, marijuana or cigarette use 7 days to 2 years prior to the interview date.[54]

[b] Addiction Severity Index (ASI), a semi-structured instrument which is used in face-to-face interviews. It asks information on medical, employment/support, drug and alcohol use, legal, family/social, and psychiatric.[55]

[c] Risk Assessment Battery (RAB) is a self-administered assessment which determines the likelihood of contracting HIV (through needle sharing practices and sexual activity associated with HIV transmission).[56]

[d] Risk Behaviour Survey (RBS): questionnaire administered by interviewer measuring injection and sexual HIV risk behaviours over the past 30 days.[31]

Table A1: Characteristics of Included Clinical Studies

First Author, Publication Year, Country	Study Design, Length of Follow-up	Patient Characteristics, Study Sample Size	Intervention(s)	Comparator(s)	Main Clinical Outcomes
· Woody, 2014[31] Long-term follow-up: · Hser, 2015[44]	less, or patient referred for ongoing clinical treatment. Follow-up to 32 weeks. ITT analysis in primary study Follow up 2 to 8 years (mean of 4.5 years) post randomization in Hser, 2015[44]	greater than 5 times, or ALP no greater than 3 times the ULN N = 1269			Death, positive opioid urine test at follow-up interview (n = 795)
Magura, 2009[34] US	Open-label RCT Duration of treatment in jail: 31.8 days with MET and 23.2 days with SUB (described as maintenance treatment). Treatment duration post-release NR but interview conducted 3 month post-release	Incarcerated men with opioid dependence to heroin and other non-prescribed opioids; sentence of 10 to 90 days N = 133	SUB, initial dose of 4 mg to 8 mg, then step up to 32 mg n = 77	MET oral solution, initial dose of 30 mg/ step up to 70 mg/ day n = 56	Treatment completion while in jail, reporting to assigned treatment modality after release, opioid use after release, re-arrest / re-incarceration, adverse events
Kamien, 2008[32] US	Double-blind, double dummy RCT Treatment duration: 17 weeks of maintenance treatment	Patients dependent to heroin or prescription opioids; duration of drug: 9-12 years N = 268	low dose SUB: 8 mg BUP+ 2 mg NAL, n = 82 high dose SUB: 16 mg BUP+ 4 mg NAL, n = 58	low dose MET oral solution: 45 mg, n = 52 high dose MET oral solution: 90 mg, n = 76	Heroin abstinence treatment retention, SAEs

Table A1: Characteristics of Included Clinical Studies

First Author, Publication Year, Country	Study Design, Length of Follow-up	Patient Characteristics, Study Sample Size	Intervention(s)	Comparator(s)	Main Clinical Outcomes
Non-RCTs					
Heikman, 2016[37] Finland	Retrospective study, collecting urine sample between October 2013 and April 2014	Opioid-dependent patients undergoing opioid maintenance treatment N=82 (200 urine samples)	SUB, mean daily dose 13.1 mg n=23	MET, mean daily dose 69.3 mg n=59	Positive urine samples for opioids and other drugs
Wiegand, 2015[38] US	Retrospective cohort analysis using an electronic database.	Newborns whose mother was treated with SUB or MET during pregnancy. Patients delivered between 01 January 2011 to 30 November 2013 N=62	SUB, mean daily dose 14.1 (SD 6.5) n=31	MET, mean daily dose 77.1 (SD 36.4) n=31	NAS, NAS peak score, duration of treatment for NAS (NAS assessed using the 13-item Modified Finnegan opioid weaning score)
Proctor, 2014[39] US	Naturalistic comparison of MET and SUB. Data abstracted from electronic medical records for 6 months or until discharge.	Patients admitted to 34 maintenance treatment facilities in the US from 01 July 2012 to 01 July 2013 N=3,233	SUB, 9.75 mg daily (SD 4.04) n=102 (Subutex also a comparator)	MET, 64.64 mg daily (SD 25.58) n=2,738	Positive urine samples for opioids, treatment retention, length of stay in treatment
McKeganey, 2013[40] UK	Naturalistic comparison of MET and SUB. Patients received MET or SUB for maintenance for 6 months prior to entering the study; treatment	Patients with opiate dependence ≤ 12 months, and had received MET or SUB for 6 months N=109	SUB for 14 months, mean dosage at study entry: 12.98 mg/day n=53	MET oral solution for 14 months, mean dosage at study entry: 76.29 mg/day n=56	Days of heroin use in past 90 days at study entry and 8-month follow up, % of patients abstinent from heroin use

Table A1: Characteristics of Included Clinical Studies					
First Author, Publication Year, Country	**Study Design, Length of Follow-up**	**Patient Characteristics, Study Sample Size**	**Intervention(s)**	**Comparator(s)**	**Main Clinical Outcomes**
	continued and patients were followed for another 8 months				
Curcio, 2011[41] Italy	Longitudinal study, one year period.	Opioid-dependent men treated as outpatients at the Italian Public Services for Addiction. Mean duration of addiction 8.4 years (SD 6.2) N=3,812	SUB, mean daily dose ranged from 10.2 mg to 14.8 mg (depending on length of treatment) n=632	MET, dose NR n=2,882	Negative urine samples for opioids, improvements in social life status and educational level.

ALP= alkaline phosphatase; ALT= alanine amino transferase; ASI = Addiction Severity Index; AST= aspartate amino transferase; DAST= Drug Abuse Screening Test; DSM-IV-TR = the Diagnostic and Statistical Manual of Mental Disorders; MET= methadone; NAS = Neonatal Abstinence Syndrome RAB = Risk Assessment Battery; RBS = Risk Behaviour Survey; SAEs = serious adverse events; SD = standard deviation; SF-36 = Short-Form Health Survey; SUB = Suboxone; TCU/SRF = Texas Christian University Self-Rating Form; TLFB = Timeline Followback Method; UK = the United Kingdom; ULN = upper limit of normal; US = the United States of America

Table A2: Descriptions Used in the Included Trials	
Study	**Supervised Administration of Medications/ Counselling**
Curcio[41]	Supervision NR; counselling NR
Kamien[32]	Supervised administration - Medication dispensed daily with no take home privileges; counselling provided
Heikman[37]	Supervision NR; counselling NR
Magura[34]	Supervised administration while in jail; counselling NR
McKeganey[40]	Supervision NR; counselling NR
Neumann[36]	Supervision NR; patients request to enrol in a chemical dependency program
Otiashvili[35]	Supervised administration, 7 days; counselling provided
Proctor[39]	Supervision NR - Medication dispensed daily and patients could earn take home privileges; counselling NR
Saxon[27]	Supervised daily administration except Sunday and Holidays or when take home privileges were permitted by local regulations; counselling NR
Study	**Definition of Treatment Retention**
Kamien[32]	Retention time measured by the percentage of patients active in the study over time calculated from the day of first dose to last dose received. Also reports the number of patients who completed treatment.
Neumann[36]	Number of patients completing treatment
Otiashvili[35]	Number of patients completing treatment
Proctor[39]	Patients with a length of stay > 179 days were classified as treatment success
Saxon[27,43]	Calculated as days in treatment since randomization Treatment completion is defined as continuing in the assigned medication group for 24 weeks without being withdrawn
Study	**Collection and Supervision of Urine Testing**
Curcio[41]	NR
Heikman[37]	Patients provided one to six urine samples during the course of the study; urine samples collected under supervision
Kamien[32]	Urine sample obtained under observation
Otiashvili[35,42]	Weekly random test using an on-site kit, conducted under video surveillance using a closed circuit television
Neumann[36]	Urine sample provided at each visit; urine samples collected under monitored circumstances at least once a month
Proctor[39]	Minimum of eight urine testing per year at random intervals; urine samples collected under camera observation
Saxon[27,33]	Weekly urine drug testing; supervision NR

