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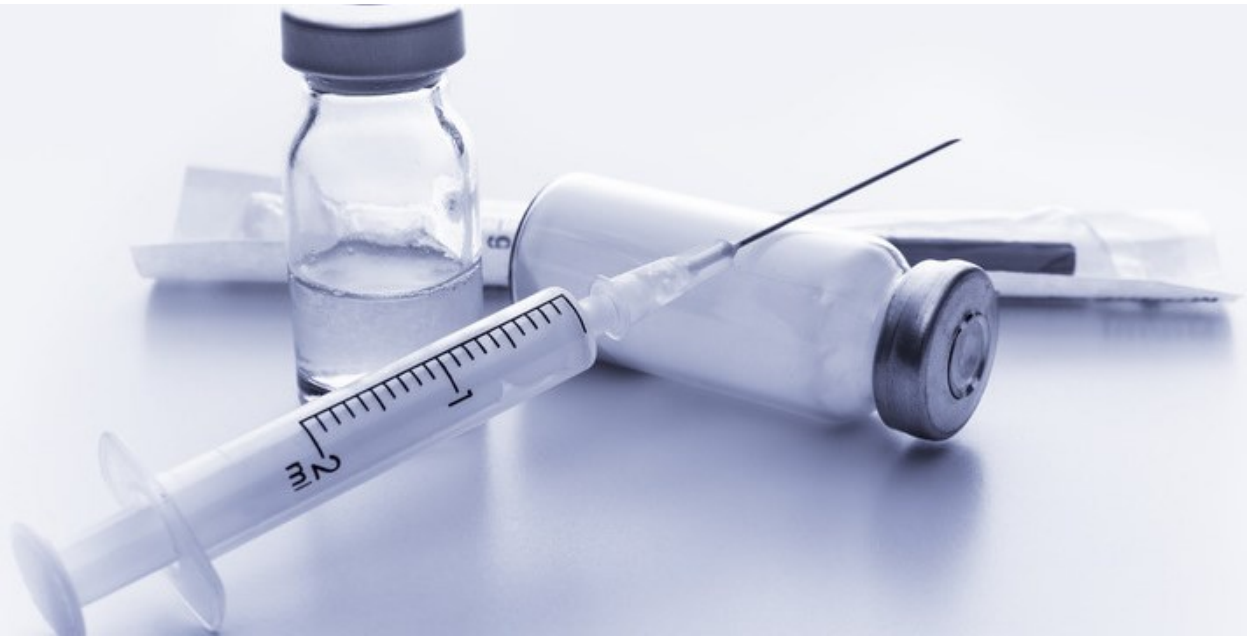
EVIDENCE BRIEF

Effectiveness of supervised injectable opioid agonist treatment (siOAT) for opioid use disorder



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Key Messages

- siOAT has been studied primarily among patients who have undergone methadone treatment in the past.
- siOAT trials have demonstrated significant benefits for retention in treatment, reducing the use of street drugs, and reducing illegal activities in this population.
- siOAT is associated with a greater number of serious adverse events compared with methadone, but these can be managed in a supervised setting.
- Hydromorphone is as effective as diacetylmorphine for siOAT, with fewer adverse events.

Issue and Research Question

Due to rising morbidity and mortality related to opioids in Canada, there is interest in expansion of treatment options for opioid use disorder. Opioid use disorder is a medical diagnosis that refers to a pattern of problematic opioid use that leads to clinically significant impairment or distress.[1] Currently, medication-assisted treatment with long-acting oral opioid agonist medications (which activate the

body's opioid receptors), such as methadone and buprenorphine, are the main evidence-based treatment approach for opioid use disorder.[2]

Supervised injectable opioid agonist treatment (siOAT) with pharmaceutical-grade heroin (diacetylmorphine, DAM) or hydromorphone (HDM), is another treatment approach that has been used among patients with chronic heroin use who have not had a satisfactory response to standard treatments with methadone or buprenorphine.[3] siOAT is currently used in several countries, such as Denmark, Germany, the Netherlands and Switzerland. As such, it can provide another option to engage people with opioid use disorder in treatment.

