

CADTH RAPID RESPONSE REPORT: SUMMARY OF ABSTRACTS

Sustained Release Oral Morphine, Injectable Hydromorphone, and Prescription Diacetylmorphine for Opioid Use Disorder: Clinical and Cost-Effectiveness, and Guidelines

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Authors: Charlotte Wells, Sarah Jones

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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: <ul style="list-style-type: none"> • 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^{1-2,4} were identified regarding the use of slow-release oral morphine for opioid use disorders. One systematic review¹ was focused on SRM maintenance in pregnant women.

The authors of one systematic review¹ 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.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.¹ The authors could not conclude that SRM is more effective than methadone in all outcomes measured.¹

The authors of a second systematic review⁴ evaluated the efficacy of SRM as a treatment for opioid dependence. SRM appeared to equal to other opioid dependence treatments for the severity of dependence, mental health, and social functioning; SRM however, appeared to be better with regards to severity of opiate withdrawal symptoms when compared with methadone.⁴ SRM was also well tolerated, and appeared to reduce cravings, depression symptomology, physical complaints, and anxiety symptoms.⁴ Quality of life appeared unchanged or worse in patients using SRM when compared to usual treatments; finances, family, and overall satisfaction were better in patients treated with usual care than in SRM patients.⁴ Medically adverse events were higher in SRM treated patients than in other opioid maintenance treatments.⁴ The authors of a third systematic review² included Ferri et al⁴ in their analysis, noting that none of the studies were in an office-based setting.

One study found retention rates for SRM maintenance treatment appeared to be quite good,⁴

Five randomized controlled trials (RCT)^{6-9,11} were identified regarding the use of SRM in patients with opioid use disorder. All of the identified RCTs used methadone as a comparator.⁶⁻⁹ One RCT⁶ examined self-reported cravings for both heroin and cocaine for patients on either methadone or SRM maintenance treatments. General heroin cravings were found to be lower in the SRM treatment group; however, cocaine craving levels did not differ significantly between treatments.⁶ Fewer cravings for heroin, along with higher treatment satisfaction and lower mental stress was also found in another RCT.⁹ Mental symptoms and satisfaction with treatment was the focus for another RCT examining SRM and methadone outcomes, finding that SRM treatment was associated with statistically significantly better mental symptoms and treatment satisfaction.⁷ However, there were no significant differences in drug or alcohol use between the treatment groups.⁷ In another RCT, SRM was found to be non-inferior to methadone treatment, and retention in treatment was not different between the groups.⁸ Both SRM and methadone are well tolerated,⁹ and safety outcomes do not appear to differ between treatments.⁸

Finally, two non-randomized studies were identified regarding SRM use in opioid dependent patients,¹²⁻¹³ one study focused on pregnant women,¹² and one focused on treatment refractory patients.¹³ The authors of one RCT¹² comparing SRM with buprenorphine and methadone found that buprenorphine medicated women had less concomitant benzodiazepine consumption than SRM or methadone treated women. No difference in quality of life was seen between the three treatment groups.¹² The authors of another non-randomized study¹³ found that patients disliked and found an intolerance to methadone treatment, but felt positively about SRM and believed it would help them lower their diacetylmorphine doses. Patients reported fewer cravings, improved sleep, and improved well-being after switching from methadone treatment to SRM.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.³ The authors concluded that HAT was associated with better retention rates than methadone.³

Three RCTs^{5,10-11} 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

1. Minozzi S, Amato L, Bellisario C, Ferri M, Davoli M. Maintenance agonist treatments for opiate-dependent pregnant women. *Cochrane Database Syst Rev* [Internet]. 2013 Dec 23[cited 2017 Apr 10];(12):CD006318. Available from: <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD006318.pub3/full>

Other Populations

2. Chou R, Korthuis PT, Weimer M, Bougatsos C, Blazina I, Zakher B, et al. Medication-Assisted treatment models of care for opioid use disorder in primary care settings [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2016 Dec. [cited 2017 Apr 10]. (AHRQ Comparative Effectiveness Technical Briefs). Available from: <https://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=2350>
See: Pharmacological Therapies
3. Timko C, Schultz NR, Cucciare MA, Vittorio L, Garrison-Diehn C. Retention in medication-assisted treatment for opiate dependence: A systematic review. *J Addict Dis.* 2016;35(1):22-35.
[PubMed: PM26467975](#)
4. Ferri M, Minozzi S, Bo A, Amato L. Slow-release oral morphine as maintenance therapy for opioid dependence. *Cochrane Database Syst Rev.* 2013 Jun 5;(6):CD009879.
[PubMed: PM23740540](#)

