Canadian Agency for Drugs and Technologies in Health

RAPID RESPONSE REPORT:
SUMMARY WITH CRITICAL APPRAISAL

TITLE: Suboxone versus Methadone for the Treatment of Opioid Dependence: A Review of the Clinical and Cost-effectiveness

DATE: 14 November 2013

CONTEXT AND POLICY ISSUES

Addiction to opioids causes major medical, social, and economic problems to both the individual and society. Opioid dependence is defined as a strong desire to use the substance, difficulty in controlling its use, the presence of a physiological withdrawal state, tolerance of the use 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] In Canada, it is estimated that there were more than 80,000 regular illegal opioid users in 2003.[3] The number of illegal drug-related overdose deaths in Canada was 958 in 2002.[3] Opioid dependence is related to the abuse of not only illegal opioid drugs (e.g. heroin), but also some of the most commonly prescription drugs, such as codeine-containing Tylenol, hydromorphone, oxycodone, morphine and others.[4]

Treatment of opioid dependence includes three approaches: stabilization, detoxification and maintenance.[5] Stabilization is usually achieved by opioid substitution treatments to ensure that the drug use becomes independent of mental state (such as craving and mood) and independent of circumstances (such as finance and physical location). The next stage is detoxification that is to withdraw from opioids. The final step is maintenance to prevent relapse.[5] Detoxification refers to the process by which the effects of opioid drugs are eliminated in a safe and effective manner, such that withdrawal symptoms are minimized.[1] Appropriate use of the detoxification agents plays a crucial role in increasing the successful detoxification rate, while minimizing the side effects and withdrawal symptoms.[1] Methadone (μ-opioid receptor agonist) or buprenorphine (μ-opioid receptor agonist and κ-opioid receptor antagonist) are recommended first-line treatments in opioid detoxification.[1,6] Naloxone is an opioid antagonist without agonist properties. In opioid-dependent patients, naloxone precipitates withdrawal.

Suboxone (buprenorphine/naloxone) was approved by Health Canada in 2007 for substitution treatment in opioid drug dependence in adults.[7] It is a fixed combination of buprenorphine (a partial μ-opioid receptor agonist) with naloxone (an opioid antagonist) in a 4:1 ratio.[8] The addition of naloxone to buprenorphine is expected to decrease the intravenous abuse of

buprenorphine, because when taken sublingually, absorption of naloxone is minimal, however it can rapidly precipitate opioid withdrawal when injected.[9,10] Suboxone is recommended for the treatment of opioid dependence for patients in whom methadone is contraindicated (such as patients at high risk of, or with QT prolongation, or hypersensitivity to methadone).[11]

The purpose of this review is to provide evidence on the comparative clinical effectiveness and cost-effectiveness of use of Suboxone compared with methadone, for the treatment of patients with opioid dependence. Subgroups such as children and pregnant women may also have access to opioids thus, the clinical benefits and risks of Suboxone for these patients will be examined as well, when evidence is available.

RESEARCH QUESTIONS

1. What is the comparative clinical effectiveness of Suboxone compared with methadone for the treatment of patients with opioid dependence?

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

KEY FINDINGS

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.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including Ovid MEDLINE, Ovid Embase, PubMed, The Cochrane Library (2013, Issue 10), 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 methodological filters were applied to limit retrieval by publication type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2003 and October 15, 2013.

Selection Criteria and Methods

One reviewer screened citations to identify publications that met the inclusion criteria. Potentially relevant articles were retrieved based on the review of titles and abstracts. Full-text articles were considered for inclusion based on the selection criteria listed in Table 1. Rapid Response reports are organized so that the evidence for each research question is presented separately.

Table 1: Selection Criteria

Population	Patients of any age with opioid dependence
Intervention	Suboxone (buprenorphine / naloxone)
Comparator	Methadone or Methadose (a commercial methadone product)
Outcomes	Clinical efficacy (e.g. use of opioid including heroin and other drugs of abuse, retention in treatment, harms reduction, health-related quality of life, and safety), Cost-effectiveness
Study Designs	Health technology assessment (HTA), systematic review (SR) and meta-analysis (MA), randomized controlled trial (RCT), non-randomized study, and economic evaluation

Exclusion Criteria

Studies were excluded if they did not satisfy the selection criteria in Table 1, or were full text articles published prior to January 2003. Health technology assessments, meta-analyses, and systematic reviews were excluded if there was incomplete reporting of methods or if they were superseded by a more recent or more rigorous review. Studies that were deemed to have incomplete reporting of outcomes, such as not reporting numerical values for outcomes, were excluded. Economic evaluations were excluded if they were not cost-effectiveness or cost-utility analyses.

