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Acknowledgments:

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada’s health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.
Research Questions

1. What is the comparative clinical effectiveness of sustained release oral morphine (SROM) versus standard of care (i.e., methadone or buprenorphine/naloxone) in opioid use disorder?

2. What is the comparative clinical effectiveness of injectable hydromorphone or prescription diacetylmorphine versus standard of care (i.e., methadone or buprenorphine/naloxone) in opioid abuse disorder?

3. What is the comparative clinical effectiveness of SROM versus injectable hydromorphone or prescription diacetylmorphine in opioid use disorder?

4. What is the cost-effectiveness of SROM in opioid use disorder?

5. What is the cost-effectiveness of injectable hydromorphone or prescription diacetylmorphine in opioid use disorder?

6. What are the evidence-based guidelines regarding the use of SROM, injectable hydromorphone or prescription diacetylmorphine for opioid abuse treatment?

Key Findings

Four systematic reviews, seven randomized controlled trials, two non-randomized studies and one economic evaluation were identified regarding sustained release oral morphine, injectable hydromorphone, or prescription diacetylmorphine for opioid use disorder. Additionally, one evidence-based guideline was identified regarding sustained release oral morphine, injectable hydromorphone, or prescription diacetylmorphine for opioid use disorder.

Methods

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were 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, 2012 and March 31, 2017. Internet links were provided, where available.

Selection Criteria

One reviewer screened citations and selected studies based on the inclusion criteria presented in Table 1.
Table 1: Selection Criteria

| Population | Adult (18 years and older) patients requiring treatment for opioid use disorder; Subgroups of interest:  
|            | • Pregnant women  
|            | • Patients who have contraindications to or have failed conventional treatment (i.e. refractory to conventional treatment) |

| Intervention | Q1.3-4.6: Sustained release oral morphine (SROM)  
|             | Q2.5.6: Injectable hydromorphone or prescription diacetylmorphine (also referred to as heroin-assisted therapy [HAT]) |

| Comparator | Q1-2: Standard of care (i.e., buprenorphine/naloxone, methadone)  
|           | Q3: Injectable hydromorphone or prescription diacetylmorphine (or HAT)  
|           | Q4-5: Placebo; Standard of care; Alternative interventions of interest (i.e., injectable hydromorphone, SROM, prescription diacetylmorphine)  
|           | Q6: No comparator |

| Outcomes | Q1-3: Clinical effectiveness (e.g., retention in treatment, heroin use, use of other drugs of abuse [including opioids]), quality of life, withdrawal symptoms, mental health scores; Safety (e.g., mortality, toxicity, adverse events)  
|          | Q4-5: Cost effectiveness outcomes (e.g., cost per quality adjusted life year, cost per health benefit gained)  
|          | Q6: Evidence based guideline recommendations regarding the appropriate use (including role of witness ingestion, appropriateness as a substitute for standard of care, dosing regimens, settings of use) of the interventions of interest in patients with opioid use disorder |

| Study Designs | Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, economic evaluations, evidence-based guidelines |

Results

Rapid Response reports are organized so that the higher quality evidence is presented first. Therefore, health technology assessment reports, systematic reviews, and meta-analyses are presented first. These are followed by randomized controlled trials, non-randomized studies, economic evaluations, and evidence-based guidelines.

Four systematic reviews, seven randomized controlled trials, two non-randomized studies and one economic evaluation were identified regarding sustained release oral morphine, injectable hydromorphone, or prescription diacetylmorphine for opioid use disorder. Additionally, one evidence-based guideline was identified regarding sustained release oral morphine, injectable hydromorphone, or prescription diacetylmorphine for opioid use disorder. No relevant health technology assessments were identified.

Additional references of potential interest are provided in the appendix.

Overall Summary of Findings

Intervention Compared to Standard Care

*Sustained/Slow-Release Oral Morphine (SROM)*
Three systematic reviews\textsuperscript{1-3,4} were identified regarding the use of slow-release oral morphine for opioid use disorders. One systematic review\textsuperscript{1} was focused on SROM maintenance in pregnant women.

The authors of one systematic review\textsuperscript{1} concluded that slow-release morphine (SRM) was more effective than methadone for abstinence from heroin use for pregnant women, with no side effects in the mother.\textsuperscript{1} However, in the children, there was one case of obstructive apnea and one case of central apnea in the SRM and methadone groups, respectively.\textsuperscript{1} The authors could not conclude that SRM is more effective than methadone in all outcomes measured.\textsuperscript{1}

The authors of a second systematic review\textsuperscript{4} evaluated the efficacy of SROM as a treatment for opioid dependence. SROM appeared to equal to other opioid dependence treatments for the severity of dependence, mental health, and social functioning; SROM however, appeared to be better with regards to severity of opiate withdrawal symptoms when compared with methadone.\textsuperscript{4} SROM was also well tolerated, and appeared to reduce cravings, depression symptomology, physical complaints, and anxiety symptoms.\textsuperscript{4} Quality of life appeared unchanged or worse in patients using SROM when compared to usual treatments: finances, family, and overall satisfaction were better in patients treated with usual care than in SROM patients.\textsuperscript{4} Medically adverse events were higher in SROM treated patients than in other opioid maintenance treatments.\textsuperscript{4} The authors of a third systematic review\textsuperscript{4} included Ferri et al\textsuperscript{6} in their analysis, noting that none of the studies were in an office-based setting.