Randomized Controlled Trials

5. Demaret I, Quertemont E, Litran G, Magoga C, Deblire C, Dubois N, et al. Efficacy of Heroin-assisted treatment in Belgium: A randomised controlled trial. *Eur Addict Res.* 2015;21(4):179-87.
[PubMed: PM25832522](#)
6. Falcato L, Beck T, Reimer J, Verthein U. Self-reported cravings for heroin and cocaine during maintenance treatment with slow-release oral morphine compared with methadone: a randomized, crossover clinical trial. *J Clin Psychopharmacol.* 2015 Apr;35(2):150-7.
[PubMed: PM25679130](#)
7. Verthein U, Beck T, Haasen C, Reimer J. Mental symptoms and drug use in maintenance treatment with slow-release oral morphine compared to methadone: results of a randomized crossover study. *Eur Addict Res.* 2015;21(2):97-104.
[PubMed: PM25427944](#)
8. Beck T, Haasen C, Verthein U, Walcher S, Schuler C, Backmund M, et al. Maintenance treatment for opioid dependence with slow-release oral morphine: a randomized cross-over, non-inferiority study versus methadone. *Addiction* [Internet]. 2014 Apr [cited 2017 Apr 10];109(4):617-26. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4226326>
[PubMed: PM24304412](#)

9. Hammig R, Kohler W, Bonorden-Kleij K, Weber B, Lebentrau K, Berthel T, et al. Safety and tolerability of slow-release oral morphine versus methadone in the treatment of opioid dependence. *J Subst Abuse Treat.* 2014 Oct;47(4):275-81.
[PubMed: PM25064422](#)
10. Blanken P, Hendriks VM, Koeter MW, van Ree JM, van den BW. Craving and illicit heroin use among patients in heroin-assisted treatment. *Drug Alcohol Depend.* 2012 Jan 1;120(1-3):74-80.
[PubMed: PM21782351](#)
11. Colom FJ, Casas M, Perez de Los CJ, Del RM, Roncero C, Castells X, et al. Feasibility of double-blind clinical trials with oral diacetylmorphine: a randomized controlled phase II study in an inpatient setting. *Eur Addict Res.* 2012;18(6):279-87.
[PubMed: PM22854605](#)

Non-Randomized Studies

Pregnant Women

12. Metz VE, Comer SD, Wuerzl J, Pribasnik A, Fischer G. Characteristics and quality of life of opioid-dependent pregnant women in Austria. *Arch Womens Ment Health* [Internet]. 2014 Dec [cited 2017 Apr 10];17(6):529-39. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4239179>
[PubMed: PM25023716](#)

Treatment-Refractory Patients

13. Bond AJ, Reed KD, Beavan P, Strang J. After the randomised injectable opiate treatment trial: post-trial investigation of slow-release oral morphine as an alternative opiate maintenance medication. *Drug Alcohol Rev.* 2012 Jun;31(4):492-8.
[PubMed: PM21919979](#)

Economic Evaluations

14. Nosyk B, Guh DP, Bansback NJ, Oviedo-Joekes E, Brissette S, Marsh DC, et al. Cost-effectiveness of diacetylmorphine versus methadone for chronic opioid dependence refractory to treatment. *CMAJ* [Internet]. 2012 Apr 3 [cited 2017 Apr 11];184(6):E317-E328. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3314060>

Guidelines and Recommendations

15. A guideline for the clinical management of opioid use disorders [Internet]. Victoria (BC): Guidelines & Protocols Advisory Committee; 2017. [cited 2017 Apr 11]. Available from: http://www2.gov.bc.ca/assets/gov/health/practitioner-pro/bc-guidelines/bc_oud_guidelines.pdf
See: III) Alternative Agents

Appendix — Further Information

Previous CADTH Reports

16. Treatment for opioid dependency: A review of guidelines [Internet]. Ottawa (ON): CADTH; 2012 Sep 14. (CADTH rapid response report: summary with critical appraisal). Available from: <https://cadth.ca/sites/default/files/pdf/htis/sept-2012/RC0390%20Opioid%20Dependency%20Guidelines%20Final.pdf>
See: Detoxification and opioid withdrawal management

Randomized Controlled Trials – Alternate Comparator

17. Oviedo-Joekes E, Guh D, Brissette S, Marchand K, MacDonald S, Lock K, et al. Hydromorphone Compared With Diacetylmorphine for Long-term Opioid Dependence: A Randomized Clinical Trial. *JAMA Psychiatry*. 2016 May 1;73(5):447-55.
[PubMed: PM27049826](#)

Review Articles

18. Garcia-Portilla MP, Bobes-Bascaran MT, Bascaran MT, Saiz PA, Bobes J. Long term outcomes of pharmacological treatments for opioid dependence: does methadone still lead the pack? *Br J Clin Pharmacol*. [Internet] 2014 Feb [cited 2017 Apr 11];77(2):272-84. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4014027>
[PubMed: PM23145768](#)