Critical Appraisal of Individual Studies

Critical appraisal of a study was conducted based on an assessment tool appropriate for the particular study design. The Downs and Black checklist[12] was used for RCTs and non-randomized studies. The economic evaluations were assessed using the 35-item Drummond's checklist.[13,14] A numeric score was not calculated for each study. Instead, the strengths and limitations of each study were summarized and described.

SUMMARY OF EVIDENCE

Quantity of Research Available

One hundred and twenty-one articles were identified from the literature search. Upon screening titles and abstracts, 28 potentially relevant articles were selected for full-text review. Of these, 19 did not satisfy the inclusion criteria and were excluded. The nine included reports of eight unique clinical studies and comprised four RCTs (a secondary analysis on data from one RCT was performed), two non-RCTs and two economic evaluations. No relevant health technology assessments, systematic reviews or meta-analyses were identified. The selection process is described in Appendix 1.

Summary of Study Characteristics

Characteristics of the included clinical trials and economic evaluations are summarized below and details are provided in Appendix 2.

Clinical Effectiveness

In the included RCTs and non-randomized trials, the baseline patient characteristics such as demographics, drug history, treatment history were similar between two treatment groups.

Randomized-controlled trials

Four relevant RCTs comparing Suboxone with methadone were identified.[15-18] Three RCTs[15,17,18] were published from the US, and one[16] was published in 2012 from Georgia. The number of recruited patients in these studies ranged between 54 to 1,269. Drugs being misused included heroin, cocaine, cannabis, amphetamines and other prescription opioids. The mean duration of drug use ranged from 20 days to 12 years. Treatment durations in these trials ranged between three to six months. All RCTs reported retention in treatment and use of opioids at study end (assessed by self-report or urine test). Safety data were reported in all but one RCT.[15] One American study[17] evaluated the effects of Suboxone or methadone on liver health, and indicated that results on drug use will be analyzed in a future paper. In addition, secondary analysis on data from this RCT was performed and the results were published in a different journal.[19] Two patients from the original RCT were excluded from the analysis due to pregnancy and change in treatment plan during the study.

Non-randomized-controlled trials

Two prospective cohort studies comparing Suboxone with methadone in adult patients were identified.[20,21] One[20] was published in 2013 from the UK, and another one[21] was published in 2007 from Finland. The number of patients enrolled in these non-RCTs ranged from 33 to 71. These studies reported on days of opioid use and change in cognitive performance (attention, working memory and verbal memory) after the treatment with Suboxone or methadone.

Cost-Effectiveness

A recent economic evaluation was conducted in Greece, to evaluate the cost-effectiveness of opioid substitution treatment (mainly methadone and buprenorphine) in this country.[22] The investigated study drugs were methadone and buprenorphine monotherapy, and Suboxone. The data used were retrospectively retrieved from the local health authority databases. The expenses included personnel, drugs/consumables, medical consultations/diagnostic investigations, maintenance of equipment and buildings, and overheads. No discount rates were applied. Prices (in Euros) were those of the Greek National Health System in 2008. The clinical effectiveness was assessed using the completion of treatment and the number of deaths that were related to the use and/or overdose of illicit opioid drugs.

An economic evaluation by Doran et al.[23] was performed in Australia to examine the cost-effectiveness of high-dose buprenorphine, Suboxone, low-dose buprenorphine, and methadone. A treatment provider perspective was adopted with a reference year of 1998 to 1999. 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. Three economic models were examined: comparison of methadone with low dose buprenorphine, comparison of methadone with high dose buprenorphine, and comparison of methadone with Suboxone. The third model is relevant to our review. 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.

Summary of Critical Appraisal

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

Randomized controlled trials

All four RCTs[15-18] clearly stated the objective and the selection criteria and described patient characteristics, interventions and outcomes. One RCT was a double-blind, double-dummy RCT and described the methods of blinding clearly.[18] Two stated that they had an open-label design.[15,17] For one RCT, it was unclear whether it was a blinded trial.[16] A sample size calculation was reported in one RCT.[18] In the largest RCT enrolling 1269 patients,[17] the authors indicated that the US Food and Drug Administration required a minimum of 300 evaluable participants on each medication, hence a power calculation was not performed. No power calculation was reported for the other two RCTs.[15,16] All of the four RCTs reported results for patients who had completed the study or had evaluable data. Intention-to-treat analysis was not specified in any of these trials. The proportion of patients who completed the study was generally low. One RCT, conducted in Georgia,[16] reported a completion rate of higher than 80% in the randomized population. In the other three RCTs, the completion rates ranged between 20% to lower than 50% in the overall population. The dropout rates were comparable between treatment groups, except for the Saxon study (more patients with Suboxone dropped out the study than those with methadone, 54% versus 26%, respectively). Generalizability was limited as it was uncertain as to whether the study patients were representative of all patients.

