# Appendix 2 (as supplied by the authors): Supplemental Information – Guideline Development Methodology

**General Overview**. For all three recommendations, relevant search terms and structured search strategies were constructed and used to search PubMed and the Cochrane Library databases (i.e., the Cochrane Central Register of Controlled Trials including the Cochrane Drugs and Alcohol Group trials register), using a hierarchical approach, where identification and selection of meta-analyses and systematic reviews of randomized controlled trials was prioritized, followed by individual randomized controlled trials, quasi-experimental studies, prospective and retrospective observational cohort studies, and lastly, expert opinion (e.g., clinical practice guidelines, position papers, consensus statements issued by a recognized professional organization or authority).

Initial exploratory searches had no temporal restrictions from initial date of publication index (variable depending on database used) to August 1, 2018; results were evaluated in a cumulative fashion in order of most recent date of publication. Using the hierarchical approach, once a relevant high-quality meta-analysis or systematic review was identified for a particular topic, clinical question, or recommendation, subsequent structured literature searches were conducted bridging the time period covered by the prior review to date of search, and supplemented by review of selection criteria used in, review of all citations included/excluded from, and review of all citations that subsequently cited that particular meta-analysis or systematic review. If more than one relevant high-quality meta-analysis or systematic review was identified for a particular recommendation, the supplementary review process described above was used for each.

Additional structured searches specific to each topic, clinical question, and recommendation were conducted as needed and to supplement initial searches, either on request of or in response to feedback from the guideline review committee. The medical writer conducted literature reviews, examined titles, abstracts, and full-text from literature searches for relevance to guideline recommendations, and prepared narrative evidence summaries for the guideline committee's review and consideration.

A more detailed description of methodology used to conduct literature searches, prepare evidence summaries, and derive and score each individual recommendation using the GRADE criteria[1,2] is provided below.

**1. Injectable opioid agonist treatment should be considered for individuals with severe, treatment refractory opioid use disorder and ongoing illicit injection opioid use.**

**Clinical Question:** Should injectable opioid agonist treatment be considered for individuals with severe, treatment refractory opioid use disorder and ongoing illicit injection opioid use?

**Population:** Male and female adults with long-term or "chronic" heroin or opioid dependence, (almost)

 

daily use of injection heroin, and at least one previous oral methadone treatment attempt—no restriction on methadone treatment at or immediately prior to study enrollment.

**Setting:** Studies conducted in any outpatient drug treatment setting. No geographical restrictions were applied.

**Intervention:** Injectable opioid agonist treatment (i.e., "maintenance") with diacetylmorphine or hydromorphone alone or in combination with oral methadone.

**Comparator (Control or Experimental):** No interventions, oral methadone treatment, waiting list for conventional treatments, detox, rehab, optimized oral methadone, and any other treatments which are compared against heroin.

**Outcomes of Interest:** Primary outcomes – retention in treatment, opioid use, use of other (non-opioid) substances, death, adverse events; Secondary outcomes – criminal offense, incarceration or imprisonment, social function, side effects, adverse events, morbidity and mortality, physical and mental health symptoms, proportion of participants receiving injectable medications at least 28 days in prior 30 days.

**Study Design:** Meta-analyses, systematic reviews, and randomized controlled trials.

**Search Strategy:** Search strategies, terms, and vocabulary specific to the database used (PubMed, the Cochrane Library) were used to search for the population (individuals with opioid use disorder), intervention and comparator (diacetylmorphine or hydromorphone versus methadone) and study type (meta-analysis, systematic review, randomized controlled trial).

General examples of population search terms used include: opioid use disorder, opioid addiction, opioid abuse, opioid dependence, with substitution of opioid with opiate and specific opioid types (e.g., heroin) as appropriate.

General examples of intervention search terms used include: injectable opioid agonist treatment, diacetylmorphine, hydromorphone, opioid substitution treatment, opioid replacement treatment – with substitution of treatment with therapy, opioid with opiate used as appropriate.

*Quality of Evidence: Moderate; Strength of Recommendation: Conditional.*

*The evidence to support the use of injectable opioid agonist treatment using diacetylmorphine or hydromorphone for individuals with severe, treatment-refractory opioid use disorder, which the guideline review committee graded as* ***moderate quality****, is from a) systematic reviews of randomized clinical trials reporting safety and efficacy of diacetylmorphine with or without oral methadone compared to oral methadone for the treatment of chronic, treatment refractory opioid use disorder,*[3,4] *and b) a randomized*

*non-inferiority trial comparing safety and efficacy of injectable hydromorphone to injectable diacetymorphine.*[5]

*In determining strength of this recommendation, which the guideline review committee has graded as* ***conditional****, the quality of evidence reviewed above was considered in addition to the expert opinion of the guideline review panel.*

**2. For patients who are determined to be likely to benefit from injectable opioid agonist treatment, both diacetylmorphine and hydromorphone are acceptable treatment options.**

**Clinical Question:** For patients determined likely to benefit from injectable opioid agonist treatment, is one medication preferable to the other?

