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NONTRADITIONAL ALCOHOL AND OPIOID AGONIST TREATMENT INTERVENTIONS

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Synopsis

Despite the availability of effective medications and psychosocial interventions for the management of a substance use disorder (SUD), some individuals repeatedly fail the most aggressive treatment regimens. For such individuals, alternative treatment options exist seeking to mitigate the negative consequences of the use of harmful substances. Participation in a managed alcohol program or the use of sustained release oral morphine or injectable opioid agonist treatment, are examples of such non-standard approaches. This chapter will review the available evidence of these treatment modalities.

Keywords

Managed alcohol; injectable opioids; severe opioid use disorder; severe alcohol use disorder; sustained release oral morphine

INTRODUCTION

A spectrum of severity exists among individuals with alcohol and/or drug use disorders. Some may repeatedly fail the most aggressive standard treatment regimens. For such individuals, who can experience the worst medical complications and intensive utilization of health services, nonstandard approaches should be considered to mitigate the negative consequences of the use of harmful substances.

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These approaches include managed alcohol programs (MAPs), sustained-release oral morphine (SROM) as an opioid agonist treatment, injectable opioid agonist treatment (OAT), and safe injecting facilities. These modalities fall outside the realm of standard medical care, and may not currently be legal in certain locales, but are adopted with some success in other regions. Understanding the current evidence of effectiveness for these nontraditional treatment approaches and the specific populations addressed was the goal of this review.

MANAGED ALCOHOL PROGRAMS

The goal of MAPs is both to eliminate barriers for shelter among individuals with an alcohol use disorder (AUD), which has historically proven challenging, and to provide access to alcohol in a supervised, controlled environment to mitigate the potential harms of ongoing use.¹ AUD is a common comorbidity among individuals who are unstably housed, with estimates approximating between 53% and 73%.^{2,3} Such individuals are subject to poor health and social outcomes, including criminal justice system encounters, chronic medical illness, prolonged hospital stays,⁴ and high rates of mortality.⁵ For many, conventional treatment approaches for the management of an AUD has proven unsuccessful, and consideration of participation in an MAP can offer an effective harm-reduction strategy.

To date, MAPs have been described in several countries, including Canada, Ireland, Norway, and Australia.⁶ Eligibility criteria may vary, but participation in an MAP is generally reserved for those who are chronically homeless, have a severe AUD (using criteria from the Diagnostic and Statistical Manual of Mental Disorders (DSM) IV or V), have demonstrated evidence of harm to self and community, and for whom abstinence-based programs have failed or been refused.⁷ Most MAPs reported in the literature to date have described the use of an MAP in a community-based residential setting,⁸ although non- housing-based programs have been reported as well.⁹ Community MAPs are generally small, ranging from 8 to 35 participants.^{8–10} Although the operational details vary among different programs, MAPs generally provide alcohol in relatively small doses at regular intervals, typically 1 standard drink (SD) per hour administered by a nurse or other staff worker, with total daily amounts ranging from 9 to 16 SD per day.⁶

Several positive outcomes have been reported in 3 Canadian pilot studies on community MAPs.^{7,8,11} A reduction in alcohol consumption has been reported in 2 studies: an average decrease in daily alcohol consumption among 10 MAP participants, from 45.6 ± 28.8 SDs (pre-MAP) to 8.3 ± 3.5 SDs (during MAP)⁷ (representing a daily decrease of approximately 38 sixteen-ounce pints of beer) and a reduction in alcohol consumption over a 6-month period of MAP participation (n = 18) from an average of 19.1 SDs at MAP initiation to 10.4 SDs 6 months later.¹¹ In contrast, a small-scale study of 7 participants reported no overall change in alcohol consumption during 9 months.⁸ Despite mixed results for the effect of MAP on quantity of alcohol consumption, importantly all 3 studies reported a reduction in self-reported intake of non-beverage alcohol, such as mouthwash or rubbing alcohol.^{7,8,11} The potential for underreporting of non-MAP consumption (ie, alcohol obtained independent of an MAP) has appropriately been cited as a study limitation.^{8,12}