Non-randomized-controlled trials

Both of the non-randomized studies[20,21] were prospective studies. However, it was unclear if the outcome assessors or patients were blinded to the treatment. Patient characteristics were described in one study. Both studies described the interventions and outcomes. Both studies provided P-values though not always for all outcomes. Generalizability was uncertain as to whether the study patients were representative of all patients. Both studies had small sample size.

Economic evaluations

The economic evaluation reports[22,23] were considered to be of high methodological quality according to the Drummond checklist. The research question was well defined and the analysis method was clearly stated. The key parameters on which the analysis was based were justified and the time horizons were clearly specified. Sensitivity analyses were performed in both reports. One limitation of the Australian report was that the investigators based their analyses on retrospective data (cost and efficacy data) collected almost 10 years ago. In addition, the discount rate was not reported in this analysis. The generalizability of the study results to Canadian setting is uncertain due to the relatively old data. The long-term cost-effectiveness of the selected treatments is unclear since the time horizon in both economic evaluations was relatively short (six months to one year).

Summary of Findings

The overall findings are summarized below and detailed findings from the individual clinical studies are provided in Appendix 4.

What is the comparative clinical effectiveness of Suboxone compared with methadone for the treatment of patients with opioid dependence?

Opioid use

Randomized-controlled trials

In one RCT including 54 patients,[15] clinical outcomes were reported for patients who completed the six month treatment with Suboxone or methadone. In 26 patients (48.1%, 13 in each group) who remained in the study, five patients in the Suboxone group compared with 0 from the methadone group reported illicit opioid use (P = 0.039). The between-group difference in positive urine test for opioid use was not found to be statistically significant (five patients in the Suboxone group compared with 2 in the methadone group, P > 0.05).

In the double-blind RCT by Kamien et al.,[18] patients in the combined Suboxone groups (low dose and high dose groups combined) reported numerically fewer days of heroin use in the past 30 days, when compared with combined methadone groups, P = 0.05. Higher doses of Suboxone or methadone were associated with larger reduction in days of heroin use, compared with lower doses Suboxone or methadone; however, statistical tests of differences in days of heroin use between Suboxone and methadone in respective high- or low-dose group were not performed.

Non-randomized-controlled trials

One non-RCT[20] in patients who had already received 6 months treatment with Suboxone or methadone at study entry found that significantly more Suboxone-treated patients reported “abstinent from heroin use in the past 90 days” compared with those treated with methadone (71.4% versus 37.7%). “Days of heroin use in the past 90 days” were similar at 6-months, however those in the Suboxone group reported significantly fewer days of heroin use after 14 months of treatment, compared with the methadone group (Suboxone: reduced from 38.64 days to 8.5 days; methadone: reduced from 37.40 days to 24.15 days). In terms of “treatment motivation”, significantly more patients with methadone viewed their drug use as a problem and indicated their intention to adhere to treatment. Attrition from 8-month assessment was similar between methadone and Suboxone.

Retention in treatment

Randomized-controlled trials

In the Neumann study,[15] there was no significant difference in the numbers of patients who had completed the treatment of SUB or MET, 13 patients in each group.

In the Saxon study,[17] patients in the Suboxone group completed fewer weeks of treatment (mean 18.5 weeks) as compared to those in the methadone group (mean 25.8 weeks), P < 0.0001. In the secondary analysis using data from this RCT,[19] significantly fewer Suboxone patients (46%) than methadone patients (74%) completed treatment at 24 weeks, P < 0.01.

Kamien and coworkers reported similar retention time between Suboxone and methadone: 12.1 weeks, 13.2 weeks, 12.5 weeks and 12.3 weeks for patients in low dose Suboxone, high dose Suboxone, low dose methadone and high dose methadone groups, respectively.[18] The between-group differences in retention time were not statistically significant.

Non-randomized-controlled trials

In the non-RCT by McKeganey,[20] there were no statistically significant differences in rates of attrition from the 8-month follow-up assessment (rates of attending: 67.9% for Suboxone versus 62.3% for methadone, P > 0.05).

