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CADTH RAPID RESPONSE REPORT:
SUMMARY WITH CRITICAL APPRAISAL

Injectable Opioid Agonist Treatment for Patients with Opioid Dependence: A Review of Clinical and Cost-Effectiveness

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Abbreviations

DAM	diacetyl morphine
HDM	hydromorphone
ICER	incremental cost effectiveness ratio
Met	methadone
NAOMI	North American Opiate Medication Initiative
QALY	quality adjusted life year
RCT	randomized controlled trial
SALOME	Assessment of Long-term opioid Maintenance Effectiveness
WTP	willingness-to-pay

Context and Policy Issues

Opioids have analgesic and central nervous system depressant effects and have been used as medication for pain relief.[1] However, opioids also have the potential to cause euphoria and have been misused, resulting in opioid dependency and consequently increased morbidity and mortality.[1] Opioid dependency is a serious problem and impacts public health with considerable clinical, social and economic implications.[2,3] The Centers of Disease Control and Prevention estimated that in the US, the economic burden resulting from the misuse of prescription opioids is $78.5 billion per year (which includes costs for health care, productivity loss, treatment for dependency, and criminal justice involvement).[2] In Canada, overdose deaths resulting from opioid dependency are on the rise and are a serious concern. It was estimated that in Canada in 2018, there were at least 4,460 deaths due to opioid overdose and 94% of these were determined to be unintentional overdose; this is a 9.4% increase in overdose deaths from 2017, and 48% increase from 2016.[4]

Opioid agonists have the ability to suppress opioid cravings and withdrawal symptoms from acute effects of other opioids, and have been used as a treatment option for opioid dependency. Opioid agonists include drugs such as methadone, buprenorphine, diacetylmorphine (DAM) and hydromorphone (HDM). In some individuals with opioid dependency, even with repeated treatment with oral opioid agonists no benefit was achieved.[4] Injectable opioid agonists have shown some promise in treating opioid dependency in these individuals.[4] Injectable opioid agonists have a rapid onset of action and shorter duration to reach peak values in comparison to oral opioid agonists, and hence there is potential for overdose issues. Administration of injectable opioid agonist under supervision would allow for immediate action to be taken in case of overdose to help ensure safety, although take-home dosing has also been studied.[3,5]

The purpose of this review is to summarize the evidence on the clinical effectiveness and cost-effectiveness of injectable opioid agonist treatment (with DAM or HDM, alone or in combination with methadone or buprenorphine/naloxone), compared with alternative pharmacological treatments or no treatment, for individuals with opioid dependency.

Research Questions

1. What is the clinical effectiveness of injectable opioid agonist treatment for patients with opioid dependence?
2. What is the cost-effectiveness of injectable opioid agonist treatment for patients with opioid dependence?

Key Findings

Five relevant reports were identified. These comprised one systematic review, two randomized controlled trials (RCT), and two economic evaluations.

One systematic review found that compared to patients treated with other treatments (i.e., methadone, or any other treatment program) those treated with injectable diacetylmorphine (DAM) (with or without the addition of methadone) had statistically significantly greater retention in treatment, reduction in illicit drug use, reduction in criminal activities, and fewer convictions and imprisonments, but no statistically significant difference in mortality and greater occurrence of adverse events.

One RCT showed that injectable hydromorphone (HDM) was not inferior to injectable DAM with respect to days of street opioid use, and proportions of urinalysis positives for street heroin metabolites in urine samples. There were no statistically significant between-group differences with respect to retention to treatment, criminal activity, and physical health and psychological health, however there was statistically significantly higher risk of adverse events related to the intervention in the DAM group compared to the HDM group.

One crossover RCT with 28 patients showed that there was statistically significant improvement after injectable DAM treatment compared to before treatment with respect to anxiety, anger, emotional excitement and well-being, and statistically significantly less heroin craving with injectable DAM compared to injectable placebo.

The results of the economic evaluations, considering a lifetime time horizon and societal perspective, indicated that DAM and HDM treatments each provided more benefits than methadone treatment, and at lower cost for individuals who had previously used other treatment options. Based on incremental cost-effectiveness ratios, it was found that both DAM and HDM dominated methadone. One evaluation reported that the probability of DAM being cost-effective was 76% at a willingness-to-pay (WTP) threshold of $0 per QALY gained, and 95% at a WTP threshold of $100,000 per QALY gained. The second evaluation did not report the WTP threshold.

Findings need to be interpreted with caution, considering the overall limited quantity of evidence, and that the economic evaluations were based on several assumptions.

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including PubMed, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH

(Medical Subject Headings), and keywords. The main search concepts were injectable opioid agonist treatment and opioid dependence. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2010 and April 26, 2020.

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	Adults (≥ 18 years) with opioid dependence
Intervention	Injectable opioid agonist treatment (iOAT) (hydromorphone or diacetylmorphine), alone or in combination with methadone or buprenorphine/naloxone
Comparator	Alternative pharmacological treatment, any formulation (e.g., alternative iOAT, buprenorphine/naloxone, methadone, injectable buprenorphine); no treatment
Outcomes	Q1: Clinical benefits and harms (e.g., retention in treatment, illicit drug use, overdose rates, mortality, health-related quality of life, social functioning [e.g., attendance at school or work], emotional and psychological functioning [e.g., anxiety, depression, sleep], adverse events) Q2: Cost-effectiveness (e.g., incremental cost per health benefit or QALY gained)
Study Designs	Health technology assessments, systematic reviews, randomized controlled trials, non-randomized studies, and economic evaluations

iOAT = injectable opioid agonist treatment; QALY = quality adjusted life year.

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2010. Systematic reviews in which all relevant studies were captured in other more recent or more comprehensive systematic reviews were excluded. Primary studies retrieved by the search were excluded if they were captured in one or more included systematic reviews. Secondary analyses of included primary studies that did not include any additional relevant outcomes were excluded.

Critical Appraisal of Individual Studies

The included publications were critically appraised by one reviewer using the following tools as a guide: A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2)[6] for systematic reviews, the Downs and Black checklist[7] for randomized studies, and the Drummond checklist[8] for economic evaluations. Summary scores were not calculated for the included studies; rather, the strengths and limitations of each included publication were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 140 citations were identified in the literature search. Following screening of titles and abstracts, 110 citations were excluded and 30 potentially relevant reports from the

electronic search were retrieved for full-text review. Two potentially relevant publications were retrieved from the grey literature search for full-text review. Of these 32 potentially relevant articles, 27 publications were excluded for various reasons, and five publications met the inclusion criteria and were included in this report. These comprised one systematic review,[3] two RCTs,[9,10] and two economic evaluations. [11,12] No relevant non-randomized studies were identified. Appendix 1 presents the PRISMA[13] flowchart of the study selection.

Summary of Study Characteristics

The study characteristics are summarized below. Additional details regarding the characteristics of included publications are provided in Appendix 2. In the literature, various terms were used for "heroin", such as diacetylmorphine (DAM) and diamorphine. For the purpose of consistency, we will use the term DAM throughout the main text. However, street heroin will be referred to as street heroin.

Study Design

The included systematic review[3] was published in 2011. It had a broad focus and included eight studies of which seven studies were relevant for this review. These seven studies were RCTs published between 1980 and 2010. The systematic review conducted meta-analyses and reported pooled estimates when possible, and when not possible presented results of the individual studies separately.

Two relevant primary studies[9,10] were identified. One was a double-blind, non-inferiority RCT[9] published in 2016 and is also referred to as the Study to Assess Long-term Opioid Medication Effectiveness (SALOME). The second study was a cross-over RCT[10] published in 2013.

Two relevant economic evaluations[11,12] were identified. Both evaluations were cost utility analyses, with lifetime time horizons and societal perspectives. Both evaluations used semi Markov cohort models and conducted sensitivity analyses. The models included four states: treatment, relapse, abstinence, and death. Clinical and cost data were obtained from the North American Opiate Medication Incentive (NAOMI) trial, SALOME trial, published articles and databases for one evaluation,[11] and from the NAOMI trial, other published articles and databases for the other evaluation.[12]

Country of Origin.