Other important health outcomes related to participation in an MAP have been evaluated. One study (n = 17) demonstrated an improvement in emergency health service utilization with a reduction in monthly emergency room visits following program enrollment (0.79 ± 1.25 to 0.51 ± 1.17 ; $P = .004$).⁷ Improved engagement with both psychiatric¹³ and general medical care has also been demonstrated among MAP participants.⁷ Subjective reports from MAP participants noted an improvement in mental health and reduction in psychosocial harms,^{8,11} whereas MAP program staff reported less volatility and hostility among participants after program enrollment.⁸ Trends of liver enzymes among MAP participants have shown mixed results, with one study demonstrating a reduction,¹¹ another reporting stability,⁷ and a third demonstrating an increase⁸ following MAP enrollment.

Other benefits have been reported with MAP participation: a reduction in police reports (1.07 ± 0.66 per month to 0.52 ± 0.68 ; $P = .018$)⁷; and crime reduction from 4.77 ± 7.83 days to 2.79 ± 2.32 days per 100 days.¹² Community MAPs often provide shelter for those unstably housed. Qualitative studies of these participants have demonstrated an improved sense of community, safety, and quality of life,¹⁴ with the setting itself being capable of both facilitating recovery¹⁵ and acting as an entry point for some individuals requiring end-of-life care.¹⁶ Retention rates in all 3 Canadian MAP studies were high, and ranged between 82% and 100% (with study durations of between 6 months and 2 years).^{7,8,11} Of note, however, a 2012 Cochrane Review failed to identify any studies eligible for inclusion and thus was unable to determine the efficacy of MAP,⁶ suggesting further research with a focus on the development of relevant measures of MAP success.

Similar MAP programs exist in acute care settings. For example, St. Paul's Hospital located in Vancouver, Canada, has an in-hospital MAP that uses a formalized protocol to guide the continuation of alcohol administration for individuals enrolled in a community MAP, provided no medical contraindication exists to do so. Furthermore, in this setting, newly initiated in-hospital MAP has occasionally been prescribed as a harm-reduction approach to mitigate the potential negative consequences of ongoing alcohol use in an unsupervised fashion (eg, consumption of non-beverage alcohol, or quantities of alcohol in excess of what would be provided as part of MAP) or lack of access to alcohol all together (eg, leaving hospital against medical advice). Although regular clinical assessments and the use of benzodiazepines remains the standard of care for inpatient alcohol withdrawal syndrome, hospital MAP may offer benefits similar to those described in community MAP settings to select high-risk patients. Such an approach, however, is not without challenges. Particularly problematic is how to effectively manage a community MAP patient who presents to hospital with a medical complication related to alcohol consumption. Although discontinuing MAP in-hospital is a reasonable first step, formulating and engaging such an individual in his or her medical treatment plan can prove problematic. Furthermore, what to do with an individual newly initiated on MAP in-hospital at the time of discharge also can be a challenge because community MAPs are frequently at capacity. To date, provision of an MAP in an acute care setting has exposed numerous ethical and medico-legal concerns, and little is known about the potential benefits of MAP in this setting.

In summary, although not currently available in the United States, community MAPs do exist in several other countries as an attempt to reduce the harms associated with severe

AUD among participants who have been unsuccessfully stabilized with conventional pharmacologic or psychosocial treatment options. Many of these programs operate in a setting that concurrently provides MAP participants with access to low-barrier housing. Although beyond the scope of this review, the value of these housing interventions from a public health perspective can be significant and should not be overlooked. To date, several observational studies evaluating community MAPs have demonstrated a reduction in alcohol consumption, a reduction in emergency department presentations and criminal activity, as well as improved health and quality of life among participants. Given the study sample sizes and potential for reporting bias, however, these results should be interpreted with caution. To date, no randomized controlled trials have been undertaken to determine the effectiveness of MAP in either community or acute care settings; individuals most likely to benefit from MAP are unclear. Furthermore, to our knowledge, no economic evaluation of MAPs currently exists. Further research is needed to address these important questions.