Patient perceptions toward disease and treatment

In the non-RCT by McKeganey,[20] at study entry (after six months treatment with Suboxone or methadone), significantly higher scores of the Texas Christian University Self-Rating Form (TUC/SRF) were reported in patients treated with methadone than those with Suboxone, indicating that they were more likely to view their drug use as a problem and show readiness for adherence to treatment.

Cognitive performance

One non-RCT evaluated the effects of Suboxone or methadone on patient's cognitive abilities using specific tests.[21] Results showed that Suboxone was superior to methadone in attention testing. Similar test results were observed in the Suboxone group and the methadone group for working memory and verbal memory.

Safety

Randomized-controlled trials

The Neumann study reported similar rates of self-reported adverse effects between the Suboxone group and the methadone group, eight patients (61.5%) versus nine patients (69.2%), respectively.[15] However, no further descriptions on adverse events were provided.

Significantly more adverse events were reported in the Suboxone group than the methadone group in a Georgia study,[16] 108 events versus 80 events, respectively, P = 0.003. The most commonly reported events in both groups were insomnia, constipation and depression, but were mild to moderate in intensity. There were no reports of deaths, overdoses, suicide attempts or other serious adverse events.

In one RCT which focused on liver health,[17] rates of serious adverse events (SAEs) were not significantly different between treatment groups, 38 patients (5.2%) in the Suboxone group versus 45 (8.7%) in the methadone group. The SAEs reported for Suboxone included persistent

headache, non-cardiac chest pain, spontaneous abortion, suicidal ideation, suicidal threat, cholecystitis, accidental benzodiazepine overdose, and suicide plan by heroin overdose; while SAEs observed for methadone included alprazolam overdose, drug intoxication requiring hospitalization, hospitalization for vomiting, bradycardia, change in metal status, inadvertent methadone overdose, gastric ulcer, and one death from accidental acute combined use of cocaine and methadone.

In the Kamien study,[18] SAEs were experienced by one patient treated with Suboxone and four patients treated with methadone. There were no other safety data reported in this study.

Non-randomized-controlled trials

None of the non-randomized studies examined the safety of the use of Suboxone.

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

In the Greek cost-effectiveness analysis, the estimated patient total costs for one year were 2,876 euros for treatment with Suboxone, while it was 5,626 euros for treatment with methadone. In terms of the clinical effectiveness, Suboxone increased the percentage of treatment completion approximately 1.5-fold, and percentage of deaths in the Suboxone group was 2.5-fold smaller compared with that in the methadone group. As a result, the cost-effectiveness analysis demonstrated that Suboxone therapy was dominating the other two drugs, methadone and buprenorphine monotherapy. The incremental cost-effectiveness ratio (ICER) for Suboxone versus methadone was -795.03 euros with respect to “treatment completion”, and was -1,410.7 euros with respect to “percentage of avoided deaths”.

In the Australian economic evaluation, the mean treatment costs over a 6-month period were AUD$1,593 for Suboxone, and AUD$1,415 for methadone. 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 Suboxone and 6.84 days for methadone. Therefore, the ICER for the comparison between Suboxone and methadone was AUD$357 (confidence interval: -1,520 to 2,367). The results suggested that the combination of buprenorphine and naloxone was more expensive but more effective than methadone for patients with opioid dependence. However, the between-treatment difference in cost-effectiveness was not statistically significant.

Limitations

Most of the included clinical trials had small sample size and power calculations were not described. Results from these underpowered studies should be interpreted with caution, since a difference between treatment groups may not be detected. In addition, all studies reported results from the evaluable population, or from patients who had completed the study. However, the proportions of patients that remained in the study were low. Effectiveness of Suboxone in patients who withdrew the study earlier is uncertain.

Adverse effects were insufficiently reported and not all studies reported on adverse events. Infection was reported in a number of studies but the reporting of infection varied (e.g. catheter related infection, blood stream infection, and exit site infection). Also, the studies were not powered to detect adverse events, so differences in rare event rates may not be detectable.

The studies were conducted at single centers, mainly tertiary hospitals so generalizability of the findings may be limited.