NR=not reported

Table A3: Characteristics of Included Economic Evaluations

First author, Publication Year, Country	Type of Analysis, Perspective	Intervention, Comparator	Study Population	Time Horizon	Main Assumptions
Gouveia, 2015[45] Portugal	cost-effectiveness and cost-utility analyses social perspective	SUB, MET	Opioid dependence	1 year	Assumed an average daily dose of 8 mg for SUB and 75 mg for MET; several assumptions made on effectiveness inputs obtained from the literature
Maas, 2013[46] UK	cost-effectiveness analysis perspective of the drug treatment clinic	SUB, MET	Patients at three drug service clinics requesting OST	6 months	Patients with <5 opioid-free urine samples were deemed be continuing to use opioids
Geitona, 2012[47] Greece	cost-effectiveness analysis based on retrospective data from 2 local health authority database	SUB, MET, BUP	Opioid users participating in OST programs in Greece	1 year	The cost for SUB patients was as same as BUP patients, since they received the same clinical management
Doran, 2005[48] Australia	cost-effectiveness analysis	SUB, MET, BUP	Heroin dependence	6 months	Each patient was provided with 8 mg of BUP on days 1 and 2 and then proceed to a dose of 16 mg BUP + 4 mg NAL for the remainder of the study period

BUP = buprenorphine; MET= methadone; NAL=naloxone; OST = opioid substitution treatment; SUB = Suboxone

Table A4: Characteristics of Included Guidelines

Objectives			Methodology		
Intended users/ Target population	**Intervention and Practice Considered**	**Major Outcomes Considered**	**Evidence collection, Selection and Synthesis**	**Recommendations development and Evaluation***	**Guideline Validation**
Handford, 2011[50] Centre for Addiction and Mental Health (CAMH), Canada					
Users: Physicians, pharmacists, policy-makers Targets: adults and adolescents with opioid dependence in Ontario	Initiation, maintenance and discontinuation of SUB maintenance treatment	Effectiveness, safety and cost-effectiveness	Searches of electronic databases, 1980 to 2009. 341 articles reviewed in full-text.	Systematic review with evidence table used to analyze the evidence. Expert consensus used to formulate recommendations. Grading of recommendations adapted from the Canadian Task Force on Preventative Health.	Internal and external peer review
Soyka, 2011[51] The World Federation of Societies of Biological Psychiatry (WFSBP), Germany, Switzerland, USA, Netherland, Austria					
Users: clinicians Targets: adults with opioid use disorders	Pharmacological agents used in the treatment and management of opioid use disorders	Efficacy, safety, tolerability, and feasibility	Searches of electronic databases, up to January 2010.	Guidelines developed by the authors and arrived at consensus with the WFSBP Task Force on Substance Use and Related Disorders (22 international experts).	Not stated

CAMH = Centre for Addiction and Mental Health; SUB = suboxone; WFSBP = World Federation of Societies of Biological Psychiatry
*refer to Appendix 4 for Grades of Recommendations

APPENDIX 3: Critical Appraisal of Included Publications

Table A5: Strengths and Limitations of Randomized Controlled Trials and Non-randomized Studies using Downs and Black[20]

Strengths	Limitations
RCTs	
Neumann, 2013[36]	
• Objectives and inclusion/ exclusion criteria were stated. • Patient characteristics, interventions, and outcomes were described. • Randomized but open label study. Computerized random numbers were used for the randomization procedure. Allocation sequence was concealed from the researcher enrolling patients. • Number discontinued or lost to follow up were reported	• Sample size calculation was not described • Intent-to-treat analysis was not performed • Generalizability limited; uncertain as to whether study patients were representative of all patients. • Funding source was not declared.
Otiashvili, 2013[35] - Piralishvili, 2015[42]	
• Objectives and inclusion/ exclusion criteria were stated. • Patient characteristics, interventions, and outcomes were described. • Randomized, but open-label study. Computerized random numbers were used for the randomization procedure. • ITT analysis • Number discontinued or lost to follow up were reported	• Sample size calculations were not described • Generalizability limited; uncertain as to whether study patients were representative of all patients. • Industry provided Suboxone.
Saxon, 2013[27] - Potter, 2013[33] - Hser, 2014[43] - Woody, 2014[31] - Hser, 2015[44]	
• Objectives and inclusion/ exclusion criteria were stated. • Patient characteristics, interventions, and outcomes were described. • Randomized but, open label study. For the randomization procedure, software was used. • Choice of sample size was justified. • ITT analysis performed in primary analysis	• Generalizability limited; uncertain as to whether study patients were representative of all patients (Patient chosen from 9 federal treatment programs in the US. Initial randomization scheme of 1:1 SUB: MET was changed to 2:1 18 months after trial initiation due to high drop-out rate with SUB.)[43] • Industry involved in the study design and provided Suboxone.
Magura, 2009[34]	
• Objectives and inclusion/ exclusion criteria were stated. • Patient characteristics, interventions, and outcomes were described. • Randomized, but open-label study. Random numbers generator used. Treatment assignments in sealed envelopes. • Number discontinued or lost to follow up were reported	• No sample size calculations. • Intent-to-treat analysis was not performed. • Generalizable to incarcerated men.
Kamien, 2008[32]	
• Objectives and inclusion/ exclusion criteria were stated. • Patient characteristics, interventions, and	• Not clear if intent-to-treat analysis was performed • Industry provided Suboxone • Generalizability limited; uncertain as to whether study

Table A5: Strengths and Limitations of Randomized Controlled Trials and Non-randomized Studies using Downs and Black[20]