OPIOID AGONIST TREATMENT

Use of traditional opioid agonist medications (ie, buprenorphine or methadone) for the treatment of opioid use disorder (OUD) may not be successful, as a consequence of medication adverse effects or repeated unsuccessful treatment attempts. For such individuals, alternative treatment options could be considered to facilitate patient engagement in care and optimize treatment outcomes. These approaches are not currently legal in the United States, although they merit review given the current evidence and the opioid overdose epidemic in the United States.

Slow Release Oral Morphine (SROM)

SROM is an alternative treatment option with limited evidence to suggest benefit for the treatment of OUD.^{17–21} A 2013 Cochrane Review, which included 3 randomized controlled trials, found no significant difference in treatment retention for SROM when compared with methadone but a higher incidence of adverse events.¹⁹ Since this review, additional studies focused on SROM have been published. A randomized, non-inferiority, crossover study demonstrated SROM to be non-inferior to methadone (n = 157) for the proportion of heroin-positive urine samples.¹⁷ A randomized controlled trial of participants previously treated with methadone (n = 276) reported SROM to be an effective, well-tolerated treatment option for OUD with a beneficial side-effect profile compared with methadone.²¹ The study noted a shorter QTc interval on electrocardiogram, higher treatment satisfaction, and a reduction in mental stress and heroin cravings among participants being prescribed SROM compared with methadone. Similar findings were noted in 2 additional studies.^{18,20} Furthermore, among 67 patients who were intolerant to methadone or experienced inadequate withdrawal suppression with its use, 1 multicenter study demonstrated the feasibility and tolerability of transitioning from methadone to SROM with several measurable improvements being subsequently observed (eg, a reduction in opioid withdrawal symptoms, reduced cravings, and fewer psychological problems)²² The possible explanations for these outcomes were not discussed in detail in the studies included herein and warrant further research.

Despite preliminary research suggesting SROM to be a beneficial alternative treatment option for OUD, no recommendations currently exist in the United States endorsing SROM's use for this purpose, and in fact, such a practice currently remains illegal. In British Columbia, Canada, authors of the Guideline for the Clinical Management of Opioid Addiction do endorse SROM as a treatment option for patients with OUD who have been unsuccessful with or who have contraindications to first-line and second-line treatment options.^{23,24} Specific indications and contraindications for SROM treatment according to the guideline can be found in Table 1. Furthermore, use of only the once-daily 24-hour formulation of SROM is endorsed by the guideline and the importance of daily witnessed ingestion is emphasized. Additionally, the guideline demonstrates how the provision of SROM can be seamlessly integrated into Canada's existing health care infrastructure, as eligible patients are assessed and evaluated in a clinic setting with daily witnessing of the medication occurring at a pharmacy (as occurs currently with methadone).

Specific details regarding induction and dosing of SROM can be found in Appendix 3 of the guideline.²⁴ To summarize, a starting dose of 30 to 60 mg of SROM is recommended, with titration occurring every 48 hours according to an individual's withdrawal symptoms. For patients transitioning from methadone to SROM, a conversion factor of 1:4 can be applied (eg, 60 mg methadone = 240 mg SROM). Current literature reports a mean SROM daily dose range between 235 and 791 mg, with the full range of SROM being between 60 and 1200 mg/d. Given the paucity of literature regarding best practice for SROM treatment for OUD and the risk for overdose and diversion, close observation and follow-up with the patient is essential until a stable dose is achieved.