None of the clinical trials or economic evaluations was conducted in Canada, so applicability to the Canadian setting is unclear.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

Inconsistent results of clinical effectiveness and safety of the use of Suboxone in patients with opioid dependence were observed across the included studies of this review. Results from randomized controlled trials indicated that in adult patients, compared with methadone, treatment with Suboxone may have similar effects on retention in treatment, and heroin or other opioid use. Rates of adverse events for Suboxone were similar to methadone. The results should be interpreted with caution, due to the small sample sizes, relatively short study durations (3 to 6 months therapy), and high discontinuation rates. Data from non-randomized controlled trials suggested that Suboxone had similar effect as methadone on number of days of heroin use. In addition, compared with methadone, Suboxone did not show significant difference in cognitive performance in the study population after 6 weeks treatment.

Two economic evaluations conducted outside of Canada demonstrated the cost-effectiveness benefits related to Suboxone when comparing with methadone for opioid-dependent patients.

Opioid dependence is a chronic, relapsing illness and patients usually need long-term maintenance treatment. The limited evidence suggested that Suboxone may be an alternative in the study population. There is no evidence available on other clinically relevant outcomes, such as health-related quality of life, mortality. Also, there is a lack of evidence to evaluate the benefits/risks of Suboxone in special populations (children, pregnant women, or others). Evidence on Suboxone compared with Methadose, a commercial product of methadone, is also unavailable. There was no Canadian economic study identified to examine the cost-effectiveness of the use of Suboxone in Canadian population.

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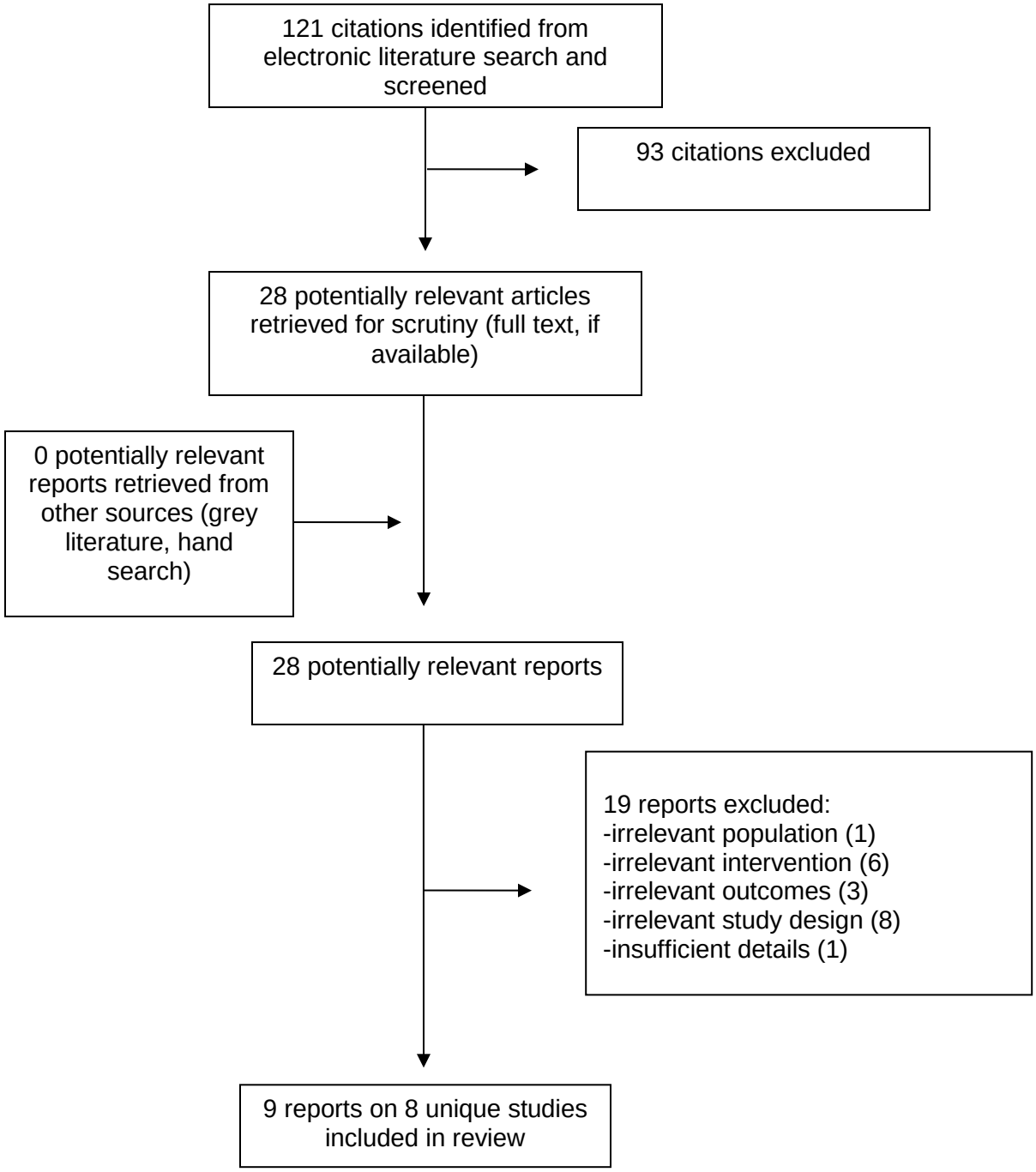
APPENDIX 1: Selection of Included Studies