The first author of the systematic review[3] was from Portugal. Of the seven relevant studies, two studies were from the UK, and one study each was from Canada, Germany, the Netherlands, Spain, and Switzerland.

The first author of the RCT[9] was from Canada and the study was conducted in Canada. The first author of the cross-over RCT[10] was from Switzerland and the study was conducted in Switzerland.

The first authors of both economic evaluations[11,12] were from Canada, and the studies on which the evaluations were based were conducted in Canada.

Patient Population

The included systematic review[3] involved 1,793 participants who were chronically dependent on DAM. In the individual studies in this systematic review, the mean age in years ranged between 24 and 39 (4 studies), 18 to 65 (1 study), ≥25 (1 study), and >20 (1

study). The proportion of males ranged between 61% to 90% in five studies, and was not reported in two studies. History of drug use was greater than two years in six studies and 26.5 days in the past month in one study.

The RCT[9] included 202 adults with opioid dependency. The mean age was 45 years, the proportion of males was 70%, and the mean history of street heroin use was 15 years. The crossover RCT[10] included 28 adults with DAM dependency. The mean age was 41 years, proportion of males was 67%, and mean duration of dependency was seven years.

One economic evaluation[11] involved adults with severe opioid use disorder (opioid dependency) who had been using illicit opioids, even though other treatment options were available (individuals who participated in the SALOME trial). The other economic evaluation[12] involved adults with chronic opioid dependence refractory to treatment (individuals who participated in the NAOMI trial).

Interventions and Comparators

In the systematic review,[3] the interventions in the included studies were injectable DAM, injectable DAM plus methadone, injectable DAM plus oral methadone, DAM maintenance, or self-injected DAM; the comparators were methadone, oral methadone, or waitlist (i.e., any other drug treatment program could be used). As the studies were pooled, in the rest of this report the various intervention will be collectively referred to as “injectable DAM”, and the various comparators will be collectively referred to as “other treatments”. In instances where the comparator group was methadone only it will be referred to as the methadone group. Treatment duration ranged between six months and 12 months.

In the RCT (the SALOME study)[9] injectable hydromorphone (HDM) was compared with injectable DAM over a duration of six months, and in the crossover RCT[10] injectable DAM was compared to injectable placebo, before and 60 minutes after treatment.

One economic evaluation[11] compared injectable HDM, injectable DAM, and oral methadone. Comparisons between injectable HDM and injectable DAM were indirect, since this evaluation used data from one RCT (NAOMI) that compared DAM to methadone and another RCT (SALOME) that compared HDM to methadone (i.e., methadone was a common comparator). The other economic evaluation[12] compared injectable DAM with oral methadone.

Outcomes

The systematic review[3] reported on retention in treatment, relapse to street heroin, use of other substances, mortality, medical adverse events, criminal offense, incarceration, and social functioning.

The RCT (SALOME study)[9] reported on street opioid use, urinalyses positive results, physical and mental symptoms (using Maudsley Addition Profile [MAP]), illegal activities, crack cocaine use, and adverse effects. The crossover RCT[10] reported on drug cravings, state anxiety, state anger, emotional excitement, and well-being. The various assessment tools are described in Appendix 4, Table 9.

Both economic evaluations[11,12] reported incremental cost-effectiveness ratios (ICER), i.e., cost per quality adjusted life year (QALY).

Summary of Critical Appraisal

An overview of the critical appraisal of the included publications is summarized below. Additional details regarding the strengths and limitations of included publications are provided in Appendix 3.

The systematic review[3] was well-conducted overall, however details of the interventions and comparators were not clearly reported and there were some inconsistencies between information presented in the text and figures. A comprehensive literature search was conducted. The objective, the study characteristics, and article selection were described. Article selection and data extraction were done independently by two reviewers. Quality assessment of the studies was conducted and the risk of bias was generally low. Meta-analyses were conducted appropriately. It was unclear if publication bias was explored. The authors reported that there were no conflicts of interest.

In the RCT (SALOME study)[9] the objective, and inclusion and exclusion criteria were stated; the patient population, intervention, and outcomes were described; the randomization procedure was described; and both patients and investigators were blinded to treatment groups. A sample size calculation was undertaken and the appropriate number of patients were recruited. Both intention-to-treat and per protocol analyses were conducted. The authors reported that there were no conflicts of interest.

In the cross-over RCT[10] the objective, and inclusion and exclusion criteria were stated; and the patient population, intervention, and outcomes were described, but details of the outcome measures were sparse. The randomization procedure was not described. The patients and experimenter were blinded to the administered substance in the first session but were unblinded at the second session (i.e., after crossover). It was unclear if a sample size calculation was conducted. Intention-to-treat analyses were presented. The authors reported that there were no conflicts of interest.

Both economic evaluations[11,12] were generally well described. The objectives, time-horizons, perspectives taken, sources for clinical and cost data, and discounting were reported. The models used were described, and assumptions were reported and appeared to be reasonable. Sensitivity analyses were conducted by varying different model parameters to ensure the validity of the model. Incremental analyses were reported. Conclusions were consistent with the results reported. In one economic[11] evaluation it was reported that the authors had no conflicts of interest. In the other economic evaluation,[12] of the nine authors, two authors had financial involvement with the pharmaceutical industry, hence potential for bias cannot be ruled out.

Summary of Findings

The main findings are summarized below. Appendix 4 presents details of the main study findings and authors' conclusions.

Clinical Effectiveness of Injectable Diacetylmorphine or Hydromorphone

One relevant systematic review,[3] one relevant RCT (SALOME study)[9] and one relevant crossover RCT[10] involving adults with opioid dependency were identified. Details of the major findings are presented in Appendix 4, Table 8 (for the systematic review) and Table 9 (for the primary studies).

Retention in treatment

The systematic review[3] found that there was statistically significantly greater retention in treatment in the injectable DAM group compared to the methadone group or the other treatment group.

The RCT (SALOME study)[9] showed that for adults with opioid dependency, injectable HDM was non-inferior to injectable DAM with respect to retention to treatment.

Illicit drug use or opioid craving

The systematic review[3] found that there was a significantly greater reduction in illicit drug use in the injectable DAM group compared to the methadone group (three studies). Also, in this systematic review, four studies showed greater reduction in illicit drug use in the injectable DAM group compared to the other treatment group (statistically significant in three studies; no significant between-group difference in one study).

The RCT (SALOME study)[9] showed that for adults with opioid dependency, injectable HDM was non-inferior to injectable DAM with respect to street opioid use (self-reported) and proportions of urinalyses positives found for street heroin metabolites.

In the cross-over RCT[10] involving adults with opioid dependency, it was found that there was statistically significantly less craving for drugs with injected DAM compared to injected placebo.

Criminal activities and incarceration

In the systematic review[3] there was greater reduction in criminal offenses in the injectable DAM group compared to the methadone group in three studies, with the between-group difference being statistically significant in two of these studies; and fewer convictions and imprisonments with injectable DAM compared to methadone (one study). Also, in this systematic review, it was reported that there were fewer charges in the injectable DAM group compared to the other treatment group (statistically significant in one study and statistical significance was not reported in one study); and statistically significantly greater improvement with injectable DAM in terms of imprisonment (2 studies).

The RCT (SALOME study)[9] showed that for adults with opioid dependency, injectable HDM and injectable DAM were not statistically significantly different with respect to days of criminal activities.

Physical, psychological and social aspects

In the systematic review[3] one study reported a slightly better (statistical significance was not reported) employment status in the injectable DAM group compared to the methadone group, one study reported statistically significant improvements in work status in both injectable DAM and methadone groups compared to before treatment, and two studies reported that there was no statistically significant difference in employment status between the injectable DAM group and the other treatment group (

The RCT (SALOME study)[9] showed that for adults with opioid dependency, injectable HDM and injectable DAM were not statistically significantly different with respect to physical health and psychological health (based on Maudsley Addiction Profile).

In the cross-over RCT[10] involving adults with opioid dependency, it was found that there was statistically significant improvements after injectable DAM treatment compared to

before treatment with respect to anxiety, anger, emotional excitement and well-being; and statistically significantly less heroin craving with injectable DAM compared to injectable placebo. There was statistically significant increase in anger and emotional excitement but no statistically significant difference in anxiety and well-being after injectable placebo treatment compared to before treatment.