SROM treatment efficacy should be based on several outcomes, including the alleviation of opioid withdrawal symptoms and a reduction or elimination of illicit opioid use and cravings. Monitoring for compliance and/or ongoing use of illicit opiates is particularly challenging, however. The value of quantitative, point-of-care urine drug tests is limited, given SROM and heroin use will give a positive test result, but can provide useful information when the result is negative for opiates (indicating diversion) or positive for fentanyl. Given the challenges associated with ongoing monitoring for heroin use, the potential for diversion and risk for lethality among non-tolerant individuals, the guideline recommends indefinite daily witnessed ingestion of SROM (ie, no take-home doses) (see Appendix 4 of the guideline). Only in exceptional circumstances in which a patient has demonstrated high clinical stability or when daily witnessed ingestion presents a significant barrier to treatment can graduated take-home dosing be considered.

Injectable Opioid Agonist Treatment

Injectable opioid agonist therapy is another option for the treatment of OUD when first-line treatment is not effective (eg, buprenorphine, methadone). Individuals with severe OUD who inject opioids but have not benefited from first-line or second-line oral OAT despite repeated treatment attempts are generally the population for which injectable OAT may be considered.

Injectable diacetylmorphine (ie, prescription heroin) is one injectable OAT option currently available for select populations in Denmark, Germany, the Netherlands, Canada, and

Switzerland for the treatment of heroin addiction.^{25–27} Among individuals with long-term (ie, greater than 2 years) daily heroin use with previous treatment failures in outpatient settings, meta-analyses of clinical trials have demonstrated the efficacy of diacetylmorphine in comparison with methadone for the treatment of an OUD.²⁸ More specifically, use of injectable diacetylmorphine resulted in a reduction in self-reported illicit heroin use, criminal activity, and involvement in sex work, as well as improved overall health and social functioning.^{28–30} These meta-analyses include a 2011 Cochrane Review that examined 8 randomized controlled trials and found that supervised injection of diacetylmorphine, prescribed alone or combined with flexible doses of methadone, was superior to oral methadone alone in retaining treatment-refractory patients (risk ratio 1.44, 95% confidence interval [CI] 1.19–1.75) in treatment while helping reduce the use of illegal or nonmedical drugs.²⁸ The authors of the Cochrane Review concluded that there is value in co-prescribing diacetylmorphine with flexible doses of methadone and that, due to the higher risk of adverse events related to the study medication diacetylmorphine compared with methadone, treatment with diacetylmorphine should be considered for those who have not benefited from oral agonist treatment.²⁸ Subsequent to the 2011 review, a 2015 systematic review and meta-analysis was conducted on the efficacy of injectable diacetylmorphine.³⁰ Six randomized controlled trials (conducted in Switzerland, the Netherlands, Spain, Germany, Canada, and England) were identified and included in the analysis (Table 2). These 6 trials also were included in the Cochrane Review from 2011; however, the approach in this study differed from that of the Cochrane Review, as only trials in which heroin was prescribed and provided in a supervised setting (as opposed to prescribed, unsupervised, or take-home administration) were included in this review. The outcome confirmed the previous review in finding a greater reduction of illicit heroin use among individuals who received prescribed, supervised injectable diacetylmorphine compared with those who received oral methadone treatment only.³⁰

Regarding injectable OAT treatment duration, one study in the United Kingdom found median injectable diacetylmorphine OAT duration to be 6 years.³¹ Additionally, in Switzerland it was found that, among injectable diacetylmorphine patients who were retained in treatment long-term (50% after 2.5 years), approximately 62% did eventually transition to less intensive treatment, such as oral OAT.³² However, a loss of treatment benefit (ie, an increase in street heroin use post-treatment to levels comparable with that of the control group) has been found repeatedly when prescription diacetylmorphine treatment was discontinued at a predetermined end date.^{33,34} Thus, the authors of the Treatment Assisted by Diacetylmorphine (TADAM) study in Belgium, in line with World Health Organization recommendations for other OATs, recommend that supervised injection of diacetylmorphine be provided as an open-ended treatment.³³