**Population:** Male and female adults with long-term or "chronic" heroin or opioid dependence, (almost) daily use of injection heroin, and at least one previous oral methadone treatment attempt—no restriction on methadone treatment at or immediately prior to study enrollment.

**Setting:** Studies conducted in any outpatient drug treatment setting. No geographical restrictions were applied.

**Intervention:** Injectable opioid agonist treatment (i.e., "maintenance") with diacetylmorphine. Comparator (Control or Experimental): Injectable opioid agonist treatment (i.e., "maintenance") with hydromorphone.

**Outcomes of Interest:** Primary outcomes – retention in treatment, opioid use, use of other (non-opioid) substances, death, adverse events; Secondary outcomes – criminal offense, incarceration or imprisonment, social function, side effects, adverse events, morbidity and mortality, physical and mental health symptoms, proportion of participants receiving injectable medications at least 28 days in prior 30 days.

**Study Design:** Meta-analyses, systematic reviews, and randomized controlled trials.

**Search Strategy:** Search strategies, terms, and vocabulary specific to the database used (PubMed, the Cochrane Library) were used to search for the population (individuals with opioid use disorder), intervention and comparator (diacetylmorphine or hydromorphone versus methadone) and study type (meta-analysis, systematic review, randomized controlled trial).

General examples of population search terms used include: opioid use disorder, opioid addiction, opioid abuse, opioid dependence, with substitution of opioid with opiate and specific opioid types (e.g., heroin) as appropriate.

General examples of intervention search terms used include: injectable opioid agonist treatment, diacetylmorphine, hydromorphone, opioid substitution treatment, opioid replacement treatment – with substitution of treatment with therapy, opioid with opiate used as appropriate.

*Quality of Evidence: Low; Strength of Recommendation: Strong.*

*The evidence to support offering individuals with opioid use disorder who are not benefitting from oral opioid agonist treatments either diacetylmorphine or hydromorphone, which the guideline review committee graded as* ***low quality****, is from a) systematic reviews of randomized clinical trials establishing the safety and efficacy of diacetylmorphine compared to oral methadone,[3,4] a randomized non-inferiority trial comparing safety and efficacy of injectable hydromorphone to injectable diacetylmorphine, which was conducted in response to regulatory barriers which limit access to diacetylmorphine in Canada,[5] and c) expert opinion of the guideline review panel.*

*In determining strength of this recommendation, which the guideline review committee has graded as* ***strong****, the quality of evidence reviewed above was considered as well as the expert opinion of the guideline review panel.*

**3. Injectable opioid agonist treatment should be provided as an open-ended treatment, with decisions to transition to oral OAT made collaboratively with the patient.**

**Clinical Question:** Is there evidence to support a pre-determined length of treatment with injectable opioid agonist treatment?

**Population:** Male and female adults with long-term or "chronic" heroin or opioid dependence, (almost) daily use of injection heroin, and at least one previous oral methadone treatment attempt—no restriction on methadone treatment at or immediately prior to study enrollment.

**Setting:** Studies conducted in any outpatient drug treatment setting. No geographical restrictions were applied.

**Intervention:** Injectable opioid agonist treatment (i.e., "maintenance") with diacetylmorphine with or without oral methadone.

**Comparator (Control or Experimental):** The best available treatment, oral methadone.

**Outcomes of Interest:** Primary outcomes – retention in treatment, opioid use, change in outcome domain compared to during diacetylmorphine treatment, cocaine use, mental health, physical health, criminal involvement.

**Study Design:** Randomized controlled trials and observational studies.

**Search Strategy:** Search strategies, terms, and vocabulary specific to the database used (PubMed, the Cochrane Library) were used to search for the population (individuals with opioid use disorder), intervention and comparator (diacetylmorphine or hydromorphone versus methadone, discontinuation of injectable treatment) and study type (meta-analysis, systematic review, randomized controlled trial, observational study).

General examples of population search terms used include: opioid use disorder, opioid addiction, opioid abuse, opioid dependence, with substitution of opioid with opiate and specific opioid types (e.g., heroin) as appropriate.

General examples of intervention search terms used include: injectable opioid agonist treatment, diacetylmorphine, hydromorphone, opioid substitution treatment, opioid replacement treatment – with substitution of treatment with therapy, opioid with opiate used as appropriate, discontinuation.

*Quality of Evidence: Low; Strength of Recommendation: Strong.*

*The evidence to support offering iOAT as an open-ended treatment, which the guideline review panel graded as* ***low quality****, is from a) two randomized controlled trials comparing oral methadone plus injectable diacetylmorphine to oral methadone alone,[6,7] b) an observational study comparing individuals who voluntarily transitioned from injectable diacetylmorphine to oral methadone prior to the completion of a randomized controlled trial to those who were involuntarily transitioned at the end of the 12-month trial,[8] and c) the expert opinion of the review panel.*

*In determining strength of this recommendation, which the guideline review committee graded as* ***strong****, the evidence above was considered, as well as its alignment with a recommendation from the World Health Organization that opioid agonist treatment be provided as an open-ended treatment,[9] and the expert opinion of the guideline review panel.*

# References


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