Mortality

In the systematic review[3] it was reported that there was no statistically significant difference in mortality in the injectable DAM group compared to the methadone group (four studies pooled) or in the injectable DAM group compared to the other treatment group (5 studies).

Safety

In the systematic review[3] it was reported that there was a statistically significant greater number of adverse events related to the intervention in the injectable DAM group compared to the methadone group (three studies).

The RCT (SALOME study)[9] showed that for adults with opioid dependency, there was a statistically significantly higher risk of adverse events related to the intervention in the injectable DAM group compared to the injectable HDM group. The most common related adverse events included drowsiness, and minor or moderate histamine reactions. The most common related serious adverse events included seizures and opioid overdoses.

Cost-Effectiveness of Injectable Diacetylmorphine or Hydromorphone

Two relevant economic evaluations[11,12] were identified. Details of major findings and author's conclusions are presented in Appendix 4, Table 10.

Comparison between injectable hydromorphone, injectable diacetylmorphine and oral methadone

The economic evaluation[11] suggested that over a lifetime time horizon both injectable DAM and injectable HDM provided more benefits than oral methadone and at lower cost; QALYs were 8.4 (7.4 to 9.5) for DAM and 8.3 (7.2 to 9.5) for HDM versus 7.4 (6.5 to 8.3) for methadone, and costs in Canadian dollars were 1.01 million (0.6 million to 1.59 million) for DAM, and 1.02 million (0.72 million to 1.51 million) for HDM versus 1.15 million (0.71 million to 1.84 million) for methadone. Based on ICERs, it was found that both DAM and HDM dominated methadone.

Comparison between injectable diacetylmorphine and oral methadone

The economic evaluation[12] suggested that over a lifetime time horizon injectable DAM provided more benefit than oral methadone and at lower cost; QALYs were 7.92 (7.32 to 8.53) for DAM versus 7.46 (6.91 to 8.01) for methadone, and costs in Canadian dollars were 1.10 million (0.72 million to 1.71 million) for DAM versus 1.14 million (0.74 million to 1.78 million) for methadone. Based on ICERs it was found that DAM dominated methadone. Probabilistic sensitivity analysis showed that for lifetime, the probability of DAM being cost-effective was 76% at a WTP threshold of $0 per QALY gained, and 95% at a WTP threshold of $100,000 per QALY gained.

Limitations

Conclusions were based on statistical significance in the included publications; none of the studies mentioned what was considered a clinically important difference in outcomes. No

studies were identified that compared injectable DAM and injectable HDM with other treatment options of interest such as buprenorphine or slow-release morphine. Many of the same sources of data were used for the two economic evaluations, so findings were not totally exclusive (i.e., some data were represented twice in this report).

One primary study included in the systematic review and one selected primary study were conducted in Canada, and the two economic evaluations were mostly based on Canadian data. Hence the findings can be generalized to the Canadian setting, however, it should be noted that generalizability is dependent on the assumptions on which the evaluations were based (Appendix 2, Table 4).

Conclusions and Implications for Decision or Policy Making

Five relevant publications were identified regarding the clinical effectiveness and cost effectiveness of injectable opioid agonist treatment (with DAM or HDM, alone or in combination with methadone) compared with alternative pharmacological treatments or no treatment, for individuals with opioid dependency; these comprised one systematic review,[3] two RCTs,[9,10] and two economic evaluations.[11,12]

The systematic review[3] found that patients in the injectable DAM group, compared to those in the methadone group or other treatment group, had significantly greater retention in treatment, reduction in illicit drug use, reduction in criminal activities, and fewer convictions and imprisonments; but no statistically significant difference in mortality and greater occurrence of adverse events.

The RCT (SALOME study)[9] showed that for adults with opioid dependency, injectable HDM was not inferior to injectable DAM with respect to days of street opioid use and proportions of urinalysis positives for street heroin metabolites. There were no statistically significant between-group differences for injectable HDM compared to injectable DAM, with respect to retention to treatment, criminal activity, and physical health and psychological health, however there was statistically significantly higher risk of adverse events related to the intervention in the DAM group compared to the HDM group.

One crossover RCT[10] showed that there was statistically significant improvement after injectable DAM treatment compared to before treatment with respect to anxiety, anger, emotional excitement and well-being, and statistically significantly less heroin craving with injectable DAM compared to injectable placebo.

One economic evaluation[11] compared injectable DAM, injectable HDM, and oral methadone treatments, and found that over a lifetime time horizon, both DAM and HDM provided more benefits than methadone and at lower cost. Based on ICERs, it was found that both DAM and HDM dominated methadone. The WTP threshold was not reported. The other economic evaluation[12] compared injectable DAM with oral methadone and found that over a lifetime time horizon DAM provided more benefit than methadone and at lower cost. The probability of DAM being cost-effective was 76% at a WTP threshold of $0 per QALY gained, and 95% at a WTP threshold of $100,000 per QALY gained.

An evidence brief[14] on the effectiveness of supervised injectable opioid agonist treatments for opioid dependency was identified in the search but did not meet the inclusion criteria for this report (due to study design). The evidence brief summarized findings from a variety of study types and included findings from secondary analyses of primary studies and qualitative studies, which may provide some useful insights and are discussed here. It was

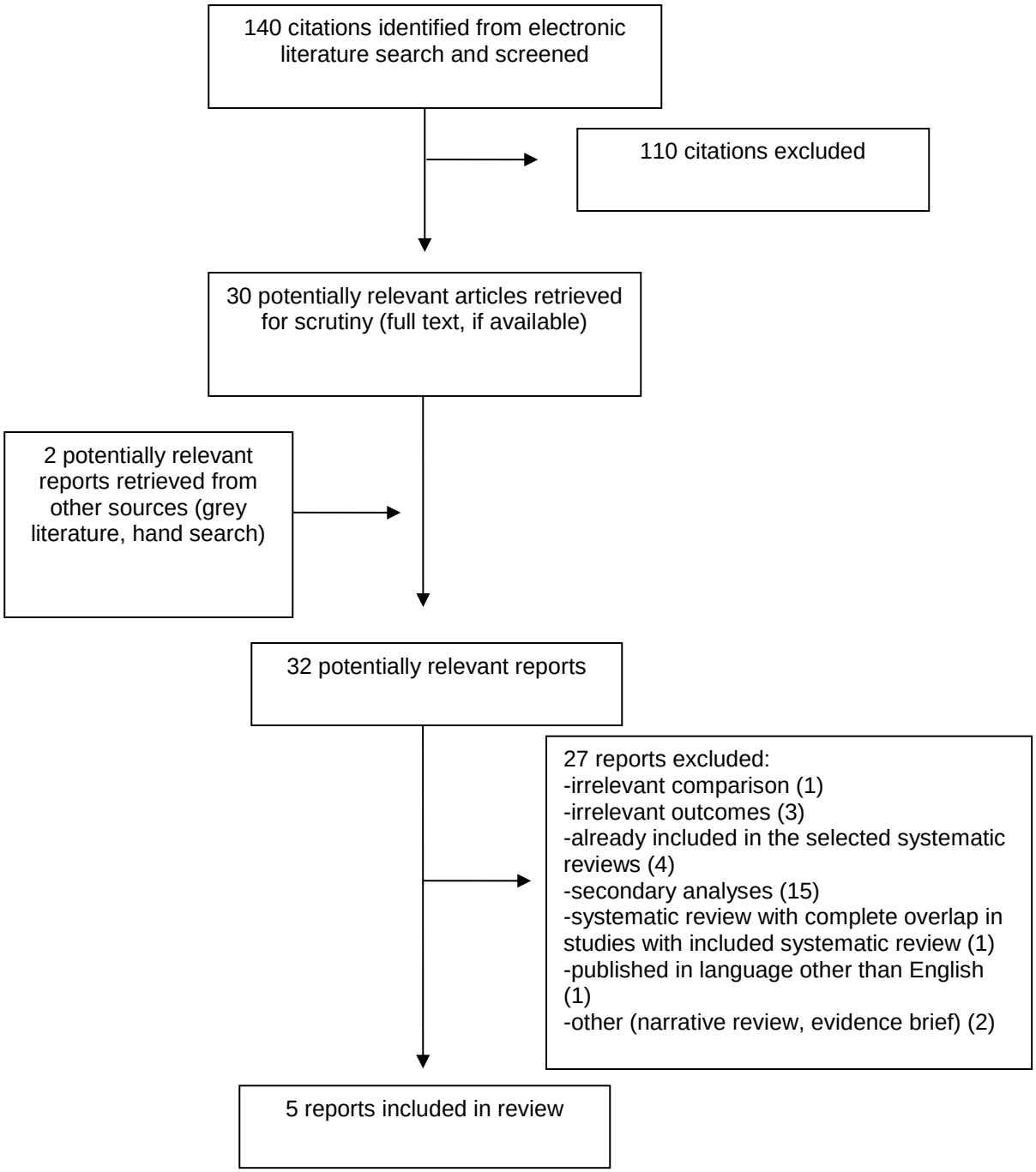
reported that for treatment with injectable DAM there was better response in individuals with higher motivation at baseline, and reduced effect in individuals with psychiatric comorbidity. There was no significant advantage demonstrated with injected DAM compared to oral methadone for women participants, Indigenous participants, and participants with no prior maintenance experience. For comparison between injectable HDM and injectable DAM, it was reported that with both treatments there were significant improvements in use of street heroin, opioids, and crack cocaine in Indigenous participants; and there were no significant differences in outcomes between male and female participants. Findings from qualitative studies indicated that some participants found it less appealing injecting in a clinical environment, some participants treated with DAM under supervision perceived benefits of building a relationship with staff and having a collective identity with others at the clinic, and some participants thought that supervised injectable treatment gave them stability but found the scheduling demanding. The evidence brief reported that for individuals with opioid use disorder who had undergone methadone treatment in the past; both injectable DAM and injectable HDM demonstrated significant benefits for retention in treatment, reduction in street drug use, and reduction in illegal activities; and HDM was associated with fewer adverse events compared to DAM. The overall conclusions of this evidence brief are therefore in agreement with the conclusions of this current report.