Strengths	Limitations
outcomes were described. • Double-blind randomized study. Computerized random numbers were used for the randomization procedure. Allocation sequence was concealed. • Sample size calculations described • Number discontinued or lost to follow up were reported	patients were representative of all patients.
Non-RCTs	
Heikman, 2016[37]	
• Objectives and selection criteria were stated. • Interventions and outcomes were described. • Not manufacturer-sponsored	• Patient characteristics not described (affects the generalizability of results). • No statistical testing done. P-values not provided.
Wiegand, 2015[38]	
• Objectives and selection criteria were stated. • Patient characteristics, interventions, and outcomes were described. • Statistical testing done. Adjustments made for covariates. • Not manufacturer-sponsored	• No attempt made at blinding assessors to opioid treatment • Statistically significant difference between women treated with MET for opioid dependence and analgesia compared to SUB
Proctor, 2014[39]	
• Objectives and selection criteria were stated. • Patient characteristics, interventions, and outcomes were described. • Statistical testing done. • Entire population was sampled; results may be generalizable	• No attempt made at blinding assessors to opioid treatment • Compliance / adherence to treatment unknown
McKeganey, 2013[40]	
• Objectives and selection criteria were stated. • Patient characteristics, interventions, and outcomes were described. • P-values provided	• Generalizability limited; uncertain as to whether study patients were representative of all patients. • Industry-sponsored study
Curcio, 2011[41]	
• Objectives and selection criteria were stated. • Statistical testing done.	• Patient characteristics, interventions, and outcomes not well described. • Industry-sponsored study • Limited generalizability (i.e., Italian men)

Table A6: Strengths and Limitations of Economic Studies using Drummond[21]	
Strengths	**Limitations**
Gouveia, 2015[45]	
• Clearly described purpose of the study • Clearly described objectives of study and specified perspective (social) • Provided detailed information on clinical inputs such as effectiveness • Resource use and costs were described	• Time horizon of 1 year • Discount rate was not applied • Sensitivity analyses conducted, but the range or distribution of values were not clearly described • Sponsored by manufacturer • The study was conducted using euro cost information which may limit the generalizability to Canada
Maas, 2013[46]	
• Clearly described purpose of the study • Clearly described objectives of the study and specified perspective (drug treatment clinics) • Provided detailed information on clinical inputs such as effectiveness • Resource use and costs were described • Not manufacturer-sponsored	• Comparators not appropriately described • Time horizon of 6 months • Discount rates was not applied • The study was conducted using cost information from the UK which may limit the generalizability to Canada • No sensitivity analyses performed
Geitona, 2012[47]	
• Clearly described purpose of the study • Clearly described research question and specified viewpoint (societal) • Appropriately defined comparators • Provided detailed information on clinical inputs such as effectiveness • Resource use and costs were described • In sensitivity analyses, the range or distribution of values were clearly described	• Time horizon of 1 year • Discount rate was not applied • The study was conducted using euro cost information from Greece which may limit the generalizability to Canada • Sponsored by manufacturer
Doran, 2005[48]	
• Clearly described research question • Provided detailed information on clinical inputs such as effectiveness • Resource use and costs were described and justified • Perspective was clearly described (a treatment provider perspective) • Appropriately defined comparators • Modeled clinical success • Not sponsored by manufacturer	• Analysis was based on data from a single clinical trial which was conducted almost 10 years ago • Discount rates was not described • Time horizon of 6 months • The study was conducted using AUD cost information which may impact its generalizability to Canada

Table A7: Strengths and Limitations of Guidelines using AGREE II[22]	
Strengths	**Limitations**
CAMH guideline, Handford, 2011[50]	
• Clearly defined objectives, scope and target populations • Guideline was an developed based on systematic review • Recommendation explicitly linked to supporting evidence • The recommendation was clearly presented • Guideline update plan was described • Conflict of interest declared	• Patients views and preferences not clearly described
WFSBP guidelines, Soyka, 2011[51]	
• Clearly defined objectives, scope and target populations • Guideline was an developed based on existing guidelines, systematic review • Recommendation explicitly linked to supporting evidence • The recommendation was clearly presented • Conflict of interest declared	• Patients views and preferences not clearly described • Guideline update plan was not described • Number of studies reviewed not stated • Peer-review of guidelines not stated

CAMH = Centre for Addiction and Mental Health; WFSBP = World Federation of Societies of Biological Psychiatry

APPENDIX 4: Grading of Recommendations and Levels of Evidence Used in Included Guidelines

Table A8: Grading of Recommendations and Levels of Evidence

Guidelines, First Author, Publication Year	Quality level of evidence and strength of recommendations
CAMH guideline Handford, 2011[50]	**Levels of evidence** I Evidence from randomized, controlled trial(s) II-1 Evidence from controlled trial(s) without randomization II-2 Evidence from cohort or case-control analytic studies, preferably from more than one centre or research group II-3 Evidence from comparisons between times or places with or without the intervention; dramatic results in uncontrolled experiments could be included here III Opinions of respected authorities, based on clinical experience; descriptive studies or reports of expert committees ***Grades of recommendation*** A There is good evidence to recommend the action. B There is fair evidence to recommend the action. C The existing evidence is conflicting and does not allow making a recommendation for or against the use of the action; however, other factors may influence decision making. D There is fair evidence to recommend against the action. E There is good evidence to recommend against the action. I There is insufficient evidence (in quantity and/or quality) to make a recommendation; however, other factors may influence decision-making.
WFSBP guidelines, Soyka, 2011[51]	**Category of evidence (main criteria)** A: Full evidence based on two or more RCT showing superiority to placebo or on one or more RCT showing superiority to or equivalent to active comparator; etc. B. Limited positive evidence from one or more RCTs C. Evidence from uncontrolled trial or case report/expert opinion -C1: from uncontrolled trial -C2: from case report -C3: from expert opinion D: inconsistent results E: negative evidence F: lack of evidence Recommendation grade(RG) 1: Category A evidence and good risk-benefit ratio 2: Category A evidence and moderate risk-benefit ratio 3: Category B evidence 4: Category C evidence 5: Category D evidence

CAMH = Centre for Addiction and Mental Health; WFSBP = World Federation of Societies of Biological Psychiatry