One study found retention rates for SROM maintenance treatment appeared to be quite good.\textsuperscript{4}

Five randomized controlled trials (RCT)\textsuperscript{6-9,11} were identified regarding the use of SROM in patients with opioid use disorder. All of the identified RCTs used methadone as a comparator.\textsuperscript{6-9} One RCT\textsuperscript{6} examined self-reported cravings for both heroin and cocaine for patients on either methadone or SROM maintenance treatments. General heroin cravings were found to be lower in the SROM treatment group; however, cocaine craving levels did not differ significantly between treatments.\textsuperscript{6} Fewer cravings for heroin, along with higher treatment satisfaction and lower mental stress was also found in another RCT.\textsuperscript{9} Mental symptoms and satisfaction with treatment was the focus for another RCT examining SROM and methadone outcomes, finding that SROM treatment was associated with statistically significantly better mental symptoms and treatment satisfaction.\textsuperscript{7} However, there were no significant differences in drug or alcohol use between the treatment groups.\textsuperscript{7} In another RCT, SROM was found to be non-inferior to methadone treatment, and retention in treatment was not different between the groups.\textsuperscript{8} Both SROM and methadone are well tolerated,\textsuperscript{9} and safety outcomes do not appear to differ between treatments.\textsuperscript{8}

Finally, two non-randomized studies were identified regarding SROM use in opioid dependent patients;\textsuperscript{12-13} one study focused on pregnant women,\textsuperscript{12} and one focused on treatment refractory patients.\textsuperscript{13} The authors of one RCT\textsuperscript{12} comparing SROM with buprenorphine and methadone found that buprenorphine medicated women had less concomitant benzodiazepine consumption than SROM or methadone treated women. No difference in quality of life was seen between the three treatment groups.\textsuperscript{12} The authors of another non-randomized study\textsuperscript{13} found that patients disliked and found an intolerance to methadone treatment, but felt positively about SROM and believed it would help them lower their diamorphine doses. Patients reported fewer cravings, improved sleep, and improved well-being after switching from methadone treatment to SROM.\textsuperscript{13}
Heroin Assisted Therapy (HAT)/Injectable Hydromorphone/Prescription Diacetylmorphine

One systematic review examined retention rates in varying opioid maintenance treatments among treatment-refractory patients, including HAT. The authors concluded that HAT was associated with better retention rates than methadone.3

Three RCTs5,10-11 were identified that examine the use of hydromorphone, prescription diacetylmorphine, or HAT in opioid dependent patients. All of the identified RCTs used methadone as a comparator.5,10-11 HAT treated patients who were refractory to methadone treatment reported significantly greater improvements on street heroin use,5,10 physical health, and mental health when compared to methadone-treated patients.5 Heroin cravings were reduced in one RCT through the use of HAT, but not in the methadone maintenance treatment group.10

Sustained-Released Oral Morphine Compared to Heroin Assisted Therapy

SROM was compared with oral diacetylmorphine and methadone in an inpatient setting in one identified RCT.11 The authors found no statistically significant difference between any treatment type on any outcome studied.11

Cost-Effectiveness Studies

One economic evaluation was identified regarding cost-effectiveness of diacetylmorphine when compared to methadone for treatment-refractory opioid dependent patients.14 The time periods compared were 1-year, 5-year, 10-year, and lifetime horizons. Diacetylmorphine was the superior treatment in all time horizons compared to methadone, mostly due to a reduction in criminal activity costs.14 The probability of diacetylmorphine being cost effective was 76% at a willingness to pay of $0, and 95% at a willingness to pay $100,000 per quality-adjusted life years gained.

Evidence-Based Guidelines

One evidence-based guideline was identified regarding SROM, injectable hydromorphone, and prescription diacetylmorphine for opioid use disorder.15 Strict policies to prevent abuse of SROM should be used when prescribing this to patients, including urine drug testing. Only the once-daily, 24 hour formulations of SROM have been tested in clinical trials, and therefore, the authors recommend against using any other formulation of SROM to treat patients.

Treatment refractory patients to methadone may benefit from injected hydromorphone or prescription diacetylmorphine in a structured clinical setting, however the authors noted that these treatments were out of the scope of this particular guideline and therefore they could not make definitive recommendations.15

References Summarized

Health Technology Assessments

No literature identified.

Systematic Reviews and Meta-analyses
Pregnant Women


Other Populations

   Available from:
   https://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=2350
   See: Pharmacological Therapies

   PubMed: PM26467975

   PubMed: PM23740540

Randomized Controlled Trials

   PubMed: PM25832522

   PubMed: PM25679130

   PubMed: PM25427944

   http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4226326
   PubMed: PM24304412


Non-Randomized Studies

Pregnant Women


Treatment-Refractory Patients


Economic Evaluations


Guidelines and Recommendations


See: III) Alternative Agents
Appendix — Further Information

Previous CADTH Reports

See: Detoxification and opioid withdrawal management

Randomized Controlled Trials – Alternate Comparator

PubMed: PM27049826

Review Articles

PubMed: PM23145768