

**THE IMPACT OF CHRONIC PAIN  
IN PATIENTS WITH OPIOID  
ADDICTION**

Ph.D. Thesis – BB. Dennis; McMaster University – Health Research Methodology

**CHRONIC PAIN: A RED HERRING OR RISK FACTOR  
IN THE MANAGEMENT OF PATIENTS RECEIVING  
OPIOID SUBSTITUTION THERAPY**

**By**

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of Patients Receiving Opioid Substitution Therapy

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## ABSTRACT

**Background:** The consequences of continued opioid abuse among patients treated with opioid substitution therapy (OST) are serious and can result in abnormal cardiovascular function, overdose, and mortality. Conflicting evidence exists that both implicates and refutes the role of chronic non-cancer pain (CNCP) as a major risk factor for continued opioid abuse within the addiction treatment setting. This thesis aims to 1) evaluate the impact of chronic pain on the treatment outcomes of patients with opioid addiction receiving OST, 2) determine whether a clinical or inflammatory profile exists to distinguish pain in this population, 3) explore the sources of heterogeneity in previous studies examining this question, 4) determine the best therapy for patients with chronic pain, and 5) evaluate the most effective treatment for opioid addiction. We anticipate chronic pain to be an important predictor of continued opioid abuse such that patients with comorbid pain will require careful consideration when managed on OST.

**Methods:** We systematically reviewed the literature to determine the impact of pain in opioid addiction patients receiving methadone maintenance treatment (MMT). We determined the clinical and inflammatory profile of MMT patients using data from the Genetics of Opioid Addiction (GENOA) research collaborative between the Canadian Addiction Treatment Centres (CATC) and the Population Genomic Program. GENOA is a prospective cohort study aimed to determine the genetic, biological, and psychosocial determinants of treatment prognosis for opioid addiction patients receiving MMT. GENOA recruits patients  $\geq 18$  years of age meeting the

DSM-IV criteria for opioid dependence. All GENOA participants are receiving MMT for the management of opioid addiction. Baseline data from the GENOA pilot study (n=235) were used to evaluate the impact of pain on illicit opioid use behaviour and determine the clinical and inflammatory profile of patients with comorbid pain. We explored sources of heterogeneity in previous studies using data from the full-phase GENOA study (n=444), examining the prognostic value of different pain measures for predicting illicit opioid use. We then performed a multiple treatment comparison of all opioid substitution and antagonist therapies in efforts to determine the best intervention for improving treatment outcomes for patients with comorbid pain. We lastly determined the most effective treatment for opioid addiction by performing a network meta-analysis using data from a systematic review of opioid maintenance therapy trials.

**Results:** Our initial systematic review confirmed a lack of consensus in the literature, whereby some studies suggest pain increases risk for illicit opioid use and other studies suggest pain has no effect on substance use behaviour. Findings from the analysis of GENOA pilot data confirmed chronic pain to be an important predictor of sustained opioid abuse and also showed patients with pain to have elevated Interferon-Gamma. Using data from the GENOA prospective cohort study we determined the brief pain inventory (a commonly used pain measurement in previous studies) to be highly sensitive with poor prognostic value. Our final reviews propose 1) there is limited evidence to suggest any OST is superior for managing patients with comorbid pain, and 2) heroin and high-dose methadone are the most effective

treatments for improving treatment retention. The final systematic review and network meta-analysis in this thesis also highlighted a major problem in the field of opioid addiction, primarily the lack of consensus as to what outcomes matter for determining success in patients with addiction.

**Conclusion:** Patients with comorbid pain and addiction are at high-risk for continued opioid abuse and should be managed closely by clinicians administering OST.