APPENDIX 5: Main Study Findings and Author's Conclusions

Table A9: Summary of Findings of Included Studies

<table>
<tr><th>Main Study Findings</th><th>Author's Conclusions</th></tr>
<tr><td colspan="2">RCTs</td></tr>
<tr><td colspan="2">Neumann, 2013[36]</td></tr>
<tr><td>Comparison of SUB versus MET in patients with chronic pain + opioid addiction (13 patients in each group available for analysis at the end of the 6-month follow-up)
<table>
<tr><th>Outcome</th><th>SUB (n=26)</th><th>MET (n=28)</th><th>P value</th></tr>
<tr><td>Completers, n</td><td>13</td><td>13</td><td></td></tr>
<tr><td>Positive urine test for opioids, n (%)</td><td>5 (38.5)</td><td>2 (15.4)</td><td>NS</td></tr>
<tr><td>Self-reported opioid use, n (%)</td><td>5 (38.5)</td><td>0</td><td>0.039</td></tr>
<tr><td>Treatment retention, n/N (%)</td><td>13/26 (50.0)</td><td>13/28 (46.4)</td><td>NS</td></tr>
<tr><td>Self-reported side effects, n patients (%)</td><td>8 (61.5)</td><td>9 (69.2)</td><td>NS</td></tr>
</table>
· 26 (48.1%) of patients completed the study. Others were lost of follow-up (n=13), did not comply with treatment (n=10), were discharged (n=3), had a psychiatric problem (n=1), or were placed on parole (n=1).
· Five patients who completed the study switched to the other medication (not specified in which treatment group they were analysed).</td><td>"Treatment retention and analgesia did not differ between the two treatment conditions after 6 months of continuous treatment." P.6</td></tr>
<tr><td colspan="2">Otiashvili, 2013[35] - Piralishvili, 2015[42]</td></tr>
<tr><td>Comparison of SUB versus MET in adult patients with opioid dependence (at 12 weeks)
<table>
<tr><th>Outcome</th><th>SUB (n=40)</th><th>MET (n=40)</th><th>P value</th></tr>
<tr><td>Lost to follow-up, n</td><td>5</td><td>7</td><td></td></tr>
<tr><td>Completed 12-week treatment</td><td>35</td><td>33</td><td></td></tr>
<tr><td>Completed 20-week follow-up assessments, n</td><td>33</td><td>33</td><td></td></tr>
<tr><td>Included in primary analysis, n</td><td>40</td><td>40</td><td></td></tr>
<tr><td>Positive urine test for opioids, n/N (%)</td><td>1/431 (0.2)</td><td>6/406 (1.5)</td><td>0.03</td></tr>
<tr><td>Treatment retention, n (%)</td><td>35 (87.5)</td><td>33 (82.5)</td><td>NR</td></tr>
<tr><td>Adverse events, n events</td><td>108</td><td>80</td><td>0.003</td></tr>
</table>
· Patients discontinued Suboxone due to arrest (n=1), administrative discharge (n=3), and self-withdrawal (n=2). Patients discontinued methadone due to refusal to take medication (n=1), administrative discharge (n=2), self-withdrawal (n=2), loss to follow-up (n=1), and family conflict (n=1)
· Reduction in opioid craving and improvement in HIV risk injection behavior (e.g., less needle sharing), with no statistically significant difference between groups (Table 3, P.15)[35]
· No change in sexual risk behavior.[35]
· Most common adverse events: insomnia, constipation, depression</td><td>"Daily observed methadone or buprenorphine-naloxone are effective treatments for non-medical buprenorphine and other opioid use in Georgia." P. 1[35]</td></tr>
</table>

Table A9: Summary of Findings of Included Studies

Main Study Findings	Author's Conclusions

Saxon, 2013[27] - Potter, 2013[33] - Hser, 2014[36] - Woody, 2014[31] - Hser, 2015[44]

Comparison of SUB versus MET in adults with opioid dependence and normal liver function

Outcomes	SUB	MET	P value
Participant flow* from Saxon et al.[27]			
· Randomized, n	740	529	
· Evaluable, n	340	391	
· Evaluable, completed 24 week assessment	335	378	
· Evaluable, completed week 28 follow-up	283	339	
· Evaluable, completed week 32 follow-up	261	330	
Treatment retention, weeks (SD)[27]	18.5 (12.7)	25.8 (10.0)	<0.0001
Completion at 24 weeks, %[43]	46.1	74.1	<0.01
Serious adverse events, n patients (%)[27]	38 (5.2)	45 (8.7)	NS
Types of serious adverse events	persistent headaches, non-cardiac chest paint, spontaneous abortion, suicidal ideation, suicidal threat, cholecystitis, benzodiazepine overdose	benzodiazepine overdose, drug hospitalization for intoxication, hospitalization for vomiting, bradycardia, change in mental status, methadone overdose, gastric ulcer	
At 60-month follow-up interview[44]	**(n=464)**	**(n=331)**	
Opioid use (positive urine), %	42.8	31.7	<0.01
Not in any treatment, %	46.3	37.0	<0.01
In MET treatment, %	37.3	48.2	<0.01
in BUP treatment, %	12.3	10.0	NS
Death, n (%)	23/630 (3.6)	26/450 (5.8)	0.10

Initial randomization scheme of 1:1 (BUP:MET) was changed to 2:1 after 18 months because of higher drop-outs with Suboxone.[27] 25% of Suboxone participants dropped out within the first 30 days of treatment.[43]

*Patients were deemed not evaluable if they missed 14 consecutive days or more of medication, opted out, withdrew consent, received an administrative discharge, or had a change in their medical eligibility.[27]

From Hser, 2014:[43]

- Dose of MET > 60 mg = > 80% treatment retention
- Dose of MET ≥ 120 mg = 91% treatment completion
- Linear relationship between dose of BUP and treatment retention
- Dose of BUP 30 to 32 mg = 60% treatment completion

From Woody, 2014:[31]

- Reduction in in HIV risk behaviours and in sexual risk behaviours, with no statistically significant difference between groups

"MET participants were retained longer in treatment than BUP* participants." P. 71[27]
***** referred to SUB

Table A9: Summary of Findings of Included Studies

Main Study Findings	Author's Conclusions

Magura, 2009[34]

Comparison of SUB versus MET in incarcerated men with opioid dependence

Outcome	SUB	MET	P value
Randomized (during time in jail)	**n=77**	**n=56**	
Medicated, n	n=60	n=56	
Not medicated, n	n=17	n=0	
Completed treatment in jail, %	82	75	NS
Days in treatment	23.2	31.8	0.05
Withdrawn from treatment due to suspected diversion, n patients (%)	6 (10)	1 (1.8)	NR
WDAEs, n patient (%)	1 (1.7) headache	1 (1.8) tic	NS
Post-release	**n=60**	**n=56**	
Reported to assigned treatment modality after treatment in jail, %	48	14	<0.001
Re-incarceration, %	40	50	NS
At 3-month follow-up interview (self-report)	**n=43**	**n=38**	
Not interviewed, n	17	18	
Opioid use, last 30 days, mean (SD)	13.7 (14.3)	14.4 (13.4)	NS
Arrested after release, mean (SD)	0.69 (0.95)	0.71 (0.77)	NS

Reasons not medicated with Suboxone while in jail: decided against treatment (n=4), medical staff unavailable to induct (n=3), took methadone on day of induction (n=3), medical rule out (n=3), no show (n=2), decided to complete methadone detox (n=1), violated jail policy (n=1)

Reasons not interviewed at 3-month follow-up: Suboxone, not located (n=9), refused (n=5), never released from jail (n=1), in nursing home (n=1), out of state n=1). Methadone, not located (n=10), refused (n=1), never released from jail (n=2), out of state (n=1), in a therapeutic community (n=2), incarcerated elsewhere (n=2)

"…these study results offer a promising new treatment option for chronic opioid-dependent, incarcerated offenders…" P.9