siOAT has been studied in several randomized controlled trials, including two in Canada: the North American Opiate Medication Initiative (NAOMI) and the Study to Assess Longer-term Opioid Medication Effectiveness (SALOME).[4,5] In November 2016, the Government of Canada issued a *Joint Statement of Action to Address the Opioid Crisis*, signed by Health Ministers and many other health organizations across the country.[6] These commitments included increasing access to siOAT, including DAM and HDM. In Canada, as of September 2016, physicians may apply for special permission to prescribe DAM under Health Canada's Special Access Programme, and Vancouver's Crosstown clinic has provided siOAT to clients outside of clinical trials since 2014.[7]

The implementation of siOAT may be facilitated by current efforts to expand supervised consumption services across Canada, as the treatment also requires infrastructure to supervise injections.[6,8] Additionally, the Government of Canada recently announced in June 2017 that it has implemented new regulations to allow DAM to be imported into Canada, among a list of other drugs, in jurisdictions that request it for urgent public health reasons.[9]

Given the public health importance of opioid-related harms in the population and interest in expanded options for the treatment of opioid use disorder, we sought to review the published literature on this topic.

This Evidence Brief asks: *What is the evidence of effectiveness of supervised injectable opioid agonist treatment with diacetylmorphine (DAM) or hydromorphone (HDM) on treatment retention (i.e., individual remaining on treatment), drug use, social, health or other outcomes among people with opioid use disorder compared to patients using another treatment or no treatment?*

It is beyond the scope of this evidence brief to review thoroughly the clinical, professional regulatory, legal, economic or other logistic issues related to the implementation of siOAT. There are many different terms used in the literature to refer to the intervention drug commonly referred to as heroin (initially a proprietary name, also a street drug name). For consistency throughout our review, we use the term diacetylmorphine (DAM) for this intervention. Original articles may have referred to alternative terms including "diamorphine," "heroin-assisted treatment (HAT)," and "supervised injectable heroin (SIH)."

Methods

The evidence base for this review consists of review of the published literature relevant to our question.

PHO Library Services conducted a database search on February 21, 2017 and updated on September 6, 2017 in line with a peer-reviewed search strategy. Four databases were searched (Ovid MEDLINE,

Embase, PsycINFO, and CINAHL Plus with Full Text) using relevant search criteria (subject terms, key words, English language, dates limited from 2007 to present). Duplicate references were removed by the library staff.

Studies were eligible if they were:

- written in the English language,
- represented primary data, research findings, or a systematic search and synthesis of the literature,
- reported on adults with opioid use disorder or opioid dependence (diagnosed by any criteria) treated with injectable opioid agonist treatment (DAM or HDM) in the intervention group.

We included studies with a comparison group using another treatment (regardless of route of administration) or no treatment. We also included qualitative studies, as long as qualitative methodology was described. Outcomes of interest were the impacts on treatment retention, drug use patterns, and social, health or other outcomes presented in the literature. Title and abstracts were screened for eligibility by two reviewers using standardized criteria and verified by a third reviewer. Discrepancies were resolved by consensus. For articles potentially eligible on title and abstract screening, full text articles were retrieved and two reviewers assessed each article for eligibility using the same eligibility criteria and consensus process for discrepancies. The reference lists of items that met the inclusion criteria were also scanned to locate any additional relevant articles.

For included articles, relevant information was extracted from each article by one reviewer. A second reviewer independently extracted the data on 20% of the included articles and compared results with the other reviewer for reliability.

Relevancy and validity of included articles were checked using Public Health Ontario's (PHO) Meta Quality Appraisal Tool (MetaQAT).[10] Two reviewers then independently applied specific methodological quality appraisal tools for each included article based on its study design. The Health Evidence (HE) Quality Assessment Tool for Review Articles was selected to appraise the two systematic reviews included in this brief.[11] The Effective Public Health Practice Project's quality assessment tool (EPHPP), a tool for quantitative studies, was used for randomized controlled trials (n=24).[12] The Newcastle-Ottawa Scale (NOS)[13] was used to assess the quality of non-randomized studies including cross-sectional studies (rated on a scale of 10; n=3) and cohort studies (rated on a scale of 9, n=2).[13] Also, the Critical Appraisal Skills Programme (CASP) checklist for qualitative studies[14] and their economic evaluation checklist[15] was used for the three qualitative and two economic evaluations included in this brief. The full search strategy with key words, data extraction tables, and quality ratings for each article, are available from PHO on request.