Contention in the previous literature likely resulted from the use of pain measurements with poor prognostic value. No OST demonstrated superiority for managing patients with chronic pain. While our findings indicate heroin is the most effective treatment across multiple endpoints, we use this thesis to provide readers with 1) a sense of the feasibility issues associated with heroin administration, 2) a summary of the limitations of this evidence base, and 3) recommendations for how to improve the addiction trials' design for future research

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## LIST OF ABBREVIATIONS

MMT	Methadone maintenance treatment
BPI	Brief Pain Inventory
RCT	Randomized controlled trial
COA	Continued Opioid Abuse
TNF- $\alpha$	Tumor necrosis factor alpha
IL	Interleukin
IFN- $\gamma$	Interferon Gamma
CCL2	Chemokine (C-C motif) ligand 2
OATC	Ontario Addiction Treatment Centre
GENOA	GENetics of Opioid dependence
LAAM	Levomethadyl acetate
OST	Opioid substitution therapy
DEF	Data extraction form
WHO	World Health Organization
EMBASE	Excerpta Medica DataBase
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
NOS	Newcastle-Ottawa Scale
CNCP	Chronic Non-cancer Pain
NMA	Network Meta-analysis
AGREE	Appraisal of Guidelines for Research & Evaluation II

NICE	National Institute for Health and Care Excellence (NICE)
GRADE	Grading of Recommendations Assessment, Development and Evaluation
OR	Odds Ratio
MAP	Maudsley Addiction Profile
MOOSE	Meta-analysis of Observational Studies in Epidemiology
NIH	National Institutes of Health

## **DECLARATION OF ACADEMIC ACHIEVEMENT**

I am the primary author of all studies included in this thesis. I contributed substantially to each work by taking a lead role in conceiving the question, writing the protocol, planning and performing the statistical analysis, as well as drafting the manuscript. Detailed lists of author contributions are provided at the end of each study.

## CHAPTER 1

### 1.1 THESIS OBJECTIVES

Opioid addiction is a major source of morbidity and mortality world wide that continues to decrease the quality and duration of life for its sufferers.<sup>1,2</sup> This chronic relapsing disorder affects more than 1 million persons in North America<sup>3</sup> and 15 million persons worldwide.<sup>4</sup> In recent years opioid abuse, misuse, and diversion have risen dramatically and current estimates suggest 25 million people initiated using illicit opioids between 2002 and 2011.<sup>5</sup> The increase in global opioid abuse patterns are paralleled by a rising mortality rate and it is estimated 69,000 people die from opioid overdose each year.<sup>4</sup> Risk for HIV,<sup>6</sup> hepatitis,<sup>6</sup> and cardiac disease (e.g. infective endocarditis)<sup>7,8</sup> is high among patients with opioid addiction and without treatment these patients incur a 50-fold increase in death.<sup>2</sup>

Frontline therapies for opioid addiction include methadone maintenance treatment (MMT), buprenorphine, and levomethadyl acetate (LAAM)—of which methadone is the oldest and most commonly employed.<sup>9</sup> These treatments are long-acting opioids prescribed under the close supervision of an addiction specialist. They are known collectively as opioid substitution therapies (OSTs). While these treatments are demonstrated effective for reducing illicit substance use and improving patient retention in treatment,<sup>10,11</sup> they are most effective for engaged patients willing to comply with treatment.





review was to identify the optimal therapy for patients with opioid addiction and comorbid pain. This review also evaluates the most recently published Canadian, American, and British OST guidelines to determine how the evidence for managing comorbid pain in addiction patients is being translated to practice.

The final paper in this thesis—Study 5 (Chapter 7)—aims to evaluate the optimal therapy for patients with opioid addiction. Study 5 is a systematic review and network meta-analysis of 60 trials evaluating OSATs, and the first network meta-analysis of OSATs to date. The protocol detailing the review methods was published.<sup>21</sup> This review evaluates effectiveness of OSATs for improving patient retention and reducing illicit opioid use. This paper highlights a major problem in the field of opioid addiction, primarily the lack of consensus as to what outcomes are important or relevant for determining treatment success in addiction patients. Study 5 provides readers with 1) a sense of the feasibility issues associated with OSAT administration, 2) summary of the limitations of this evidence base, 3) recommendations for how to improve the addiction trials' design for future research.

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## 2.1 ABSTRACT

**Background:** While chronic pain has been said to impact patient’s response to methadone maintenance treatment for opioid dependence, the reported findings are inconsistent. These discrepancies may be a direct result of variations in the measurement of chronic pain or definitions of response to methadone treatment. The goal of this study is to evaluate the association between pain and substance use behaviour to determine the real impact of comorbid pain in the methadone population. We also aim to examine sources of variation across the literature with a specific focus on the measurement of pain.