Kamien, 2008[32]

Comparison of SUB versus MET in opioid-dependent patients (17-week trial)

Outcomes	SUB	MET	P value
Randomized, n			
Low dose	82	52	
High dose	58	76	
Completed trial, n (%)			
Low dose	16 (19.5)	18 (34.6)	
High dose	14 (24.1)	22 (28.9)	
Self-reported days of heroin use in the past 30 days, mean (SE)			0.05*
Low dose			
At baseline	26.9 (0.8)	26.7 (0.8)	
At week 16	5.8 (2.4)	9.0 (2.5)	
High dose			
At baseline	26.3 (1.1)	26.3 (0.9)	

"Addiction and retention did not differ among groups. Buprenorphine-naloxone is a viable alternative to methadone in clinical practice." P. 5

Table A9: Summary of Findings of Included Studies

Main Study Findings				Author's Conclusions
At week 16	3.1 (1.7)	4.3 (1.6)		
Patients with 12 consecutive opioid-free urine samples, %				
Low dose	10	12	NS	
High dose	17	16	NS	
Treatment retention, weeks (SE)			NR	
Low dose	12.1 (0.2)	13.2 (0.2)		
High dose	12.5 (0.2)	12.3 (0.2)		
SAEs, n event	1 hospitalization for abscess due to heroin injection, high blood pressure, lung mass with shoulder infection	4	NR	
*SUB group (low and high doses combined) reported less heroin use than the MET group (low and high doses combined, $P = 0.05$)				
Percentage of opioid-free urine samples over time among drug groups and among drug doses did not differ statistically significantly.				
No statistically significant difference between treatment groups in successful induction				
non-RCTs				
Heikman, 2016[37]				
Comparison of SUB versus MET in patients undergoing opioid maintenance treatment				"This study revealed a significant degree of polydrug abuse with MET and SUB patients." P.49
Outcomes	**SUB (n=23)**	**MET (n=59)**	**P value**	
Polydrug use				
urine sample provided, n	60	140	NR	"…opioid maintenance therapy did not completely suppress abuse of opioids…" P.50
positive urine samples, %	33.3	51.4		
· Most prevalent drug of abuse: benzodiazepines (29%) vs. 9% for opioids				
· Most prevalent abused opioids: buprenorphine				
· All morphine positive urine samples given by MET patients				
Wiegand, 2015[38]				
Comparison of SUB versus MET in newborns of women treated for opioid dependence				"…there was less frequent neonatal abstinence syndrome, lower peak neonatal abstinence syndrome scores, and a shorter overall hospitalization for the newborns of mothers treated with buprenorphine and naloxone." P.367
Outcomes	**SUB (n=31)**	**MET (n=31)**	**P value**	
Babies treated for NAS, %	25.1	51.6	0.01	
OR (95% CI)	2.55 (1.31 to 4.98)			
Peak NAS score (range 1 to 25), mean (SD) – *higher score means more severe withdrawal*	9.0 (4.4)	10.7 (3.7)	0.02	
Length of hospitalization, mean days (SD)	5.6 (5.0)	9.8 (7.4)	0.02	
NAS=Neonatal abstinence syndrome				
· No statistically significant differences in maternal outcomes (e.g., mode of delivery, weight gain, prenatal care visits)				
· No statistically significant differences in: head circumference, birth weight, length, NICU admission, being born prematurely, and Apgar scores at one and five minutes.				

Table A9: Summary of Findings of Included Studies

Main Study Findings	Author's Conclusions
Proctor, 2014[39]	
Comparison of SUB versus MET in opioid-dependent patients (at 6 months) **Outcomes** / **SUB* (n=102)** / **MET (n=2,738)** / **P value** Treatment retention, % — 30.3 — 48.3 — 0.001 OR (95% CI) — 2.48 (1.57 to 3.92) Length of stay in treatment, mean days (SE) — 119.35 (20.82) — 169.86 (5.02) — <0.001 Positive urine test for opioids, % — 11.1 — 17.4 — NR *excludes the findings from Subutex	"…comparable illicit drug use rates, and that methadone was associated with the highest rate of patient retention in treatment at 6 months." P.431
McKeganey, 2013[40]	
Comparison of SUB versus MET in heroin users **Outcomes** / **SUB (n=53)** / **MET (n=56)** / **P value** Days of heroin use in the past 90 days, mean (SD) 6-month time-point — 38.64 (31.05) — 37.40 (38.66) — NR 14-month time-point — 8.5 (12.52) — 24.15 (33.27)	"MET and SUB were highly and equally effective for preventing relapse to regular heroin use". P.97
Curcio, 2011[41]	
Comparison of SUB versus MET in men with opioid dependence (study is over one year) **Outcomes** / **SUB (n=632)** / **MET (n=2,883)** / **P value** Negative urine test for opioids, % — 53 — 30 — <0.001 Improvement in social life status (married or co-habiting), n (%) — 398 (63) — 1,124 (39) — <0.001 Improvement in educational level (high school diploma), % — 43 — 32 — <0.001	"The current study also confirms… the efficacy of buprenorphine/ naloxone for detoxification treatment in opiate-dependent patients." P.873
Economic Evaluations	
Gouveia, 2015[45]	
Analysis is based on a model developed by the York Health Economics Consortium. Model used data reported by Marino and Lazzaro 2011[57] and data retrieved from the literature. Assessment criteria for outcome assessment: heroin-free days and QALYs. CEA and CUA (ICER, ICUR, 2011 euros): -Effectiveness: 284 heroin-free days with SUB vs. 247 days with MET (difference of 37 days); total QALYs with SUB is 0.5901 and 0.5707 with MET (difference of 0.0193 QALYs) -Cost for one year: €2,079.3 with SUB, €1,965.0 with MET (difference of €114.3) -ICER (€/heroin-free days): €3.06 -ICUR (€/QALY): €5,914.1	"…B/N combination is cost-effective and has the potential to generate substantial health gains at low costs for the Portuguese health system." P.48