Further research investigating long-term effects of DAM and HDM compared with other treatments for individuals with opioid dependency may provide a greater understanding of the effects of these treatments, and usefulness and feasibility of implementing such treatment programs. Also, studies investigating specific subgroups such as Indigenous people, and people with various psychiatric conditions, may allow identification of groups that are likely to benefit most. Economic evaluations exploring models considering different probabilities and frequency of entering the various health states, could provide greater insights.

References

1. Strain E. Pharmacotherapy for opioid use disorder. In: Post TW, ed. *UpToDate*. Waltham (MA): UpToDate; 2020: www.uptodate.com. Accessed 2020 Apr 25.
2. National Institute on Drug Abuse. Opioid overdose crisis. 2020; https://www.drugabuse.gov/drugs-abuse/opioids/opioid-overdose-crisis. Accessed 2020 May 27.
3. Ferri M, Davoli M, Perucci CA. Heroin maintenance for chronic heroin-dependent individuals. *Cochrane Database Syst Rev.* 2011;12:CD003410.
4. Canadian Research Initiative in Substance Misuse (CRISM). National injectable opioid agonist treatment for opioid use disorder operational guidance. Vancouver (BC): Canadian Research Initiative in Substance Misuse (CRISM); 2019: https://crism.ca/wp-content/uploads/2019/09/CRISM_National_IOAT_Operational_Guideline-17Sept2019-English-FINAL.pdf. Accessed 2020 May 27.
5. Guidance for injectable opioid agonist treatment for opioid use disorder. Vancouver (BC): British Columbia Centre on Substance Use (BCCSU); 2019: https://www.bccsu.ca/wp-content/uploads/2019/03/BC_iOAT_Guideline.pdf Accessed 2020 May 27.
6. Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ.* 2017;358:j4008.
7. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Community Health.* 1998;52(6):377-384.
8. Higgins JPT, Green S, editors. Figure 15.5.a: Drummond checklist (Drummond 1996). *Cochrane handbook for systematic reviews of interventions*. London (GB): The Cochrane Collaboration; 2011: http://handbook-5-1.cochrane.org/chapter_15/figure_15_5_a_drummond_checklist_drummond_1996.htm. Accessed 2020 May 27.
9. Oviedo-Joekes E, Guh D, Brissette S, et al. Hydromorphone compared with diacetylmorphine for long-term opioid dependence: a randomized clinical trial. *JAMA Psychiatry.* 2016;73(5):447-455.
10. Blum J, Gerber H, Gerhard U, et al. Acute effects of heroin on emotions in heroin-dependent patients. *Am J Addict.* 2013;22(6):598-604.
11. Bansback N, Guh D, Oviedo-Joekes E, et al. Cost-effectiveness of hydromorphone for severe opioid use disorder: findings from the SALOME randomized clinical trial. *Addiction.* 2018;113(7):1264-1273.
12. Nosyk B, Guh DP, Bansback NJ, et al. Cost-effectiveness of diacetylmorphine versus methadone for chronic opioid dependence refractory to treatment. *CMAJ.* 2012;184(6):E317-328.
13. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol.* 2009;62(10):e1-e34.
14. Ontario Agency for Health Protection and Promotion (Public Health Ontario), Leece P, Tenenbaum M. Evidence brief: effectiveness of supervised injectable opioid agonist treatment (siOAT) for opioid use disorder. Toronto (ON): Queen's Printer for Ontario; 2017: https://www.publichealthontario.ca/-/media/documents/eb-effectiveness-sioat.pdf?la=en. Accessed 2020 May 27.

Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Systematic Review

Study citation, country, funding source	Study designs and numbers of primary studies included	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Ferri et al. 2011,[3] Portugal. Sources of support: -Internal (Department of epidemiology, ASL, RME, Italy; Agency of public health, Italy; European monitoring centre for drugs and drug abuse, EMCDDA). -External (none)	Systematic review included 7 relevant RCTs published between 1980 and 2010. One RCT each from Canada, Germany, the Netherlands, Spain, and Switzerland, and two RCTs from the UK. Four of the RCTs were multi-centre studies. (This systematic review had a broad objective and included 8 studies of which 7 studies were relevant for our report)	Adults (≥18 years) who were chronically dependent on heroin, diagnosed using any set of criteria. Exclusion criteria: individuals with severe psychiatric disorder, severe physical disorder, pending jail sentence, being pregnant, or breast feeding were excluded. N =1,793 (range: 51 to 1,032 in individual studies). Age (years): mean age ranged between 24 and 39 (4 studies), 18 to 65 (1 study), ≥25 (1 study), and >20 (1 study). % Male: 61% to 90% (5 studies), and not reported (2 studies) History of drug use: mean duration of 6 years to 17 years (3 studies), ≥5 years (1study), >3 years, (1study), >2 years (1 study), and 26.5 days in the past month (1 study).	Supervised injectable heroin (i.e., DAM) with or without methadone versus oral methadone (5 RCTs). Self-injected heroin (i.e., DAM) plus oral methadone versus waitlist (1 RCT); note: those in the waitlist group were encouraged to select any available drug treatment program. Heroin (i.e., DAM) maintenance versus oral methadone (1 RCT). All participants received some kind of psychosocial support. Treatment was provided in outpatient setting.	Primary: Retention in treatment, relapse to street heroin, use of other substances, mortality, and medical adverse events. Secondary: Criminal offence, incarceration/imprisonment, and social functioning. Duration of treatment ranged from 6 months to 12 months.

DAM = diacetylmorphine; HDM = hydromorphone; RCT = randomized controlled trial.