The bulk of the literature on injectable OAT to date focuses on injectable diacetylmorphine as opposed to injectable hydromorphone. Although no systematic reviews currently exist evaluating the use of injectable hydromorphone, the SALOME trial (Study to Assess Longer-term Opioid Medication Effectiveness) was a phase 3, double-blind, single-site non-inferiority trial conducted in Vancouver, Canada, that compared injectable diacetylmorphine with injectable hydromorphone for the treatment of OUD. The SALOME trial was conducted based on findings from the previous North American Opiate Medication Initiative

study²⁷ (a randomized controlled trial evaluating the feasibility and effectiveness of heroin-assisted treatment compared with methadone) that demonstrated a reduction in illicit heroin use among a small number of participants (n = 25) being prescribed injectable hydromorphone, instead of diacetylmorphine, for corroboration of self-reported illicit heroin use. Results from the SALOME study (n = 202) demonstrated injectable hydromorphone to be non-inferior to diacetylmorphine in reducing illicit opioid use and retaining individuals in treatment.²⁹ Injectable hydromorphone also was found to have significantly fewer adverse events than diacetylmorphine (rate ratio 0.21, 95% CI 0.06–0.69).³⁵ These preliminary results suggest that hydromorphone, a licensed analgesic in many jurisdictions, may be a viable alternative for the treatment of refractory OUD, particularly in jurisdictions in which use of diacetylmorphine may not be available or access is difficult.

The British Columbia Centre on Substance Use in Vancouver, Canada, has developed an Injectable Opioid Agonist Treatment for Opioid Use Disorder Guidance Document for injectable OAT as an alternative, high-intensity treatment for severe OUD.³⁶ The inclusion and exclusion considerations outlined in the guidance document can be found in Table 3. Three distinct models of care for injectable OAT are described in the guidance document. The first is a comprehensive and dedicated supervised injectable OAT program that may be a stand-alone facility or located at a hospital or other acute care facility. Participants attend the clinic up to 3 times daily to self-administer injectable OAT under the supervision of qualified health professionals. Patients can be linked with ancillary services housed within the clinic or referred to community services when appropriate. The second model is a supervised injectable OAT program embedded in primary care clinics or harm-reduction programs with linkage to health care professionals and community services. Such a program would operate similar to what has already been described, with patients presenting up to 3 times a daily for their witnessed prescribed medications. The last model described is an emerging pharmacy-based model in which patients receive primary and addiction care at existing clinics, with supervision of injectable OAT provided by appropriately trained pharmacists at select pharmacy locations anywhere from 1 to 3 times daily. This permits a lower intensity of treatment than the comprehensive model and allows for access to injectable OAT in community settings in which a designated clinic may not exist.

As many injectable OAT programs operate in a setting of supervised injection, the potential for additional benefits (beyond opioid-related outcomes) may exist. More specifically, a recent systematic review included 75 articles to examine the effects of supervised injection facilities (SIFs).³⁷ Briefly, SIF implementation has had a significant impact on fatal overdoses. Beyond no death by overdose having ever been reported at an SIF-designated site, 1 Vancouver-based study also demonstrated a 35% reduction in fatal overdoses in the surrounding area.³⁸ Beyond this, SIF has been shown to be associated with an improvement on injecting behaviors and consequences, including a reduction in syringe sharing (adjusted odds ratio [aOR] 0.30, 95% CI 0.11–0.82) and syringe re-use (aOR 2.04, 95% CI 1.38–3.01), as well as more regular use of sterile injection materials and requests for education on safer injection practices (aOR 1.47, 95% CI 1.22–1.77).^{39–42} Two Vancouver studies also demonstrated SIF to be associated with accessing addiction treatment services, with 18% of SIF users engaging in a detox program, 57% initiating an addiction treatment program, and 23% ceasing injection drug use entirely.^{43,44} In the surrounding areas, SIFs have not been