Table A9: Summary of Findings of Included Studies	
Main Study Findings	**Author's Conclusions**
Sensitivity analyses: -Excluding premature death: ICUR €16,604 -Inclusion of costs of crime: SUB dominant (lower cost, higher QALY)	
Maas, 2013[46]	
Data were retrieved from an RCT. Assessment criteria for outcome assessment: treatment retention and opiate abstinence. CEA (ICER, 2010-2011 UK sterling) - Effectiveness: % retained in program for 6 months or detoxed completely from illicit opiate drugs was 50% with SUB and 70% with MET (SUB 19.4% less effective at retaining patients; 7% more patients stop using illicit opiates with SUB) -Cost for 6 months: SUB has higher costs (difference is £63) -ICER: SUB is dominated by MET (treatment retention); ICER £903 per patient who stopped illicit opiate use.	"…MET program is slightly more cost-effective in terms or retaining patients in a drug treatment program, but that the SUB program is superior in terms of helping patients to stop illicit drug use." P.498
Geitona, 2012[47]	
Retrospective data used for CEA were retrieved from 2 health authority databases. Assessment criteria for outcome assessment: the completion of treatment and number of deaths. CEA (ICER, 2008 euros): - Effectiveness: % of treatment completion in SUB was 1.5-fold > than that in MET, % of deaths in SUB was 2.5-fold < than that in MET; - Cost for 1 year: €2,876 for SUB, €5,626 for MET. - ICER: €-795.03 for SUB vs. MET for "treatment completion"; €-1410.7 for "% of avoided deaths" Sensitivity analyses: The variation of different individual cost parameters did not reverse the findings of the CEA.	"Analysis of cost effectiveness demonstrated that buprenorphine-naloxone was the dominant therapy in terms of mortality avoidance and completion of treatment." (p. 77)
Doran, 2005[48]	
Data were retrieved from an RCT. Assessment criterion for outcome assessment: changes in the number of heroin-free days between baseline and study end. CEA (ICER, 1998-1999 AUD): - Effectiveness: change in number of heroin-free days between baseline and study end was 7.34 days in SUB, and 6.84 days in MET; - Cost for 6 months: AUD1,593 for SUB, AUD1,415 for MET. - ICER: AUD357 (confidence interval: -1,520 to 2,367) for SUB vs. MET for number of heroin-free days between baseline and study end. Sensitivity analyses: The variation of different individual cost parameters (dosing times, price of BUP and variation in the amount of staff time spent in contact with patients) did not reverse the findings of non-statistical significance of ICER in the CEA.	"Adopting a provider perspective suggests that the observed difference between the cost-effectiveness of MET and the other treatments was not statistically significant, indicating that high-dose BUP and the BUP/NAL combination can provide a viable alternative to MET in the treatment of heroin dependence." (p. 583)

Table A9: Summary of Findings of Included Studies		
Main Study Findings		**Author's Conclusions**
Guidelines		
Recommendations	**Level of evidence**	**Grade of recommendations**
CAMH guideline, Handford, 2011[50]		
Selecting buprenorphine/naloxone maintenance therapy 1. Once a patient is diagnosed with opioid dependence and is deemed appropriate for opioid agonist treatment, prescribers are encouraged to consider prescribing either buprenorphine/naloxone or methadone in order to increase retention in treatment and decrease opioid misuse.	I	A
Clinical assessment 2. Buprenorphine/naloxone maintenance treatment can be prescribed to patients in either a primary care setting or in a specialized addiction treatment setting.	I	A
3. Prior to initiating maintenance opioid agonist treatment the patient should meet the diagnostic criteria for opioid dependence.	III	A
4. The decision to initiate opioid agonist therapy with either buprenorphine/naloxone or methadone maintenance should be guided by the individual clinical circumstances and the patient's preferences.	III	A
Initiation, maintenance and discontinuation of buprenorphine/naloxone maintenance treatment 5. A physician should have a structured approach, such as the one suggested in the clinical considerations, to initiating buprenorphine/naloxone maintenance treatment in order to stabilize a patient at their maintenance dose as rapidly as possible while at the same time avoiding over-sedation or precipitated withdrawal.	III	A
6. Prior to initiation of buprenorphine/naloxone treatment, the patient must provide informed consent and there must be physician documentation that the patient has been informed of the physical dependence on the medication and possible long-term nature of the maintenance treatment.	III	A
7. Once a stable maintenance dose is achieved, physicians can consider nondaily dosing of buprenorphine/naloxone as effective as daily dosing of buprenorphine/naloxone with respect to retention in treatment and reduction in illicit drug use.	I	A
8. When monitoring a patient on buprenorphine/naloxone maintenance, the physician should adopt a patient–centred urine drug testing strategy that maximizes clinical utility while avoiding testing without indication.	III	A
9. In making decisions regarding the provision of take-home doses of buprenorphine/naloxone, providers should use a clinical risk stratification strategy (as described in the clinical considerations) that aims to support patient autonomy while at the same time respecting patient and public safety.	III	A
Overdose, mortality and other adverse effects 10. Policy makers should be aware that in countries where buprenorphine is equally available as methadone,	II-3	A

Table A9: Summary of Findings of Included Studies		
Main Study Findings		**Author's Conclusions**
buprenorphine has a lower attributable death rate than methadone.		
11. Limited public funding is currently the major barrier to accessibility of buprenorphine/naloxone maintenance treatment in Ontario. We recommend that policy makers remedy this barrier.	III	B
Clinicians should be aware that there is little in the medical literature to guide them in terms of which opioid maintenance agent to prescribe an individual opioid-dependent patient. In making this decision, the prescriber and patient should consider the following, which is based on clinical experience.		
12. Buprenorphine/naloxone may be preferred over methadone to treat opioid dependence in the following patient populations:		
a) When methadone is absolutely or relatively contraindicated, such as:		
i) Presence of, history of or increased risk of prolonged QT interval	I	A
ii) History of methadone allergy	III	A
b) History of significant side effects on methadone such as:		
i) Sexual side effects on methadone	II-2	B
ii) Severe sedation or constipation with methadone	III	C
c) Increased risk of toxicity from a full mu agonist:		
i) If suspect a lower tolerance to opioids	III	B
ii) If concurrent heavy or unstable use of sedating drugs/ medication	II-3	B
iii) If elderly	III	B
iv) If significant respiratory illness	III	B
d) Good prognostic factors:		
i) Briefer history (i.e., less than one year) of opioid misuse	III	C
ii) Social supports	III	C
iii) Adolescents and young adults	III	B
e) Past history of successful stabilization with buprenorphine/ naloxone	III	I
f) Patient choice and access. In particular patients residing in geographic areas where methadone is not available in a timely manner, or when challenging pharmacy access makes the possibility of alternate day dosing of buprenorphine/ naloxone desirable.	III	B
13. Methadone may be preferred over buprenorphine/ naloxone in the following patient populations:		
a) Pregnancy (specifically avoiding the naloxone component in the buprenorphine/naloxone combination product)	III	A
b) Clinical situations where opioid withdrawal during induction is particularly hazardous – i.e., cardiovascular instability	III	B
c) Prior inability to stabilize on buprenorphine/naloxone maintenance treatment	III	B
d) History of abusing buprenorphine/naloxone via injection	III	A
e) Patient side effects with or allergy to buprenorphine/ naloxone or to excipients including acesulfame	III	A