Table 3: Characteristics of Included Primary Clinical Studies

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Oviedo-Joekes et al. (SALOME study), 2016,[9] Canada. Funding: CIHR, in partnership with PHC, with additional financial support from the Inner Change Foundation, Providence Health Care Research Institute, St Paul's Hospital Foundation, and Vancouver Coastal Health	RCT: phase 3, double-blind non-inferiority trial, single center. Non-inferiority margin was determined by consensus using a Delphi process and was set at 4 days for both street heroin use and for total street-acquired opioid use.	Adults (19 years or older) with chronic opioid dependency, who were not benefiting from conventional therapies. Exclusion criteria: those with severe psychiatric or medical conditions contraindicated for diacetylmorphine or hydromorphone (e.g., stage II or greater hepatic encephalopathy), or those currently pregnant or planning on becoming pregnant were excluded. N = 202 (100 in HDM, and 102 in DAM) Age (years), mean (SD): 45 (10) in HDM, 44 (9) in DAM. % Male: 67% in HDM, 72% in DAM. Years of street heroin injection, mean (SD): 15.6 (9.5) in HDM, 15.3 (9.3) in DAM.	Injectable HDM versus injectable DAM. The drugs were self-injected under supervision of a registered nurse at the study site. Individuals could receive 3 doses per day up to 400 mg per dose and up to 1,000 mg per day.	Primary outcome: Street heroin use (defined as number of days of use in prior 30 days [self-reported]) Co-primary outcomes: Street opioid (including heroin) use (defined as number of days of use in prior 30 days). Proportion of urinalysis positives for street heroin markers in urine sample at 6 month assessment. Secondary outcomes: Proportion receiving injected medication for at least 28 days in the prior 30 days. Physical and mental symptoms based on MAP. No. of days involved in illegal activities and cracked cocaine use (self-reported). Study period: 6 months
Blum et al. 2013,[10] Switzerland. Funding was provided by the Swiss National Science Foundation.	Randomized placebo controlled cross-over trial. Patients were recruited from the Division of Substance Use Disorders of the Psychiatric Hospital of the University of Basel. (Note: This trial also included a third arm with healthy	Adults with heroin dependency Exclusion criteria: a positive breathalyzer test and physical disorder or psychiatric disorder, and other comorbid substance dependence except tobacco. N =28	Heroin (i.e. DAM) injection versus placebo injection. After one week the heroin group was switched to placebo and the placebo group to heroin.	Heroin craving, anxiety, anger, emotional excitement, and well-being Duration of treatment phase: 60 minutes. (Outcomes were assessed before and 60 minutes after treatment)

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
	individuals, which was not relevant for this report and therefore not included)	Age (years), mean (SD): 41.3 (6.6) % Male: 68% Duration of dependence (years), mean (SD): 6.7 (4.5)		

CIHR = Canadian Institutes of Health research; DAM = diacetylmorphine; HDM = hydromorphone; MAP = Maudsley Addiction Profile; PHC = Providence Health Care; SALOME = Study to Assess Long-term Opioid Medication Effectiveness; SD = standard deviation.

Table 4: Characteristics of Included Economic Evaluations

Study citation country, funding source	Type of analysis, time horizon, perspective	Population characteristics	Intervention and comparator(s)	Approach	Source of clinical, cost, and utility data used in analysis	Main assumptions
Bansback et al. 2015,[11] Canada. Funding: from CIHR, and additional support from Providence Health Care, the Inner Change Foundation, Providence Health Care Research Institute, St. Paul's Hospital Foundation, and Vancouver Coastal Health	Cost-utility analysis. Time horizon: 6 months for within-group analysis; and 50 years for life-time analysis. Perspective: societal (considering costs borne by the health care and criminal justice system; out-of-pocket costs borne by society).	Individuals with severe opioid use disorder who have been using illicit opioids, even though other treatment options were available.	Injectable HDM, injectable DAM, and oral Met were compared	Semi Markov cohort model. Health states included in the model: treatment (with DAM or Met), relapse (i.e., opioid use outside of treatment), abstinence, and death. Probabilistic sensitivity analysis (using Monte Carlo simulations: 5000) were conducted.	Clinical data obtained from trials (NAOMI, and SALOME), and published data on Canadian cohorts or local data sources. Costs of HDM, DAM and Met, health resource use, criminal involvement and criminal charges, were obtained from SALOME and NAOMI trials. Costs were in 2015 Can$. Discounting: 5%. Estimates of model parameters (probabilities of transition to health states	For the base case analysis, patient demographics and clinical characteristics were assumed to be similar to the population in the SALOME trial. For the within group analysis, findings from the SALOME trial were used. For the life-time analysis, findings from the SALOME and NAOMI trials were extrapolated. The NAOMI trial compared DAM with Met, so using DAM as a common comparator HDM was

Study citation country, funding source	Type of analysis, time horizon, perspective	Population characteristics	Intervention and comparator(s)	Approach	Source of clinical, cost, and utility data used in analysis	Main assumptions
					and death, HIV seroconversion, QALYs, and monthly costs) were obtained from SALOME and NAOMI trial data, other published reports and databases.	indirectly compared to Met. Transition to death was based on age- and sex-adjusted mortality rate for the general Canadian populations. Mortality rate in the HDM state was assumed to be same as in the DAM state, as mortality rate for HDM state was not available. Transition between health states was assumed to occur every 30 days.
Nosyk et al. 2012,[12] Canada. Funding: CIHR, the Canada Foundation for Innovation, the Canada Research Chairs Program, the, Providence Health Care, Vancouver Coastal Health, the BC Centre for Disease Control, government and universities.	Cost-utility analysis. Time horizon: 1-, 5-, 10-years and lifetime. Perspective: societal (considering costs borne by the health care and criminal justice system; out-of-pocket	Individuals with chronic opioid dependence refractory to treatment	DAM compared to Met maintenance	Semi Markov cohort model. Health states included in the model: treatment (with DAM or Met), relapse (i.e., opioid use outside of treatment),	Clinical data obtained from NAOMI trial, administrative database of BC, and other published data. The mean age of the individuals was 39.7 years. Costs for DAM, Met, medications, human resources and overhead were	The primary analysis used a hypothetical cohort of individuals similar to the participants in the NAOMI trial and was assumed to be representative of North American population that would have access to DAM treatment.

Study citation country, funding source	Type of analysis, time horizon, perspective	Population characteristics	Intervention and comparator(s)	Approach	Source of clinical, cost, and utility data used in analysis	Main assumptions
	costs borne by society)			abstinence, and death. One-way sensitivity analysis and probabilistic sensitivity analysis (using Monte Carlo simulation: 2000) were conducted.	obtained from the NAOMI trial. Additional costs were obtained from published articles. Costs were in 2009 Canadian dollars; discounting: 5%. Estimates of model parameters (probabilities of transition to health states and death, HIV seroconversion, QALYs, and monthly costs) were obtained from NAOMI trial data, other published reports and databases.	Entrance to the treatment state was assumed to be the individuals third attempt at treatment for opioid dependence. For HIV negative patients the probability of transition to death from the abstinence state was based on age- and sex-specific death rate in the general Canadian population. It was assumed that individuals with opioid dependency who were HIV positive did not have an increased risk of mortality. Transition between health states was assumed to occur every 30 days.

Can$ = Canadian dollars; CIHR = Canadian Institutes of Health Research; DAM = diacetyl morphine; DHM = hydromorphone; Met = methadone; NAOMI = North American Opiate Medication Initiative; SALOME = Study to Assess Long-term Opioid Maintenance Effectiveness.

Appendix 3: Critical Appraisal of Included Publications

Table 5: Strengths and Limitations of Systematic Reviews and Using AMSTAR 2[6]

Strengths	Limitations
Ferri et al. 2011[3], Portugal	
• The objective was clearly stated • Study selection was described, and a flow chart was presented • Multiple databases were searched. The search for the previous review of 2005 was used (i.e., Medline [from 1966 to 2005], EMBASE [from 1980 to 2005], CINHAL [until 2005] and Cochrane Central Register of Controlled Trial [CENTRAL], Issue 1, 2005). Additionally, for this update Medline 2005 to 2009 was searched. Also, relevant websites, and trial registries were searched, researchers in the field were contacted, and conference abstracts were viewed. • A list of included studies was provided • A list of excluded studies was provided • Article selection was done independently by two reviewers • Data extraction was done independently by two reviewers • Quality assessment was conducted using the Cochrane Risk of Bias tool. Risk of bias was generally low for most domains except detection bias related to subjective outcomes. Detection bias related to subjective outcomes was low in 2 RCTs, unclear in 4 RCTs, and high in 1 RCT. • Meta-analyses were conducted when possible and appropriate • It was reported that the authors had no conflicts of interest	• Unclear if publication bias was explored • Reporting of intervention details was inconsistent between the text and tables; details of interventions and comparisons were unclear

AMSTAR 2 = A MeaSurement Tool to Assess systematic Reviews 2; RCT = randomized controlled trial.