shown to be associated with an increase in drug trafficking or crime, but rather a reduction in the daily mean number of people injecting in public, fewer syringes dropped, and less injection-related litter.^{45,46} Finally, 4 studies were performed to assess if SIF was a cost-saving system. It was estimated that per year a SIF could prevent 5 to 35 new human immunodeficiency virus (HIV) infections and 3 overdose deaths.^{47–50} Over 10 years, this prevention would amount to \$14 million saved, an increase in 920 years of life, and an avoidance of 1191 new HIV infections and 54 hepatitis C infections.⁴⁸

FUTURE CONSIDERATIONS/SUMMARY

Given that the range of substance use disorders includes individuals who do not benefit from the often-effective medications and psychosocial treatments available, additional strategies to treat and reduce the harms of substances are needed.

Although this review describes 3 such modalities for which evidence exists for effectiveness, the selectivity of participants in these studies, namely individuals with a severe substance use disorder, should be emphasized to ensure promotion of such treatments are recognized to exist beyond the realm of standard medical therapy. Furthermore, it should be highlighted that much of the research presented herein has been conducted in settings outside the United States, where the provision of MAP, SROM, and injectable OAT are regulated and occur in a supportive environment. Despite these treatment approaches being legal in these countries and associated with numerous positive outcomes, many of these programs have been subjected to ongoing scrutiny and criticism. Given the current US opioid epidemic and need to engage the entire spectrum of affected individuals in care, expansion of such newer modalities merits consideration in settings of greatest need with adequate support systems to implement. MAPs are more recent innovations with very early evidence of potential benefit; they merit further examination for the severe end of the AUD spectrum for which standard treatment can seem at times to elude benefit. Although these challenging severely affected individuals can exhaust providers' repeated efforts to address their needs, the proper role of innovative medical care to mitigate harm and consequences of harmful substances merits ongoing study, testing, and description.

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Key Points

- Alternative treatment interventions for individuals with a severe substance use disorder unsuccessful with standard management have been used in some settings.
- Community-managed alcohol programs combined with low-barrier housing have been used to stabilize some individuals with a severe alcohol use disorder.
- Slow-release oral morphine and injectable opioid agonist treatment can be alternative treatment options for people with severe opioid use disorders unsuccessful with methadone or buprenorphine.

Table 1:

Indications and contraindications for the use of slow release oral morphine (SROM) as a treatment option for opioid use disorder (OUD)

Indications	Contraindications
<ul style="list-style-type: none"> Adults (≥ 19 years) with OUD On methadone while actively using another opioid 	<ul style="list-style-type: none"> Hypersensitivity to morphine sulphate or any component of the formulation Pregnant or breastfeeding Significant respiratory depression Acute or severe bronchial asthma Known or suspected paralytic ileus Currently taking monoamine oxidase inhibitors (MOAIs) or use within the past 14 days Severe respiratory compromise or obstructive disease Severe respiratory distress Delirium tremens Acute alcohol intoxication

Adapted from: Wood E, Ahamad K, Djurfors C, et al. A Guideline for the Clinical Management of Opioid Addiction. 2015. http://www.bccsu.ca/wp-content/uploads/2017/06/BC-OUD-Guidelines_June2017.pdf. Accessed July 20th, 2017.