**Methods/Design:** We performed a systematic review using an electronic search strategy across CINAHL, MEDLINE, Web of Science, PsychINFO, EMBASE, and the Cochrane Library including Cochrane Reviews and the Cochrane Central Register of Controlled Trials databases. Title, abstract, as well as full text screening and extraction were performed in duplicate. Studies evaluating the association between chronic pain and methadone maintenance treatment response were eligible for inclusion in this review.

**Results:** After screening 826 articles we identified five studies eligible for full text extraction, of which three showed a significant relationship between the presence of pain and the increase in substance abuse among patients on methadone for the treatment of opioid dependence. Studies varied largely in the definitions and measurement of both pain and response to treatment.

**Discussion:** The field of addiction medicine is at a lack of consensus as to the real effect of chronic pain on treatment response among opioid dependent patients. Whether it be the lack of a single “gold standard” measurement of response, or a lack of consistent measurement of pain, it is difficult to summarize and compare the results of these relatively small investigations.

## 2.2 INTRODUCTION

In 2011, chronic pain was reported to affect as high as 116 million Americans,<sup>1</sup> approximately 37% of the US population. Pain can be classified as nociceptive pain or neuropathic. Nociceptive pain is caused by a sensory relay of information via neural pathways,<sup>2</sup> where neuropathic pain is caused by nerve damage to the somatosensory nervous system.<sup>3</sup> Opioids are among the most commonly prescribed medications for the management of chronic pain. Opioids are highly liable for misuse, thus the relationship between chronic pain and addiction is synergistic by nature.<sup>4</sup> Opioid dependence is defined by the DSM-5 as problematic opioid use behaviour contributing to clinically significant impairment or distress.<sup>5</sup> The prevalence of chronic pain among patients with opioid dependence is relatively high and varies from 37% to 55%.<sup>6-9</sup> While it should be common practice for health care professionals to prescribe opioids with caution,<sup>6</sup> this task has become overwhelming due to the increase in the prescription of opioids world-wide. The global population of opioid users was estimated to have reached 33 million in the year 2012.<sup>10</sup>

Methadone maintenance treatment (MMT) is an opioid substitution intervention employed to stabilize and alleviate withdrawal symptoms in opioid dependent patients. Patients on methadone with comorbid pain are known to have an increased risk for psychiatric disorders, higher dose requirements, as well a decrease in social support networks.<sup>11</sup> The symptoms of pain are often under treated by physicians at addiction treatment facilities.<sup>11</sup> In addition, patients receiving methadone for opioid use disorders

who suffer from chronic pain report higher rates of illicit opioid consumption in comparison to patients without pain. This is concerning because illicit opioid consumption confers an increased risk for cardiovascular abnormalities and mortality among patients being treated with methadone.<sup>12-15</sup>

The goal of this study is to perform a thorough assessment of the literature with the aim of enhancing our understanding of comorbid pain in opioid dependent patients receiving MMT, as well as identify the important sources of variation across studies evaluating these phenomena. Results from this systematic review serve to inform health care practitioners of the possible need for treatment tailoring and improved pain management among patients with comorbid pain.

## **2.3 OBJECTIVES**

Perform a systematic review to:

1. Evaluate whether or not the presence of chronic pain is associated with poor response to MMT as measured by concurrent opioid use
2. Determine the different types of measurement tools used for chronic pain among studies on MMT patients
3. When possible, combine the results of studies selected for full text extraction in a meta-analysis to obtain a summary statistic to evaluate the impact of chronic pain on response to MMT

## **2.4 METHODS**

### **2.4.1 Data Sources and Search Strategy**

This study adheres to the reporting standards outlined by the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guidelines.<sup>16</sup> A protocol outlining the appropriate methodological design features of this systematic review was discussed and prepared before the onset of the investigation. This protocol is available upon request to the authors. An electronic search was performed in duplicate using CINAHL, MEDLINE, Web of Science, PsychINFO, Embase, and the Cochrane Library including Cochrane Reviews and the Cochrane Central Register of Controlled Trials databases. No attempt was made to evaluate the grey-literature since this evidence is not subject to the same transparency requirements and scrutiny as studies published in peer-reviewed journals. A comprehensive search strategy was designed a priori, and specifically tailored for each database. This search strategy is described in [Table 2.4.1](#). A McMaster University Faculty of Health Science librarian was consulted as needed through out the design and implementation of the study. The search was restricted to 1) completed and 2) human studies.