Table 6: Strengths and Limitations of Clinical Studies Using the Downs and Black checklist[7]

Strengths	Limitations
Oviedo-Joekes et al. (SALOME study), 2016,[9] Canada	
• The objective was clearly stated • The inclusion and exclusion criteria were stated • Patient characteristics, interventions, and outcomes were described. • Randomized study and the randomization was done using a block randomization technique with variable block size using prepared tables at the Data Center, with concealed allocation • Double blinded (patients and investigator were blinded to treatment group) • Sample size calculation was conducted, and the appropriate number of patients was recruited • Missing values were imputed using multiple imputations	• Appeared to have no major limitations

Strengths	Limitations
• Both ITT and PP analyses were conducted. • 95% CI values were reported • The authors mentioned that there were no conflicts of interest.	
Blum et al. 2013,[10] Switzerland	
• The objective was clearly stated • The inclusion and exclusion criteria were stated • Patient characteristics, intervention and outcomes were described. However details of the interpretation of scores for the outcome measures were lacking. • A randomized cross-over study. Details of randomization were not presented. • The patients and experimenter were blinded to the administered substance in the first session but were unblinded at the second session • It does not appear that there were any withdrawals, considering the short time frame of the study. • ITT analysis was conducted • P values were reported • The authors mentioned that there were no conflicts of interest.	• Unclear if sample size calculation had been conducted

CI = confidence interval; ITT = intention to treat; PP = per protocol.

Table 7: Strengths and Limitations of Economic Evaluations Using the Drummond Checklist[8]

Strengths	Limitations
Bansback et al. 2015,[11] Canada	
• Objectives were stated. • The strategies compared were stated (HDM, DAM, and Met). • Time horizon (lifetime) and perspective (societal) were stated. • Clinical data sources were stated (2 RCTs [NAOMI, and SALOME], additional data from published data on Canadian cohorts or local data sources). • Cost data source were stated (obtained from RCTs and other sources) • Discounting was reported • Model description was presented • Incremental analysis was reported. • Sensitivity analyses were conducted. • Conclusions were consistent with the results reported. Limitations were described • The authors mentioned that there were no conflicts of interest.	• As direct comparison between HDM and methadone was not available, indirect comparison was used. Though this methodology is being use increasingly, its potential susceptibility to bias cannot be ruled out. • Indirect costs such as productivity costs were not considered. • It was not possible to include a number of costs (such as possession or dealing of drugs, disorderly behavior, sex work, major driving violations or broken conditions imposed by the legal system) which are likely to have a considerable impact on society. • For lifetime analysis, transition to health states were extrapolated beyond the trial's time frame, based on assumptions. However, sensitivity analysis using varying parameters showed that results were generally robust to assumptions. • One state of relapse was used in the model. However, it is possible that some individuals who relapsed may still remain engaged with treatment; these patients would likely have greater benefits than those who did not.

Strengths	Limitations
	• From sparse information it appeared that criminal activity was higher in HDM versus DAM, but there was no reasonable explanation for this, hence there is uncertainty regarding its impact.
Nosyk et al. 2012,[12] Canada	
• Objectives were stated. • The strategies compared were stated (DAM and Met). • Time horizon (lifetime) and perspective (societal) were stated. • Clinical data sources were stated (1 RCT [NAOMI], additional data from published data on Canadian cohorts or local data sources). • Cost data source were stated (from 1 RCT [NAOMI], and additional data from published articles) • Discounting was reported • Model description was presented • Incremental analysis was reported. • Sensitivity analyses were conducted. • Conclusions were consistent with the results reported. Limitations were described. • Two of the authors received consulting and lecturing fees from industry and for the remaining authors, it was mentioned that there were no conflicts of interest.	• Indirect costs such as productivity costs were not considered. • Costs resulting from incarceration were not explicitly included in the model due to uncertainty in the probability of incarceration, and delays in adjudication and sentencing, as attributing costs to the different health states would not be possible without making considerable assumptions. • As prevalence data for Hepatitis C infection was sparse it was not explicitly included in the model. Also, cost and QALY losses related to transmission of infection from HIV and Hepatitis C virus infected individuals to the general population were not explicitly modelled. These could potentially underestimate cost-savings and QALYs gained.

DAM = diacetylmorphine; HDM = hydromorphone; NAOMI = North American Opioid Medication Initiative; QALY = quality adjusted life yea; RCT = randomized controlled trial; SALOME = Study to Assess Long-term Opioid Medication Effectiveness.

Appendix 4: Main Study Findings and Authors' Conclusions

Table 8: Summary of Findings Included Systematic Reviews

Main study findings	Authors' conclusion
Ferri et al. 2011,[3] Portugal	
Comparison of heroin (i.e., DAM) versus oral methadone Retention in treatment RR (95% CI): 1.44 (1.19 to 1.75); analysis with 4 studies including 1388 patients; heterogeneity I^2, 67%. Mortality RR (95% CI): 0.65 (0.25 to 1.69); analysis with 4 studies including 1477 patients; heterogeneity I^2, 0%. Adverse events related to intervention medication RR (95% CI): 13.50 (2.55 to 71.53); analysis with 3 studies including 373 patients; heterogeneity I^2, 0%. Relapse to street heroin Three studies reported on this outcome. Due to the diversity of criteria used in the individual studies to define this outcome, the authors mentioned that it was not possible to conduct a meta-analysis. However, they found that there was greater reduction in illicit drug use in the heroin arm compared to the methadone arm, and the between group difference was statistically significant in each of the studies. Criminal offence Three studies reported on this outcome. Due to the variation in description of this outcome, a meta-analysis was not possible. All three studies found that there was greater reduction in criminal offenses in the heroin arm compared to the methadone arm, in addition in two of these studies, the between group difference was reported to be statistically significant (MD = -5.81 [95% CI -8.68 to -2.94] in one study; and RR = 0.68 [CI 95% 0.57 to 0.81] in another study). Incarceration/imprisonment One study reported on this outcome. During the first 12 months, convictions occurred in 49.7% in the heroin group and 65.9% in the methadone group; and imprisonment occurred in 13.8% the heroin group and 23.6% in the methadone group. Social functioning (integration at work, and family relationship) One study showed that there was a slightly better employment status in the heroin group compared to the methadone group. A second study showed statistically significant improvement in both groups. A third study showed that there was a significant improvement with respect to employment satisfaction and social relation in the heroin group. **Comparison of heroin (i.e., DAM) versus other treatment**	"The available evidence suggests an added value of heroin prescribed alongside flexible doses of methadone for long-term, treatment refractory, opioid users, to reach a decrease in the use of illicit substances, involvement in criminal activity and incarceration, a possible reduction in mortaliity; and an increase in retention in treatment. Due to the higher rate of serious adverse events, heroin prescription should remain a treatment for people who are currently or have in the past failed maintenance treatment, and it should be provided in clinical settings where proper follow-up is ensured." (p. 2)"[3]

Main study findings	Authors' conclusion
Retention in treatment Relative risk (RR) (95% CI): 1.44 (1.16 to 1.79); analysis with 6 studies including 1,535 individuals; heterogeneity I^2, 84%. Mortality RR (95% CI): 0.78 (0.32 to 1.89); analysis with 5 studies including 1,573 individuals; heterogeneity I^2, 0%. Relapse to street heroin Five RCTs reported on this outcome. Due to the diversity of criteria used in the individual studies to define this outcome, the authors mentioned that it was not possible to conduct a meta-analysis. They found that in four RCTs there was greater reduction in illicit drug use in the heroin arm compared to the other treatment arm, and the between-group difference was statistically significant in each of the RCTs; and in the fifth RCT there was no between-group difference. Criminal offence In one RCT it was reported that that there was a trend (not statistically significant) for more criminal activity in the methadone group compared to those in the heroin group. In one RCT, there was statistically significant improvement in terms of any charges in the heroin group compared to the other treatment group; RR = 0.32 (95% CI, 0.14 to 0.78). Incarceration/imprisonment From 2 studies there was a protective effect with heroin provision with respect to arrests and imprisonments, RR = 0.64 (95% CI, 0.51 to 0.79) Social functioning (integration at work, and family relationship) From two studies, there was no difference between the two groups with respect to employment rate; RR = 0.86, (95% CI, 0.54 to 1.35) in one study, and RR = 1.56, (95% CI, 0.44 to 5.50) in the other study. One study showed that there was no statistically significant difference with respect to having a stable partner in the heroin group compared to the waitlist group (getting any treatment) RR = 1.33 (95% CI, 0.64 to 2.79).	