Table 2:

Six randomized trials of supervised injectable heroin (SIH) (plus flexible supplementary doses of oral methadone): key features and outcomes

Main paper	Country	Sample size; groups studied	Time to follow-up	Cochrane risk of bias ¹² using five criteria recommended by the Cochrane Handbook ¹⁸		Outcomes
Perneger <i>et al</i> ⁶	Switzerland	<i>n</i> = 51 SIH (+OM): <i>n</i> = 27 OM, detox, rehab: <i>n</i> = 24	6 months	Random sequence generation	L	Retention: SIH: 93% <i>v.</i> OM 92% Self-reported illicit heroin use: SIH: 22%, OM: 67% (<i>P</i> = 0.002) SAEs data not reported
				Allocation concealment	L	
				Incomplete outcome data	H	
				Selective reporting	H	
				Blinding (objective outcomes)		
				Blinding (subjective outcomes)		
van den Brink <i>et al</i> ³	The Netherlands	Injectable trial: <i>n</i> = 174 SIH (+OM): <i>n</i> = 76 OM: <i>n</i> = 98 (also SinH trial, <i>n</i> = 75)	12 months	Random sequence generation	U	Retention: SIH 72% <i>v.</i> OM 85% Self-reported 40% improvement in at least one domain (physical, mental, social): SIH 56% <i>v.</i> OM 31% (<i>P</i> = 0.002) SAEs: reported data limited to 11 SAEs (two definitely or probably and nine possibly related to injectable heroin)
				Allocation concealment	L	
				Incomplete outcome data	L	
				Selective reporting	L	
				Blinding (objective outcomes)	L	
				Blinding (subjective outcomes)	L	
March <i>et al</i> ⁴	Spain	<i>n</i> = 62 SIH (+OM): <i>n</i> = 31 OM: <i>n</i> = 31	9 months	Random sequence generation	U	Retention: SIH 74% <i>v.</i> OM 68% Self-reported illicit heroin use in past 30 days (mean days): SIH=8.3 <i>v.</i> OM = 16.9 (<i>P</i> = 0.02) SAEs: SIH=7 (two unrelated and five probably or definitely related to study drug) <i>v.</i> OM=7
				Allocation concealment	L	
				Incomplete outcome data	U	
				Selective reporting	U	
				Blinding (objective outcomes)		
				Blinding (subjective outcomes)		
Haasen <i>et al</i> ⁵	Germany	<i>n</i> = 1015 SIH (+OM): <i>n</i> = 515 OM: <i>n</i> = 500	12 months	Random sequence generation	L	Retention: SIH 67% <i>v.</i> OM 40% improvement in drug use (measured by either UDS and self-report): SIH 69%, OM 55% (<i>P</i> < 0.001) Improvement in physical/mental health: SIH 80%, OM 74% (<i>P</i> = 0.023) Combined reduced drug use and improved physical/mental health (responder): SIH 57% <i>v.</i> OM 45% (<i>P</i> < 0.001) SAEs: SIH = 177 (58 possibly, probably or definitely related to study drug) <i>v.</i> OM = 15
				Allocation concealment	L	
				Incomplete outcome data	U	
				Selective reporting		
				Blinding (objective outcomes)		
				Blinding (subjective outcomes)		
Oviedo-Joekes <i>et al</i> ⁶	Canada	<i>n</i> = 251 SIH (+OM): <i>n</i> = 115 OM: <i>n</i> = 111 (also SIHM +OM, <i>n</i> = 25)	12 months	Random sequence generation	L	Retention: SIH 88% <i>v.</i> OM 54% (<i>P</i> < 0.001) Self-reported reduction in illicit drug use or other illegal activities (improvement of 20% for either domain): SIH=67%, OM=48% (<i>P</i> = 0.004) SAEs: SIH = 51 <i>v.</i> OM = 18
				Allocation concealment	L	
				Incomplete outcome data	L	
				Selective reporting	L	
				Blinding (objective outcomes)		