APPENDIX 2: Characteristics of Included Studies

Table A2.1: Characteristics of Included Clinical Studies

First author, publication year, country	Study design, length of follow-up	Patient characteristics, sample size	Intervention	comparators	Main clinical outcomes
RCTs					
Neumann, 2013, US[15]	Open-label RCT Treatment duration: 6 months	Patients with chronic pain and coexistent opioid addiction to prescription opioids (not specified), duration of drug use: ~6 years N = 54	SUB (buprenorphine 4-16 mg /naloxone 1-4 mg), average daily dose: 14.93/3.73 mg n=26	MET 10-60 mg/day, average daily dose: 29.09 mg n=28	Treatment retention, opioid use (self-report or urine test)
Otiashvili, 2013, Georgia[16]	RCT, blinding unknown. Treatment duration: 12 weeks Follow-up till 20 weeks.	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, opioid use (self report or urine test)
Saxon, 2013, US[17] Hser, 2013, US[19] (secondary analysis)	Open-label RCT Treatment duration: 24 weeks Follow-up till 32 weeks	Patients with opioid dependence to injection drugs (heroin, cocaine, non-heroin opioids and amphetamines), and AST/ALT no greater than 5 times, or ALP no greater than 3 times the ULN; duration of drug use: ~20 days N = 1269 (N = 1267 in the secondary analysis)	SUB, mean maximum daily dose 22.1 mg n = 740 (340 evaluable)	MET, mean maximum daily dose 93.2 mg n = 529 (391 evaluable)	Change in ALT and AST from baseline, treatment retention
Kamien, 2008, US[18]	Double-blind, double dummy RCT Treatment	Patients dependent to heroin or prescription	SUB-1: 8 mg BUP+2 mg NAL, n = 82	MET-1: 45 mg, n = 52 MET-2: 90 mg,	Opioid abstinence achieved overtime,

First author, publication year, country	Study design, length of follow-up	Patient characteristics, sample size	Intervention	comparators	Main clinical outcomes
	duration: 17 weeks N = 268	opioids; duration of drug: 9-12 years N = 268	SUB-2: 16 mg BUP+4 mg NAL, n = 58	n = 76	retention, overall functioning
Non-RCTs					
McKeganey, 2013, UK[20]	Naturalistic comparison of MET and SUB. Patients received MET or SUB for maintenance for 6 months prior to entering the study; treatment continued and patients were followed for another 8 months	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 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 abstinent from heroin use, perceptions toward disease and treatment (measured by TCU/SRF and SF-36)
Rapeli, 2007, Finland[21]	Naturalistic comparison of MET and SUB. Patients' cognitive abilities were assessed within 6 weeks after opioid substitution treatment	Patients with opioid dependence N=50 (there was a healthy control group, n = 17)	SUB, mean dose 15.8 mg/day n = 17	MET, mean dose 53.4 mg/day n = 16	Attention, working memory and verbal memory (testing was done 3-6 hours after drug administration)

ALP=alkaline phosphatase; ALT=alanine amino transferase; AST=aspartate amino transferase; DAST=the Drug Abuse Screening Test; DSM-IV-TR=the Diagnostic and Statistical Manual of Mental Disorders; MET=methadone; SF-36=Short-Form Health Survey; SUB=Suboxone; TCU/SRF=Texas Christian University Self-Rating Form; UK=the United Kingdom; ULN=upper limit of normal; US=the United States of America

Table A2.2: Characteristics of Included Economic Evaluations

First Author, Publication Year, Country	Study Design, Time horizon	Patient Characteristics	Intervention/ Comparators	Assumptions
Geitona, 2012, Greece[22]	●cost-effectiveness analysis based on retrospective data from 2 local health authority database ●Time horizon: 1 year	Opioid users participating in OST programs in Greece	MET, BUP, SUB	The cost for SUB patients was as same as BUP patients, since they received the same clinical management
Doran, 2005, Australia[23]	●cost-effectiveness analysis ●Time horizon: 6 months	Heroin dependence	MET, BUP, SUB	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