### **2.4.2 Selection of Studies**

The literature search and data extraction were performed independently in duplicate by two authors (Dennis, B and Bawor, M). The two authors completed the title search, screened articles selected for both the title and abstract screening using predetermined inclusion criteria, and performed a full text extraction on all eligible articles using pilot tested data extraction forms. Any disagreements between raters in their title and abstract

screening or full text extraction were resolved by discussion. If discussion between the raters did not lead to a resolution, a third author (Samaan, Z) was consulted and had the final judgment as to whether the disputed article would be accepted.

The systematic review flow diagram of the article selection process can be seen in [Figure 2.4.2](#).

### **2.4.3 Inclusion and Exclusion Criteria**

The study must have investigated the association between chronic pain and continued opioid abuse in patients with opioid use disorder to be eligible for inclusion. We did not place any restriction on study design methodology, allowing randomized trials, observational studies such as case-control or cohort investigations, as well as qualitative studies to be eligible for inclusion. No restrictions were placed on the geographic locations or time-period of study. However, the study was required to have evaluated “response” to MMT, preferably a measure of continue opioid abuse by self-report or urine screening. Any incomplete studies, animal studies, or “preliminary findings” were not eligible for inclusion into this review. Additionally, studies evaluating participants on substitute opioid therapies other than methadone (i.e. buprenorphine) were not eligible for inclusion into the review.

### **2.4.4 Data Abstraction**

The two authors (Dennis, B and Bawor, M) extracted data from the studies using a pilot tested data extraction form. Information extracted included: author, date of publication,

journal of publication, number of study participants, definition of chronic pain, definition of response to MMT, percentage/number of participants with chronic pain, primary outcome of the study, measurement of pain, measurement of continued substance-use, statistical analysis performed, description of study population (i.e. income), mean methadone dose (mg/day), mean age, overall statistical findings, factors associated with treatment response, and study conclusions.

#### **2.4.5 Assessment of Methodological Quality**

Two authors (Dennis, B and Bawor, M) assessed the methodological quality of all eligible studies using a modified Newcastle Ottawa scale for observational studies<sup>17</sup> and the Cochrane Risk of Bias Tool<sup>18</sup> for randomized controlled trials. Any discrepancies between the independent raters were first resolved by discussion, if discussion did not lead to an adequate solution a third rater (Samaan, Z) was brought to make the final decision.

#### **2.4.6 Outcome Measurements**

Response to MMT was determined by evaluating a patients substance use behaviours such as a patient's ability to abstain from illicit substance use during the course of MMT. Our primary concern was the differences in opioid use behaviour in patients with pain. Continued opioid abuse can be measured through self-report or urine toxicology screening, and both of these outcome measurements were accepted.

#### **2.4.7 Statistical Analysis**

Provided there was limited heterogeneity between studies, meta-analytical methods were to be used to derive a summary statistic representing the combined result of all studies evaluating the impact of pain on response to MMT. However, as originally anticipated, the measurements for both chronic pain and opioid use were too diverse to be combined statistically. Therefore, results of this systematic review are reported narratively. Agreement levels between the independent reviewers were measured using the kappa statistic.

## 2.5 RESULTS

### 2.5.1 Study Selection

The search was performed from the date of inception of databases to November, 2014. The search strategy was applied to the CINAHL, MEDLINE, Web of Science, PsychINFO, EMBASE, and Cochrane Library including Cochrane Reviews and the Cochrane Central Register of Controlled Trials databases. Please refer to [Figure 2.4.2](#) for a detailed diagram outlining the flow of article selection. Among the 826 articles identified in the title search, only five met the inclusion criteria for this review.<sup>7,19-22</sup>

After full text extraction we noted significant methodological differences among studies, inhibiting the possibility for pooling the results of the five selected studies. The observed quadratic weighted kappa agreement among the independent reviewers for the title, abstract, and full text screening was 0.53 (95% CI 0.4, 0.6), 0.54 (95% CI 0.2, 0.87), and 1 (95% CI 0.99, 1), respectively.