Main paper	Country	Sample size; groups studied	Time to follow-up	Cochrane risk of bias ¹² using five criteria recommended by the Cochrane Handbook ¹⁸		Outcomes
				Blinding (subjective outcomes)		
Strang <i>et al</i> ⁷	England	<i>n</i> = 127 SIH (+OM): <i>n</i> = 43 OOM: <i>n</i> = 42 (also SIM+OM, <i>n</i> = 42)	6 months	Random sequence generation	L	Retention: SIH (or other treatment) 88% <i>v.</i> OOM 69% Reduction in 'street' heroin - 50% or more negative UDS during weeks 14–26 (responder): SIH 66% <i>v.</i> OOM 19% (<i>P</i> <0.0001) SAEs: SIH=7 (two probably related to study drug) <i>v.</i> OOM = 9
				Allocation	L	
				concealment	L	
				Incomplete outcome data	L	
				Selective reporting	L	
				Blinding (objective outcomes)		
				Blinding (subjective outcomes)		

SAE, serious adverse event; OM, oral methadone; OOM, optimised oral methadone; SIM, supervised injectable methadone; SIH, supervised inhalable heroin; SIHM, supervised injectable hydromorphone. L, low risk of bias; U, unclear; H, high risk of bias.

Data from: Strang J, Groshova T, Uchtenhagen A, et al. Heroin on trial: systematic review and meta analysis of randomised trials of diacetylmorphine-prescribing as treatment for refractory heroin addiction. *The British Journal of Psychiatry*. 2015;207(1): 5–14.

Table 3:

Inclusion considerations and precautions for injectable opioid agonist treatment

Inclusion Considerations		Precautions	
1	Capacity to consent to and fully understand the goals of treatment	1	Caution should be exercised in prescribing injectable OAT to patients with chronic medical conditions, such as respiratory, hepatic, or renal disease; acute conditions; or a history of recent head injury. Caution is also required for youth and older adults, in whom oral OAT or other forms of treatment may be more appropriate
2	Well-established history of injection drug use with opioids and severe opioid use disorder (DSM-V criteria)	2	The greater inherent risk of overdose with injectable treatments should be individually considered in each case
3	Current opioid injection drug use	3	Extreme caution should be exercised in prescribing injectable OAT to patients with existing injection-related infections (eg, septicemia, endocarditis, pneumonia, infective osteomyelitis), and in individuals with coagulation disorders (eg, patients prescribed anticoagulants, severe hepatic disease, deep vein thrombosis); oral treatment options should be preferentially prescribed for such patients
4	Able to attend clinic or pharmacy up to 3 times daily (physically able and reside in proximity)	4	Clinicians should carefully consider drug- drug interactions
5	Able to self-administer (ie, inject via subcutaneous, intravenous, or intramuscular route) medication under supervision	5	Caution should be exercised with pregnant women or women who become pregnant while receiving injectable OAT; this caution should be balanced against the potential harms of denying access to injectable OAT for a pregnant woman who otherwise meets eligibility criteria
6	Past experience with appropriately dosed oral agonist treatment in the form of methadone, buprenorphine/ naloxone, or slow-release oral morphine, and evidence of regular and ongoing injection opioid use while given these therapies	6	Caution should be exercised in prescribing injectable OAT to patients who cannot safely self-administer their medications, due to either inadequate venous access in “low- risk” sites (with consequent injecting in neck or groin veins), or persistently poor injecting technique not remedied by education about intramuscular injection
7	Significant risk of medical consequences of injection drug use that would likely benefit from increased health system involvement and engagement in care, or existing significant medical and/or psychiatric comorbidities (eg, HIV positive and antiretroviral nonadherence, severe mental health challenges, history of multiple overdoses)		
8	At least 18 y of age or older		
9	No coprescribed benzodiazepines and/or other sedatives		
10	Does not fit the criteria for active moderate or severe alcohol use disorder or sedative use disorder		

Abbreviations: DSM-V, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; HIV, human immunodeficiency virus; OAT, opioid agonist treatment.

Adapted from: British Columbia Centre on Substance Use (BCCSU). Guidance for injectable opioid agonist treatment for opioid use disorder. Available at: <http://www.bccsu.ca/wp-content/uploads/2017/10/BC-iOAT-Guidelines-10.2017.pdf>; with permission. Accessed Mar 21, 2018.