Main Findings

The search of the published literature identified 763 articles, from which 126 unique articles met inclusion criteria on title and abstract screening. On full text review, 36 articles were relevant to our evidence brief question. The quality assessment ratings are presented in Table 1.

Table 1: Quality appraisal of articles

Study Design	Reference number	Quality assessment tool	Rating
Systematic review	16	HE	10/10
Systematic review	17	HE	9/10
RCT – primary analysis	4	EPHPP	Strong
RCT – primary analysis	18	EPHPP	Moderate
RCT – secondary analysis	19-22	EPHHP	Strong
RCT – secondary analysis	5,23-33	EPHHP	Moderate
RCT – secondary analysis	34-37	EPHPP	Weak
RCT – follow-up	27,38	EPHPP	Moderate
Observational cohort	39	NOS-Cohort	8/9
Observational cohort	40	NOS-Cohort	6/9
Qualitative	41-43	CASP-Qual	8/9
Economic evaluation	44	CASP-Econ	11/11
Economic evaluation	45	CASP-Econ	9/11
Cross-sectional	46-48	NOS-Cross sectional	6/10

In the sections below, we have organized our finding by study design to include the following categories: systematic reviews, randomized controlled trials (RCTs) not included in systematic reviews, secondary analyses or sub-studies of existing RCTs (these were not in the scope of systematic reviews), RCT follow-up studies (studies of the RCT participants that occurred after the RCT ended), cross-sectional, and qualitative studies.

Systematic reviews

Two high-quality systematic reviews (SRs) published in 2015 and 2011 have summarized and performed meta-analysis using the data from RCTs comparing DAM treatment with methadone or other treatments for opioid use.[16,17] We found another low quality systematic review that assessed treatment retention for multiple interventions for opioid use disorder, but excluded it for our current review as it did not provide a full analysis of all aspects of the DAM trials.[49]

The studies included in both systematic reviews represent seven RCTs conducted in six countries (United Kingdom, Canada, Germany, Spain, Netherlands, and Switzerland), with results published between 1998 and 2010. The methodological quality of individual RCTs using the Cochrane risk of bias tool was rated by both reviews as generally low risk of bias, with higher risk for blinding of objective and subjective outcomes, and more uncertain risk for selection bias. The RCTs included participants with a history of treatment failures, although there was variation among studies in whether participants were currently

receiving treatment. The intervention in the RCTs consisted of supervised injectable DAM with flexible doses of methadone, although one also involved inhalable DAM and one involved injectable methadone. The control group in the RCTs consisted of oral methadone, except one compared to participants on a waiting list for methadone or current treatment. Six RCTs had a multi-component primary outcomes (such as retention, drug use, health, and social outcomes), and the UK study used street heroin use as the primary outcome.

The included studies completely overlapped, except the more recent review[17] excluded an older British trial that involved unsupervised DAM treatment. The reviewed SRs both found that DAM was an effective treatment for people who were unresponsive to standard treatments. Meta-analysis of primary outcomes demonstrated retention was higher for supervised injectable DAM compared with oral methadone (Ferri: RR 1.44 [CI 95% 1.19, 1.75]; Strang: 1.37 (1.03 to 1.83)) and there was a significant reduction in street heroin use (no meta-analysis).[16] However, there was no difference for mortality between treatments (Ferri and Strang: RR 0.65 [CI 95% 0.25, 1.69]).

Both reviews also concluded that DAM may be less safe than treatment with oral methadone, based on increased serious adverse events (SAE) (Ferri: RR 13.50 [CI 95% 2.55, 71.53]; Strang: 4.99 (1.66 to 14.99)), and recommended adequate supervision of the injectable opioid agonist treatment (herein referred to as siOAT).

RCTs not included in systematic reviews

Two additional RCTs involving injectable DAM that were published after the systematic reviews were conducted. One RCT was conducted in Canada [Oviedo 2016, EPHPP-Strong] and the other was in Belgium [Demaret 2016-EPHPP-Moderate].[4,18]

The Canadian trial (SALOME) compared injectable HDM with injectable DAM among people who had attempted previous treatment and were currently injecting opioids.[4] After six months, outcomes of street opioid use and urine markers for street heroin use in the HDM group were not inferior compared to the DAM group. There were fewer SAE in the HDM group (5 in HDM, 24 in DAM).