### 2.5.2 Study Characteristics

The descriptive characteristics of studies included in this review are summarized in [Table 2.5.2a](#). Of the five studies eligible for full text extraction, four were cross-sectional and one was a prospective cohort study. Of the studies selected, the majority (excluding Barry, 2008), were performed in relatively large populations, with sample sizes varying from 200 to 390 ([Table 2.5.2a](#)). The mean age of participants ranged from 29.6 to 49.5 years and the majority of participants were male ([Table 2.5.2a](#)).

A total of five studies were reviewed to determine the association between the presence of chronic pain and patient response to methadone maintenance therapy, as measured through a patient's ability to abstain from illicit opioids (Table 2.5.2a and Table 2.5.2b). The definition and measurement of response to MMT varied across studies. Some studies reported response to treatment as the number of days of illicit heroin or opioid abuse in the last month,<sup>21,22</sup> while other studies chose to report the percentage of chronic pain patients who report using illicit opioids, heroin, or other substances in the last 30 days.<sup>7,19,20</sup> In addition, the studies by Trafton et. al (2004) and Ilgen et. al (2006) used the same participant population, where the earlier investigation was a cross-sectional analysis of preliminary data,<sup>22</sup> and the latter reported the one-year follow up findings.<sup>21</sup>

### **2.5.3 Definition and Measurement of Chronic Pain**

Among the studies included in this systematic review, different methods were used to measure chronic pain. While some studies simply ask participants whether they are experiencing pain,<sup>19,20</sup> other studies used validated scales.<sup>7,21,22</sup> A detailed outline of the definitions and measurements used to identify patients with pain is summarized in Table 2.5.2b. Trafton (2004) and Ilgen et. al (2006) used the SF-3V6 Quality of Life Index<sup>21,22</sup> pain index, which is a self-report scale inquiring into the pain experienced by patients over a 4 week time-frame. Rosenblum et. al (2003) used the BPI scale, in addition to the BPI subscale to measure pain interference.<sup>7</sup>

Trafton (2004) and Ilgen et. al (2006) asked patients to define the pain they have experienced over the last four weeks on a scale from moderate to very severe.<sup>21,22</sup> In

comparison, Rosenblum (2003) categorized patients as having chronic pain if they reported a pain that persisted for more than 6 months that was of moderate to severe intensity and significantly interfered with daily activities.<sup>7</sup> Barry (2009) assessed the duration and intensity of pain by asking patients if they had pain in the last 7 days and if this pain has lasted at least 3 months.<sup>19</sup> In addition Barry (2009) inquired about the level and intensity of the pain using a 5 point scale (0-5 scale, 5 being unbearable).<sup>19</sup>

#### **2.5.4 Definition and Measurement of Treatment Response**

Definitions and measurement of methadone response was different across studies, limiting our ability to combine these results using meta-analysis. Some studies chose to use self-reported opioid use over a 30-day timeframe as an indicator for successful response to MMT.<sup>21,22</sup> Trafton (2004) and Illgen (2006) measured the propensity for misuse of substances with analgesic effects, evaluating the number of days of drug use (including opioids and heroin) over a 30-day timeframe, as well as the percentage of patients who injected drugs in the last 6 months.<sup>21,22</sup> Barry (2009) viewed a patients consumption of prescription and non-prescription opioids in the last 7 days as a measure of response to methadone, plainly reporting the percentage of participants (separated by chronic pain status) who have engaged in illicit opioid use.<sup>19</sup> Barry (2009) evaluated patients' reported reasons for relapse, showing pain to be commonly reported.<sup>19</sup> Barry et. al (2008) investigated health care practitioners experiences with MMT patients, where they asked practitioners to report about the demographic information of their patients, specifically what percentage of patients continue to abuse illicit opioids and other

substances in an effort to reduce pain<sup>20</sup>. Rosenblum et al. (2003) chose to investigate drug cravings, drugs used in the last 3 months and patient's reasons for using drugs.<sup>7</sup>

Similar to the measurement of chronic pain, a number of these studies relied on self-report to a priori defined questions,<sup>7,19,20</sup> while other studies chose to include a validated tool such as the Addiction Severity Index to assess the severity of substance abuse behavior.<sup>21,22</sup>

### **2.5.5 The Association Between Chronic Pain and Concurrent Opioid Abuse**

Findings of studies eligible for inclusion into the review are summarized in Table 2.5.2a.