Table A9: Summary of Findings of Included Studies		
Main Study Findings		**Author's Conclusions**
f) Patients experiencing dry mouth of severity that would interfere with dissolution and absorption of sublingual buprenorphine/naloxone tablets (dry mouth may be due to side effects of concurrent medications, chemotherapy, or conditions causing dry mouth, e.g., Sjogren's syndrome)	III	A
g) Past history of successful stabilization with methadone	III	I
h) Patient choice and access, in particular patients with limited financial resources that make reliable long-term use of buprenorphine/naloxone uncertain	III	B
WFSBP guidelines, Soyka, 2011[51]		
On page 171: "Buprenorphine and Buprenorphine/ naloxone are standard treatment for the treatment of opioid dependence. Whether the combination of buprenorphine and naloxone has advantages over buprenorphine alone requires empirical validation. There are no indications that adding contingency management to buprenorphine maintenance treatment enhances its effectiveness."	A	Grade 1
On page 177: "Methadone and buprenorphine are effective and safe in the treatment of opioid-dependent pregnant women."	NR	NR

AUD = Australian dollar; CAMH = Centre for Addiction and Mental Health; CEA = cost-effectiveness analysis; CUA= cost-utility analysis; ICER = incremental cost-effectiveness ratio; MET = methadone; MPD = Memory for Persons Data; NR = not reported; NS = not significant; QALYs = quality adjusted life years; RCT= randomized controlled trial; SAEs=serious adverse events; SD = standard deviation; SE = standard error of the mean; SUB = Suboxone; TAP = Test for Attentional Performance; WDAEs = withdrawals due to adverse events; WFSBP = World Federation of Societies of Biological Psychiatry; WMS-III LNS = Wechsler Memory Scale -3rd version

APPENDIX 6: Additional References of Potential Interest

A. Clinical Practice Guidelines

a) Methods not described

Queensland Opioid Treatment Program: clinical guidelines 2012 [Internet]. Brisbane, Australia: Queensland Health; 2012. Available from: https://www.health.qld.gov.au/publications/clinical-practice/guidelines-procedures/medicines/drugs-of-dependence/qotp-clinical-guidelines.pdf

Queensland alcohol and drug withdrawal clinical practice guidelines [Internet]. Brisbane, Australia: Queensland Health; 2012. Available from: https://www.health.qld.gov.au/publications/clinical-practice/guidelines-procedures/medicines/drugs-of-dependence/detox-guidelines.pdf

b) Buprenorphine/naloxone not main focus of guidelines

The ASAM national practice guideline for the use of medications in the treatment of addiction involving opioid use [Internet]. Chevy Chase (MD): American Society of Addiction Medicine (ASAM); 2015. Available from: http://www.asam.org/quality-practice/guidelines-and-consensus-documents/npg/complete-guideline

Guidelines for the identification and management of substance use and substance use disorders in pregnancy [Internet]. Geneva: World Health Organization (WHO); 2014. Available from: http://apps.who.int/iris/bitstream/10665/107130/1/9789241548731_eng.pdf?ua=1

Lingford-Hughes A, Welch S, Peters L, Nutt DJ. BAP updated guidelines: evidence-based guidelines for the pharmacological management of substance abuse, harmful use, addiction and comorbidity: recommendations from BAP. J Psychopharmacol [Internet]. 2012 Jul;26(7):899-952. Available from: http://www.bap.org.uk/pdfs/BAPaddictionEBG_2012.pdf

Methadone maintenance treatment program standards and clinical guidelines [Internet]. 4th ed.Toronto: The College of Physicians and Surgeons of Ontario; 2011 Feb. Available from: http://www.cpso.on.ca/uploadedFiles/members/MMT-Guidelines.pdf

B. Systematic Reviews

a) No mention of buprenorphine/naloxone but includes buprenorphine

Thyarappa Praveen,K., Law F, O'Shea J, Melichar J. Clinical evidence: opioid dependence [Internet]. London: BMJ Evidence Centre; 2011 Mar. Available from: http://clinicalevidence.bmj.com/ceweb/conditions/meh/1015/1015-get.pdf

C. Qualitative Studies

Hill DR, Conroy S, Afzal A, Lang D, Steele S, Campbell D. A comparison of methadone and buprenorphine-naloxone as opioid substitution therapy: The patient perspective in NHS

Lanarkshire. J Subst Use. 2015;20(3):168-77.

Johnson B, Richert T. Diversion of methadone and buprenorphine by patients in opioid substitution treatment in Sweden: prevalence estimates and risk factors. Int J Drug Policy. 2015 Feb;26(2):183-90.

Larance B, Lintzeris N, Ali R, Dietze P, Mattick R, Jenkinson R, et al. The diversion and injection of a buprenorphine-naloxone soluble film formulation. Drug Alcohol Depend. 2014 Mar 1;136:21-7.

Johanson CE, Arfken CL, di Menza S, Schuster CR. Diversion and abuse of buprenorphine: findings from national surveys of treatment patients and physicians. Drug Alcohol Depend. 2012 Jan 1;120(1-3):190-5.

Larance B, Degenhardt L, O'Brien S, Lintzeris N, Winstock A, Mattick RP, et al. Prescribers' perceptions of the diversion and injection of medication by opioid substitution treatment patients. Drug Alcohol Rev. 2011 Nov;30(6):613-20.

Larance B, Degenhardt L, Lintzeris N, Bell J, Winstock A, Dietze P, et al. Post-marketing surveillance of buprenorphine-naloxone in Australia: diversion, injection and adherence with supervised dosing. Drug Alcohol Depend. 2011 Nov 1;118(2-3):265-73.

Tanner GR, Bordon N, Conroy S, Best D. Comparing methadone and Suboxone in applied treatment settings: The experiences of maintenance patients in Lanarkshire. J Subst Use. 2011;16(3):171-8.

APPENDIX 7: Previous CADTH Rapid Responses on Opioid Dependence and Related Topics