The Belgian study was designed similar to most previous studies,[18] except participants who used heroin by inhalation were also included. There was a significantly higher response in the DAM group at three, six, and nine months but not at 12 months, as defined by the primary composite endpoint (street heroin use, health, and criminal involvement). The authors determined that no SAEs were related to DAM administration.

RCT secondary analyses or sub-studies

We identified 20 articles that presented secondary analyses or sub-studies of using data from RCTs in the literature. These secondary analyses were not in the scope of previous systematic reviews so we have summarized them here.

Several studies reported significant findings among the RCT populations that supported DAM over oral methadone. These included a better treatment response among patients treated with DAM who had

high motivation at baseline,[30] reduced criminal activity,[37] cost-effectiveness (largely due to the reduced cost of criminal activity),[44,45] higher satisfaction scores for injectable treatment (on 5 of 8 items, not overall score),[26] health-related quality of life (HRQL),[29] a multiple component outcome of physical and mental health,[34] and heroin craving.[24] The trial in Spain was re-analyzed using different analysis methods and still found clinical superiority of DAM compared to oral methadone for primary outcomes.[33]

We found mixed results about treatment effects on other substance use. Some studies found significant benefit of DAM for reduced alcohol[32] and benzodiazepine use,[24] but another study found no additional benefit of DAM on wider drug use (crack/cocaine, benzodiazepines, and alcohol).[23]

There was not a significant advantage of DAM over oral methadone for females (based on illegal drug use,[25] clinical response[31]), for Indigenous participants,[50] or for participants with no previous maintenance experience (NPME).[28] Additional studies found a reduced effect of DAM among people with psychiatric comorbidity,[36] no benefit of DAM treatment over methadone for physical or mental health scores on the Short Form Health Survey (SF-36).[23]

Several studies were published on comparisons between HDM and DAM. Pilot results from the NAOMI trial in Canada found similar retention, a decrease in illicit drug use, and few safety issues.[19] Secondary analyses of SALOME, the only full trial comparing injectable HDM and DAM, found that Indigenous participants receiving either treatment had a significant improvement in use of street heroin, opioids, or crack cocaine, as well as illegal activities.[21] Further, there were no significant differences in treatment outcomes between men and women, except better psychological health at six months among women.[22] Finally, exploratory analysis of patient safety controlling for dose and attendance patterns, found the participants receiving HDM were less likely to have an AE or SAE compared to DAM.[20] The authors state that AEs can be safely mitigated in a supervised setting, which is the current model of treatment delivery for HDM and DAM.

RCT follow-up studies

There were four studies that presented results of longer-term follow-up among participants in some of the RCTs described above, and compared individuals using injectable DAM with other treatment groups or people who discontinued treatment. These reported on outcomes after trial completion: one year in Germany,[27,38] two years in Spain,[40] and three years in Netherlands.[39]

The main significant findings of these studies were that those who continued receiving DAM had a better treatment response on a composite outcome score,[39] as well as significantly lower street heroin use, decrease in Opiate Treatment Index HIV risk scores, Addiction Severity Index Psychiatric Composite Score, and SF12 Mental Health scores.[40] Further, individuals who had an unsatisfactory clinical outcome on methadone and chose to switch to DAM after the trial, had significant improvements in heroin use in the second year.[38] However, individuals treated with DAM performed significantly worse under certain cognitive testing conditions (stress and monotony).[27]

Cross-sectional studies

We identified three relevant cross sectional studies that had significant results favoring DAM over other treatments. These found patients treated with injectable DAM were significantly less likely to currently use benzodiazepines (NOS 6/10),[46] less likely to have a fentanyl-positive urine drug screens,[47] and less likely to have used street heroin in the past month.[48]