APPENDIX 3: Summary of Study Strengths and Limitations

First Author, Publication Year, Country	Strengths	Limitations
Randomized controlled trial		
Neumann, 2013, US[15]	• 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, Georgia[16]	• Objectives and inclusion/ exclusion criteria were stated. • Patient characteristics, interventions, and outcomes were described. • Randomized and likely open label as there was. Computerized random numbers were used for the randomization procedure. • Number discontinued or lost to follow up were reported	• No mention about blinding • Intent-to-treat analysis was not performed • Sample size calculations were not described • Generalizability limited; uncertain as to whether study patients were representative of all patients. • Industry-sponsored study
Saxon, 2013, US[17] Hser, 2013, US[19] (secondary analysis)	• 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.	• Intent-to-treat analysis was not performed • Generalizability limited; uncertain as to whether study patients were representative of all patients. • Industry-sponsored study
Kamien, 2008, US[18]	• Objectives and inclusion/ exclusion criteria were stated. • Patient characteristics, interventions, and outcomes were described. • Double-blind randomized study. Computerized random numbers were used for the randomization	• Intent-to-treat analysis was not performed • Industry-sponsored study. • Generalizability limited; uncertain as to whether study patients were representative of all patients.

First Author, Publication Year, Country	Strengths	Limitations
	procedure. Allocation sequence was concealed. • Sample size calculations described • Number discontinued or lost to follow up were reported • Appeared to be intent-to-treat analysis, though not explicitly mentioned • P-values provided	
Non-randomized studies		
McKeganey, 2013, UK[20]	• Objectives and selection criteria were stated. • Patient characteristics, interventions, and outcomes were described. • P-values provided	• Sample size calculation was not described • Generalizability limited; uncertain as to whether study patients were representative of all patients. • Industry-sponsored study
Rapeli, 2007, Finland[21]	• Objectives and selection criteria were stated. • Patient characteristics, interventions, and outcomes were described. Interventions and outcomes were described • P-values provided	• Sample size calculation was not described • Generalizability limited; uncertain as to whether study patients were representative of all patients.
Economic Evaluations		
Geitona, 2012, Greece[22]	• 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 was short • Discount rate was not applied • Perspective was not described • The study was conducted using euro cost information from Greece which may limit the generalizability to Canada • Sponsored by manufacturer
Doran, 2005, Australia[23]	• 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 was relatively short • The study was conducted using AUD cost information which may impact its generalizability to Canada

APPENDIX 4: Main Study Findings and Authors' Conclusions

<table>
<tr><th>First Author, Publication Year, Country</th><th>Main Findings and Authors' Conclusion</th></tr>
<tr><td colspan="2">Randomized controlled trials</td></tr>
<tr><td>Neumann, 2013, US[15]</td><td>Main Findings:
Comparison of SUB versus MET in patients with chronic pain + opioid addiction (13 patients in each group completed the study)
<table>
<tr><th>Outcome</th><th>SUB</th><th>MET</th><th>P value</th></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 (%)</td><td>13 (50.0)</td><td>13 (46.4)</td><td>NS</td></tr>
<tr><td>Self-reported side effects, n (%)</td><td>8 (61.5)</td><td>9 (69.2)</td><td>NS</td></tr>
</table>
Authors' Conclusion:
After 6 months treatment, no patients in the MET group compared to 5 in the SUB group reported illicit opioid use; other differences between the two groups were not significant.</td></tr>
<tr><td>Otiashvili, 2013, Georgia[16]</td><td>Main Findings:
Comparison of SUB versus MET in adult patients with opioid dependence (at 12 weeks)
<table>
<tr><th>Outcome</th><th>SUB</th><th>MET</th><th>P value</th></tr>
<tr><td>Positive urine test for opioid use, n (%)</td><td>1 (0.2)</td><td>6 (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</td><td>108</td><td>80</td><td>0.003</td></tr>
</table>
Authors' Conclusion:
"Daily observed methadone or buprenorphine-naloxone are effective treatments for non-medical buprenorphine and other opioid use in Georgia." P. 1</td></tr>
<tr><td>Saxon, 2013, US[17]