CI = confidence interval; RCT = randomized controlled trial; RR = relative risk.

Table 9: Summary of Findings of Included Primary Clinical Studies

Main study findings	Authors' conclusion
Oviedo-Joekes et al. (SALOME study), 2016,[9] Canada	
Findings from the RCT comparing injected HDM and injected DAM **Primary and co-primary outcomes**	"This study provides evidence to suggest noninferiority of injectable hydromorphone relative to diacetylmorphine for long-term opioid

Main study findings	Authors' conclusion

Outcome	Analysis	Difference of DAM minus HDM (2-sided 90% CI)[a]
Days of street heroin use in the previous month	ITT	–2.34 (–4.14 to –0.52)
	PP	–1.44 (–3.22 to 0.27)[b]
Days of street opioid (including heroin) use in the previous month	ITT	–0.85 (–2.97 to 1.25)[b]
	PP	–0.15 (–2.09 to 1.76)[b]
Proportion of urinalyses positive for street heroin metabolites in urine sample (at the 6-month visit)	ITT	0.09 (–0.02 to 0.19)[b]
	PP	0.13 (0.02 to 0.24)[b]

[a]The CI comparison approach was used, in which noninferiority was concluded when the lower bound of the 2-sided 90% CI (corresponding to 1-sided 95% CI) lies within the non-inferiority zone. For the days of street heroin use and opioid use the non-inferiority margin was -4 days. For proportion of urinalysis positive in street heroin markers in urine sample, the non-inferiority margin was -10% of the value for DAM (i.e., 0.03 for ITT, and -0.032 for PP)
[b]Non-inferiority concluded

Secondary outcomes
ITT and PP analyses results expressed as difference of DAM minus HDM (95% CI) for the various secondary outcomes are presented below. Overall, there were no statistically significant differences between these two treatments with respect to these secondary outcomes, with the exception of days of crack cocaine use (but in ITT analysis only).

Proportion of participants receiving study medications ≥28 days
ITT → 0.03 (−0.08 to 0.14)
PP → 0.02 (−0.05 to 0.10)

Days of illegal activities
ITT → −0.98 (−3.11 to 1.04)
PP → −1.06 (−3.46 to 1.14)

Days of crack cocaine use
ITT → −2.31 (−4.73 to −0.21)
PP → −1.56 (−3.94 to 0.41)

Physical health score based on MAP
ITT → 0.00 (−2.02 to 2.03)
PP → −0.13 (−2.25 to 1.98)

Psychological health score based on MAP
ITT → −0.95 (−3.09 to 1.19)
PP → −1.40 (−3.65 to 0.85)

(Note: Maudsley Addiction Profile [MAP] scores range from 0 to 40, with higher scores indicating poorer physical or psychological health)

Safety
Comparison of HDM versus DAM, results expressed as RR (95% CI), unless stated otherwise. In most instances, it appears that AEs and SAEs were statistically significantly less with HDM compared to DAM.

Total AEs: 0.78 (0.60 to 1.01)
Total AEs with some relationship to the treatment: 0.60 (0.39 to 0.90)

dependence. In jurisdictions where diacetylmorphine is currently not available or for patients in whom it is contraindicated or unsuccessful, hydromorphone could be offered as an alternative. (p. 447)[9]

Main study findings	Authors' conclusion
Participants with related AEs: 0.61 (0.49 to 0.77), 48% in HDM and 78% in DAM *Most common related AEs (drowsiness):* 0.24 (0.14 to 0.43) *Most common related AEs (minor or moderate histamine reactions*):* 1.69 (0.69 to 4.11) *Total SAEs:* 0.43 (0.20 to 0.93) *Total SAEs with some relationship to the treatment (all resolved with no sequelae):* 0.21 (0.06 to 0.69) *Participants with related SAEs: 0.20 (0.06 to 0.68), 3% in HDM and 15% with DAM* *Most common related SAEs (seizures): 0% in HDM and 0.11% with DAM* *Most common related SAEs (opioid overdose): 0.28 (0.07 to 1.17), 0.03% in HDM and 0.11% in DAM* * "Minor histamine reactions include localized itchiness and raised blotchiness at the injection site. Moderate allergic reactions include localized itchiness, raised blotchiness at the injection site plus facial flushing, feeling pins and needles, and generalized urticarial." (P. 452)	
Blum et al. 2013,[10] Switzerland	
Findings from a cross-over RCT comparing heroin (i.e., DAM) injection with placebo injection in adults with heroin dependency. Values expressed as mean (SD) *Heroin craving (using HCQ),* Significantly less craving was reported in heroin group compared to the placebo group (P <0.0001). *State anxiety (using STAI)* In heroin group, before and after 60 mins substance application: 41.9 (10.0) and 35.11 (7.4); P < 0.001. In placebo group, before and after 60 mins substance application: 43.7 (8.9) and 42.3 (9.3); P not reported. *State anger (using STAXI)* In heroin group, before and after 60 mins substance application: 12.0 (2.6) and 10.3 (1.0); P < 0.001. In placebo group, before and after 60 mins substance application:11.3 (2.2) and 12.9 (4.0); P < 0.05. *Emotional excitation (using AMRS)* In heroin group, before and after 60 mins substance application: 19.2 (5.8) and 15.3 (3.3); P < 0.001. In placebo group, before and after 60 mins substance application: 18.9 (5.7) and 21.9 (6.8) P < 0.001. *Well-being (using AMRS)* In heroin group, before and after 60 mins substance application: 15.8 (4.0) and 18.4 (3.9); P < 0.001. In placebo group, before and after 60 mins substance application: 15.8 (3.8) and 15.1 (3.8); P not reported	
Tools used for assessing various outcomes. Maudsley Addiction Profile (MAP): scores range from 0 to 40, with higher scores indicating poorer physical or psychological health.[9]	

Main study findings	Authors' conclusion
Descriptions of the tools in the study report[10] are presented below, along with details of interpretation of scores where available. Heroin craving questionnaire (HCQ): contains nine items.[10] Beck Depression Inventory (BDI): 21-question multiple-choice self-report inventory, used to assess the depressiveness, with a score above 14 indicating mild depression.[10] State trait anxiety questionnaire (STAI): two 20-item scales, with separate measures of state and trait anxiety.[10] State trait anger expression inventory -2 (STAXI): a 57-item inventory that measures the intensity of anger as an emotional state (State Anger) and the disposition to experience angry feelings as a personality trait (Trait Anger).[10] Likert-scale short version of the adjective mood rating scale (AMRS): used to assess emotional excitation and wellbeing as two emotional domains.[10] HCQ, BDI, STAI, STAXI, AMRS tools were reported by the study authors[10] to be reliable and valid.	

AEs = adverse events; AMRS = adjective mood rating scale; BDI = Beck Depression Inventory; CI = confidence interval; DAM = diacetyl morphine, HCQ = Heroin Craving Questionnaire; HDM = hydromorphone; ITT = intention to treat; MAP = Maudsley Addiction Profile; MD = mean difference; PP = per protocol; RR = risk ratio; SAE = serious adverse events, STAI = state trait anxiety inventory; STAXI = state-trait anger expression.