Qualitative studies

Our review identified three studies (one rated as CASP 9/9,[42] and two rated as CASP-Qual 8/9.[41,43]) that presented qualitative findings among RCT participants receiving DAM treatment in Spain,[43]and in Canada[41], and participants in the Canadian trial receiving intervention or control treatments.[42] In the Spanish study, participants and family members began to perceive heroin addiction as a chronic illness, and heroin (i.e., DAM) as a legal medicine.[43] Some found it less appealing injecting in a clinical environment, had difficulty having "normal" jobs, and dissatisfaction using a nightly dose of methadone. The participants reported an improved financial situation, relationships, and health, as well as hope for the future. The Canadian study among patients treated with DAM described a benefit of forming a relationship with staff and having a collective identity with others at the clinic.[41] The Canadian study that interviewed intervention and control participants found those with supervised injectable treatment reported this model gave them stability, but found the schedule demanding. Those who received methadone were disappointed about not receiving an injectable treatment, but appreciated receiving an adequate dose and other services.[42]

Discussion and Conclusions

Our review found the available literature indicates supervised injectable opioid agonist treatment is effective for several outcomes compared with oral methadone alone. This includes retention in treatment, reducing the use of street drugs, and reducing illegal activities. These studies were generally conducted among individuals who previously did not have a satisfactory response to medication-assisted treatment for opioid use disorder. Cost-effectiveness studies suggest siOAT is cost-effective compared to methadone in this group due to decreased criminal activity. However, siOAT is associated with increased serious adverse events that could be managed in a supervised setting.[20]

Nearly all of the identified literature focuses on supervised injectable DAM, although one trial of injectable HDM found it was not inferior to DAM treatment and had fewer serious adverse events.[4] Further research on injectable HDM is needed to better understand this type of treatment.

DAM or HDM as an injectable opioid agonist treatment option is nonetheless controversial.[51] Others have published on concerns about expanding injectable DAM treatment in Canada, including its potential to detract from much needed improvements in the quality and accessibility of standard treatments with methadone and buprenorphine, as well as the safety concerns of DAM treatment.[52] However, a response from authors involved in the Canadian NAOMI trial advocate for standard treatments to remain first-line, but for DAM to be available as second-line treatment.[53] They argued that patients treated with DAM in a supervised setting would have serious adverse events treated immediately, in contrast with patients who

continued to use street heroin unsupervised.[53] A number of patients prescribed DAM also later switched to methadone treatment, indicating that DAM may have had a role to engage them in treatment.

Additional barriers to the wider use of this treatment may include direct costs related to siOAT, and ideological views about opioid use disorder (e.g., goal of abstinence from all opioids, or negative views of individuals with opioid use disorder "deserving" a high-cost treatment).[51]

Non-significant results comparing DAM treatment with methadone among sub-populations such as women, Indigenous patients, and individuals with psychiatric comorbidity may reflect remaining equity issues. Alternatively, the previous statistical analyses may have been under-powered to detect a difference between treatments. The application of this treatment among various sub-groups will need further investigation.

Limitations of our review include its rapid review methods, including our emphasis to review evidence from systematic reviews rather than primary studies. We limited the dates for our literature search to articles published from 2007 to present. Further, the inclusion and interpretation of studies that were not primary results of RCTs could introduce bias due to unmeasured confounders not controlled by the randomization process.

This rapid evidence review has found evidence to support the effectiveness of siOAT with DAM or HDM as a treatment for people with opioid use disorder who have previously not had a satisfactory response to standard treatment. It may also be an important approach for engaging people in treatment who continue to inject opioids and would not otherwise participate in treatment.

Implications for Practice

As opioid-related harms increase in the population, many have called for additional treatment options for opioid use disorder. The current evidence supports siOAT as a second-line treatment. Recent policy changes in Canada allow physicians to apply for permission to prescribe DAM and permit jurisdictions to request the import of medical DAM for urgent public health reasons. These changes may facilitate the availability of this treatment option. Further evaluation of the emerging practice with siOAT in Canada can assist with understanding implementation issues and informing program decisions.

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Specifications and Limitations of Evidence Brief

The purpose of this Evidence Brief is to investigate a research question in a timely manner to help inform decision making. The Evidence Brief presents key findings, based on a systematic search of the best available evidence near the time of publication, as well as systematic screening and extraction of the data from that evidence. It does not report the same level of detail as a full systematic review. Every attempt has been made to incorporate the highest level of evidence on the topic. There may be relevant individual studies that are not included; however, it is important to consider at the time of use of this brief whether individual studies would alter the conclusions drawn from the document.

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