Hser, 2013, US[19] (secondary analysis of Saxon et al.)</td><td>Main Findings:
Comparison of SUB versus MET in adults with opioid dependence and normal liver function
<table>
<tr><th>Outcome</th><th>SUB</th><th>MET</th><th>P value</th></tr>
<tr><td>Treatment retention, weeks (SD)</td><td>18.5 (12.7)</td><td>25.8 (10.0)</td><td><0.0001</td></tr>
<tr><td>Completion rate at 24 weeks, %</td><td>46.1</td><td>74.1</td><td><0.01</td></tr>
<tr><td>Serious adverse events, n (%)</td><td>38 (5.2)</td><td>45 (8.7)</td><td>NS</td></tr>
</table>
Authors' Conclusion:
"MET participants were retained longer in treatment than BUP* participants." P. 71
* referred to SUB</td></tr>
</table>

<table>
<tr><th>First Author, Publication Year, Country</th><th>Main Findings and Authors' Conclusion</th></tr>
<tr><td>Kamien, 2008, US[18]</td><td>Main Findings:
Comparison of SUB versus MET in opioid-dependent patients
<table>
<tr><th>Outcome</th><th>SUB</th><th>MET</th><th>P value</th></tr>
<tr><td>Self-reported days of heroin use in the past days, change from baseline, mean (SE)</td><td>Low dose: from 26.9 (0.8) to 5.8 (2.4)
High dose: from 26.3 (1.1) to 3.1 (1.7)</td><td>Low dose: from 26.7 (0.8) to 9.0 (2.5)
High dose: from 26.3 (0.9) to 4.3 (1.6)</td><td>=0.05 (low and high doses of study drugs were combined)</td></tr>
<tr><td>Treatment retention, weeks (SE)</td><td>Low dose: 12.1 (0.2)
High dose: 12.5 (0.2)</td><td>Low dose: 13.2 (0.2)
High dose: 12.3 (0.2)</td><td>NR</td></tr>
<tr><td>Serious adverse events, n</td><td>1</td><td>4</td><td>NR</td></tr>
</table>
Authors' Conclusion:
"Addiction and retention did not differ among groups. Buprenorphine-naloxone is a viable alternative to methadone in clinical practice." P. 5</td></tr>
<tr><td colspan="2">Non-randomized studies</td></tr>
<tr><td>McKeganey, 2013, UK[20]</td><td>Main Findings:
<table>
<tr><th>Outcome</th><th>Percentage of patients
SUB</th><th>MET</th><th>P value</th></tr>
<tr><td>Days of heroin use in the past 90 days (change from 6-month timepoint to 14-month timepoint, mean (SD)</td><td>38.64 (31.05) to 8.5 (12.52)</td><td>37.40 (38.66) to 24.15 (33.27)</td><td>NR</td></tr>
<tr><td>Treatment readiness at 6-month timepoint (score)</td><td>2.96 (0.35)</td><td>3.13 (0.46)</td><td><0.05</td></tr>
</table>
Authors' Conclusion:
"MET and SUB were highly and equally effective for preventing relapse to regular heroin use". P.97</td></tr>
<tr><td>Rapeli, 2007, Finland[21]</td><td>Main Findings:
Comparison of SUB versus MET in adult patients
<table>
<tr><th>Outcome</th><th>SUB</th><th>MET</th><th>P value</th></tr>
<tr><td>Attention (TAP Tonic Alertness, simple reaction time), mean (SD)</td><td>228 (13)</td><td>258 (32)</td><td>NR, favored SUB</td></tr>
<tr><td>Working memory (WMS-III LNS), mean (SD)</td><td>8.7 (1.7)</td><td>8.8 (2.6)</td><td>NR</td></tr>
</table></td></tr>
</table>

First Author, Publication Year, Country	Main Findings and Authors' Conclusion
	Verbal memory, mean (SD) 14.8 (0.4) 14.6 (1.0) NR
	Authors' Conclusion: "To preserve cognitive function, the use of SUB may be more preferable to MET use." P. 2
Economic evaluations	
Geitona, 2012, Greece[22]	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.
	Author's conclusion: "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, Australia[23]	Data were retrieved from an RCT. Assessment criteria 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 nonstatistical significance of ICER in the CEA.
	Author's conclusion: "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)

AUD=Australian dollar; CEA=cost-effectiveness analysis; ICER=incremental cost-effectiveness ratio; MET=methadone; MPD=Memory for Persons Data; NR=not reported; NS = not significant; RCT= randomized controlled trial; SD=standard deviation; SE=standard error of the mean; SUB = Suboxone; TAP=Test for Attentional Performance; WMS-III LNS=Wechsler Memory Scale -3rd version