Table 10: Summary of Findings of Included Economic Evaluations

Main study findings	Authors' conclusion
Bansback et al.[11] 2015, Canada	
Terminology used by the authors in reporting results: Dd = dominated (i.e., treatment provides equal or less benefit [QALY] and at more cost than comparator) Ds = dominates (i.e., treatment provides more or equal benefit [QALY] and at less cost than comparator) **ICER for HDM versus Met in individuals with severe opioid use disorder** (time horizon: lifetime). Base case (societal perspective)→ ICER ($ x1000 per QALY) = Ds (Ds to 883.7); probability HDM dominates was 67%. <u>Various scenarios</u> It was found that for the various scenarios: age 30 years and 50 years, crime cost 20% lower and 20% higher, resource utilization cost 20% lower and 20% higher, addiction treatment cost 20% lower and 20% higher, discount rate 5% and 0%, ICER indicated that HDM (versus Met) dominates for all the scenarios and the probabilities that HDM dominates were respectively 70%, 59%, 60%, 71%, 67%, 67%, 71%, 61%, 63%, and 57%. Considering the Ministry of Health perspective, the probability that HDM dominates would be 0%. **ICER for DAM versus Met in individuals with severe opioid use disorder** (time horizon: lifetime). Base case (societal perspective): ICER ($ x1000 per QALY) = Ds (Ds to 306.8); probability DAM dominates was 75%. <u>Various scenarios</u> It was found that for the various scenarios: age 30 years and 50 years, crime cost 20% lower and 20% higher, resource utilization cost 20% lower and 20%	"In conclusion, our study finds that injectable HDM treatment is less costly and more beneficial than methadone treatment during a life-time predominantly through reducing the costs of involvement in violent and property criminal activity. In jurisdictions where DAM treatment is not available, not providing HDM treatment would add to the societal costs" (p. 1271)"[11]

Main study findings	Authors' conclusion
higher, addiction treatment cost 20% lower and 20% higher, discount rate 5% and 0%, ICER indicated that DAM (versus Met) dominates for all the scenarios and the probabilities that DAM dominates were respectively 79%, 68%, 70%, 78%, 75%, 75%, 79%, 70%, 72%, and 60%. Considering the perspective of Ministry of Health perspective, the probability that DAM dominates would be 0%. **ICER for HDM versus DAM in individuals with severe opioid use disorder** (time horizon: lifetime). Base case (societal perspective)→ ICER ($ x1000 per QALY) = Dd (Ds to Dd); probability HDM dominated was 17% <u>Various scenarios</u> It was found that for the various scenarios: age 50 years, crime cost 20% lower and 20% higher, resource utilization cost 20% lower and 20% higher, addiction treatment cost 20% lower and 20% higher, discount rate 5% and 0%, ICER indicated that HDM (versus DAM) dominates for all the scenarios and the probabilities that HDM dominates were respectively 21%, 16%, 18%, 17%, 17%, 18%, 17%, 20%, and 23%. For Ministry of Health perspective, the probability that HDM (versus DAM) was dominated was 0%. **ICER for HDM versus DAM in individuals with severe opioid use disorder** (within trial analysis, time horizon: 6 months) The within-trial analysis showed that HDM provided similar QALYs to DAM (0.377, [95% CI, 0.361 to 0.393] versus 0.375, [95% CI, 0.357 to 0.391], but had slightly greater costs $49,830 (95% CI, $ 28,401 to $73,637) versus $ 34,320 (95% CI, $ 21,780 to $ 55,998)]. ICER ($ per QALY gained; after adjusting for baseline cost of resource utilization, property and violent crime; and baseline utility scores) was 6,683,925 (95% CI, Dd to Ds).	
Nosyk et al. 2012,[12] Canada	
ICER for DAM compared to Met in individuals with chronic opioid dependence at various time horizons. (Note: The authors mentioned that as interpretation of negative ICER is ambiguous, in these instances it was indicated as cost savings [CS] in presentation of results) <u>Time horizon = 1 year</u> DAM: Cost ($ x 1000), mean (95% CrI) = 85.9 (63.8 to 116.7); QALYs, mean (95% CrI) = 0.86 (0.83 to 0.90). Met: Cost ($ x 1000), mean (95% CrI) = 87.7 (63.9 to 119.8); QALYs, mean (95% CrI) = 0.85 (0.81 to 0.89). ICER ($ X1000 per QALY gained, mean [95% CI]) = CS (CS to 485.8) <u>Time horizon = 5 years</u> DAM: Cost ($ x 1000), mean (95% CrI) = 387.7 (293.4 to 511.6); QALYs, mean (95% CrI) = 3.43 (3.26 to 3.59). Met: Cost ($ x 1000), mean (95% CrI) = 418.3 (297.0 to 579.0); QALYs, mean (95% CrI) = 3.32 (3.14 to 3.47). ICER ($ X1000 per QALY gained, mean [95% CI]) = CS (CS to 103.4) <u>Time horizon = 10 years</u> DAM: Cost ($ x 1000), mean (95% CrI) = 696.0 (504.9 to 960.0); QALYs, mean (95% CrI) = 5.61 (5.29 to 5.90).	"Using mathematical modelling to extrapolate results from the North American Opiate Medication Initiative, we found that a treatment strategy featuring diacetylmorphine may be more effective and less costly than methadone maintenance treatment among people with chronic opioid dependence refractory to treatment. Our model indicated that diacetylmorphine would decrease costs, largely by reducing costs associated with crime, and would increase both the duration and quality of life of treatment recipients. (p. E326)"[12]

Main study findings	Authors' conclusion

Met: Cost ($ x 1000), mean (95% CrI) = 743.8 (515.1 to 1059.7); QALYs, mean (95% CrI) = 5.39 (5.08 to 5.67).
ICER ($ X1000 per QALY gained, mean [95% CrI]) = CS (CS to 78.2)

Time horizon = Lifetime
DAM: Cost ($ x 1000), mean (95% CrI) = 1096.1 (724.1 to 1707.2); QALYs, mean (95% CrI) = 7.92 (7.32 to 8.53).
Met: Cost ($ x 1000), mean (95% CrI) = 1137.6 (736.8 to 1776.5); QALYs, mean (95% CrI) = 7.46 (6.91 to 8.01).
ICER ($ X1000 per QALY gained, mean [95% CrI]) = CS (CS to 122.3)

Sensitivity analyses: ICER for DAM compared to Met in individuals with chronic opioid dependency over a lifetime

Analysis	ICER ($ x 1000) per QALY gained, mean (95% CrI)
Third party perspective[a]	CS (CS to 129.9)
Ministry of Health perspective[b]	85.6 (CS to 363.1)
Diacetylmorphine not available after initial relapse	CS (CS to 95.9)
Assumed no change in lengths of treatment/relapse episodes after first cycle	CS (CS to 105.6)
Time to discontinuation of relapse for diacetylmorphine from NAOMI trial data	CS (CS to 847.5)
Time to discontinuation of post-diacetylmorphine methadone for diacetylmorphine from NAOMI trial data	CS (CS to 106.7)
Exponential distributions set for time to discontinuation curves	CS (CS to 330.7)
Probability of HIV seroconversion set to zero	CS (CS to 147.1)
Discount rate 0%	CS (CS to 223.4)
Discount rate 3%	CS (CS to 143.1)
Equalize mortality in methadone state to mortality in diacetylmorphine state (using diacetylmorphine estimates)	CS (CS to 115.4)
Treatment start at age = 30 years	CS (CS to 123.1)
Treatment start at age = 50 years	CS (CS to 148.3)
Treatment-specific cost utilities	CS (CS to 417.3)
No improvement in HRQoL from treatment to abstinence	CS (CS to 131.3)

[a]Third party perspective includes costs to the healthcare system, and criminal justice system, but not out-of-pocket costs borne by society.
[b]Ministry of Health perspective includes only costs to the healthcare system.

Probabilistic sensitivity analysis showed that for lifetime, the probability of DAM being cost effective was 76% at a willingness-to-pay threshold of $0 per QALY gained, and 95% at a willingness-to-pay threshold of $100,000 per QALY gained.

CI = confidence interval; CrI = credibility interval; CS = cost savings; DAM = diacetyl morphine; Dd = dominated (i.e., treatment provides equal or less benefit [QALY] and at more cost than comparator) ; Ds = dominates (i.e., treatment provides more or equal benefit [QALY] and at less cost than comparator) ; HDM = hydromorhone; ICER = incremental cost-effectiveness ratio; Met = methadone; QALY = Quality adjusted life year.