Product Type and Title	Research Questions	Key Messages
2016		
Summary with Critical Appraisal **Crushed Buprenorphine or Buprenorphine-Naloxone for Opioid Dependency: A Review of the Clinical Effectiveness and Guidelines**	What is the clinical effectiveness and safety of sublingual crushed buprenorphine for treating opioid dependency? What is the clinical effectiveness and safety of sublingual crushed buprenorphine-naloxone for treating opioid dependency? What are the evidence-based guidelines regarding the administration of crushed buprenorphine or crushed buprenorphine-naloxone for the treatment of opioid dependency?	A single crossover RCT with 16 patients showed that there were no statistically significant differences with respect to opioid withdrawal or opioid craving between treatments with the whole buprenorphine tablet or the crushed tablet. The number of patients experiencing adverse events was higher in the crushed tablet group compared to the whole tablet group however there were no serious adverse events reported in either group. There was no information identified regarding the effectiveness of the crushed tablet in resolving misuse and diversion issues. No relevant studies comparing sublingual administration of crushed buprenorphine-naloxone with uncrushed buprenorphine or uncrushed buprenorphine-naloxone tablets or buprenorphine-naloxone film for the treatment of opioid dependency were identified. No evidence based guidelines on the use of crushed buprenorphine or crushed buprenorphine-naloxone were identified.
Summary with Critical Appraisal **Rapid and Ultra-Rapid Detoxification in Adults with Opioid Addiction: A Review of Clinical and Cost-Effectiveness, Safety, and Guidelines**	What is the clinical effectiveness and safety of rapid and ultra-rapid opioid detoxification (ROD and UROD) in adults with opioid addiction? What is the cost-effectiveness of ROD and UROD in adults with opioid addiction? What are the evidence-based guidelines associated with the use of ROD and UROD in adults with opioid addiction?	There is some evidence suggesting earlier peaking of, and lower scores for, withdrawal symptoms and higher rates of the commencement and continuation of maintenance treatment in patients receiving UROD, compared to patients in control groups (e.g., conventional withdrawal treatment). However, no significant differences were identified between UROD and control groups in the commencement or duration of withdrawal treatment. Mixed results were identified between UROD and control groups in the completion of withdrawal treatment and the incidence of adverse events, depending on what pharmacologic agents were used. One guideline recommended against the use of UROD, due to high risk for adverse events. No evidence on ROD or on cost-effectiveness of ROD and UROD was identified.
2014		
Summary with Critical Appraisal **Suboxone Versus Methadone for the Detoxification of Patients Addicted to Prescription Opioids: A Review of Comparative Clinical Effectiveness, Safety, and Guidelines**	What is the comparative clinical effectiveness and safety of Suboxone versus methadone when used as a tool for detoxification in patients addicted to prescription opioids? What is the comparative clinical effectiveness of Suboxone versus methadone in achieving complete opioid abstinence in patients addicted to prescription opioids?	One RCT suggests that Suboxone and methadone were similar with regards to treatment retention and decreasing use of other opioids in patients with nonmalignant chronic pain and an addiction to a prescription opioid. One guideline suggests that a daily dose of Suboxone for 1 to 3 days should eliminate signs and symptoms of opioid withdrawal, suppress opioid cravings, and eliminate illicit opioid use in adults.

Product Type and Title	Research Questions	Key Messages
	What is the comparative clinical effectiveness of Suboxone versus methadone for the relief of withdrawal symptoms and cravings in patients addicted to prescription opioids for less than 12 months? What is the comparative clinical effectiveness of Suboxone versus methadone for the relief of withdrawal symptoms and cravings in patients addicted to prescription opioids who continue to frequently misuse central nervous system depressants? What are the guidelines associated with the length of detoxification time using Suboxone in patients addicted to prescription opioids?	
Summary of Abstracts **Buprenorphine/Naloxone (Suboxone) Film versus Buprenorphine/Naloxone Tablets for the Treatment of Opioid Addiction: Comparative Safety**	What is the comparative safety of buprenorphine/naloxone (Suboxone) film versus buprenorphine/naloxone tablets for the treatment of prescription opioid addiction in adult patients?	One randomized controlled trial was identified regarding the comparative safety of buprenorphine/naloxone film versus buprenorphine/naloxone tablets for the treatment of prescription opioid addiction in adult patients.
2013		
Summary with Critical Appraisal **Suboxone versus Methadone for the Treatment of Opioid Dependence: A Review of the Clinical and Cost-effectiveness***	What is the comparative clinical effectiveness of Suboxone compared with methadone for the treatment of patients with opioid dependence? What is the cost-effectiveness of Suboxone compared with methadone for the treatment of patients with opioid dependence?	Limited evidence suggests that Suboxone may have similar clinical effects as methadone on retention in treatment and heroin use among adult patients with opioid dependence, and may be more cost-effective than methadone. There was no evidence of the comparative effectiveness of Suboxone versus methadone in other subgroups. Cost-effectiveness of Suboxone in a Canadian population is uncertain.
2012		
Summary with Critical Appraisal **Opioid Management Practices for the Prevention of Drug Diversion and Misuse: A Review of the Clinical Evidence and Guidelines**	What is the clinical evidence regarding opioid management practices to reduce drug diversion and misuse? What are the evidence based guidelines for opioid management practices to reduce opioid diversion and misuse? What is the clinical evidence regarding opioid use or prescription patterns for prediction of substance abuse?	There is no one set of policies or practices that have been consistently associated with a reduction in opioid diversion and misuse. There is some evidence to suggest increased monitoring of patients and governmental prescription monitoring programs could have some impact on reducing opioid diversion and misuse. Evidence-based guidelines suggest frequently monitoring and assessing patients, using a diverse battery of techniques to prevent opioid diversion and misuse. There may be distinct patterns of opioid use associated with substance abuse and guideline recommended opioid prescription practices may reduce substance abuse.
Summary with Critical Appraisal **Treatment for Opioid Dependence: A Review of**	What are the evidence-based guidelines for the assessment and treatment of opioid dependent patients? What are the evidence-based guidelines	Evidence-based guidelines indicate that opioid dependent patients should be assessed with the DSM-IV-TR diagnostic criteria. Methadone maintenance treatment was recommended as a standard treatment for opioid dependence

Product Type and Title	Research Questions	Key Messages
Guidelines	for the detoxification or treatment of opioid dependent pregnant women?	including pregnant opioid-dependent women. Recommendations state that detoxification should be avoided during pregnancy and that buprenorphine/ naloxone combination therapy should not be used in pregnant women.
Reference List **Suboxone for Drug Detoxification: Clinical Effectiveness and Guidelines**	What is the comparative clinical effectiveness of Suboxone versus alternative treatment options for drug detoxification? What is the comparative clinical effectiveness of short-term Suboxone versus long-term Suboxone treatment for drug detoxification? What are the evidence-based guidelines for Suboxone use for opioid detoxification?	One systematic review, four randomized controlled trials, four non-randomized studies, and six-evidence-based guidelines were identified regarding Suboxone use for drug detoxification.
2011		
Summary with Critical Appraisal **Suboxone for Short-term Detoxification: A Review of the Clinical Evidence**	What is the comparative clinical effectiveness of short-term Suboxone use versus alternative treatments for drug detoxification?	Limited evidence showed higher treatment success rate with Suboxone compared to clonidine in short term detoxification for patients with opioid dependence.
Summary of Abstracts **Treatment Programs for Prescription Drug Abuse: Clinical Effectiveness and Guidelines**	What is the clinical effectiveness of interventions for treatment of prescription drug abuse for adults in urban areas? What is the clinical effectiveness of interventions for treatment of prescription drug abuse for adults in rural areas? What is the clinical effectiveness of interventions for treatment of prescription drug abuse for youth in urban areas? What is the clinical effectiveness of interventions for treatment of prescription drug abuse for youth in rural areas? What are the evidence-based guidelines for the training of nurses providing prescription drug abuse interventions?	The clinical effectiveness of a variety of interventions for the treatment of prescription drug abuse was found. No evidence-based guidelines for the training of nurses providing prescription drug abuse interventions were identified.

*Previous report which was the basis for this update.