Trafton et. al (2004) undertook a cross sectional investigation with 251 veterans seeking methadone treatment for opioid dependence (majority male, 97%).<sup>22</sup> This study evaluated the number of days of drug use (opioids, heroin, cocaine) over a 30-day timeframe. Trafton et. al (2004) also explored injecting drug use behaviour over a 6 month time-period.<sup>22</sup> This investigation used the statistical analysis of variance measure (ANOVA) to determine whether differences exist between the chronic pain, non-chronic pain and overall populations.<sup>22</sup> The ANOVA t-tests showed significant differences ( $p=0.03$ ) exist when evaluating the mean number of days (out of 30) of illicit opioid use between the overall (1.6 days), pain (2.3 days), and non-pain (0.8 days) populations. They found no significant differences ( $p>0.05$ ) when evaluating the injecting drug use behaviour of pain ( $n=62$ ), non-pain ( $n=65$ ), and overall participant populations ( $n=63$ ).<sup>22</sup>

The Rosenblum et. al (2003) paper was a cross sectional study with 390 participants (62% male) who sought MMT to manage their opioid dependence.<sup>7</sup> Rosenblum et. al (2003) also investigated the response outcomes of short-term in-patient facility patients, however all findings were reported separately<sup>7</sup>. When determining response to treatment, Rosenblum et. al (2003) investigated drug cravings, drugs used in the last 3 months and the participant's reported reasons for relapse.<sup>7</sup> When analyzing the differences between participants with chronic severe pain and those without, Rosenblum et. al (2003) used a Mantel Hanzel Odds Ratio (OR) test the ordinal outcomes of drugs used in the last 3 months (none, 1, 2,  $\geq 3$ ) and drug cravings (none, low, high).<sup>7</sup>

Using no reported cravings as the OR reference, Rosenblum et. al (2003) found 31% chronic pain patients report no craving, 34.2% of chronic pain patients report low cravings, and 43.1% report high number of cravings. The findings showed the rates of drug craving were similar regardless of reported pain, except for the comparison of patients reporting high rates of craving in comparison to patients reporting no cravings, where the OR showed patients reporting pain have a higher reported number of cravings (OR: 1.67, 95%CI: 0.99, 2.83,  $p < 0.05$ ).<sup>7</sup> When looking at the number of times of drug use in the last 3 months, Rosenblum et. al (2003) categorized this behaviour into four categories (none, 1, 2,  $\geq 3$ ), where participants who were grouped into the  $\geq 3$  times of drug use could be considered the more severe non-responders. Among the population of patients reporting  $\geq 3$  times of drug use, 36.7% reported chronic pain.<sup>7</sup> However, using “no reported drug use,” as the reference category, they found no significant differences between the number of patients reporting pain among the different drug use categories.<sup>7</sup>

Ilgen et. al (2006) followed a prospective cohort design, where by 200 patients from the original Trafton (2004) study were followed for one year (99% male).<sup>21</sup> Ilgen et. al (2006) used a repeated measures ANOVA analysis to determine the differences between chronic pain groups and intake and 1 year follow up for the number of days of drug use (out of 30-day assessment) for heroin and illicit prescription opioids.<sup>21</sup> Ilgen et. al (2006) found the presence of chronic pain did not greatly impact participants substance use behaviours, where patients reporting pain (intake[I]:2.5 days opioid use, 1-year[1]:0.3 days opioid use/I: 21.9 days heroin use, 1: 3.1 days heroin use), no-pain (I: 0.8 days opioid use, 1: 0.0 days opioid use/I: 23.0 days heroin use, 1: 3.5 days heroin use), and the overall population (I: 1.7 days opioid use, 1: 0.2 days opioid use/I: 22.4 days heroin use, 1: 3.3 days heroin use) showed similar rates of heroin use and only a mild difference in the rate of illicit opioid use ( $p=0.012$ ), where the observed treatment effect is marginal.<sup>21</sup> When comparing the rates of substance use (heroin and opioids) at in-take and one-year follow-up, there were significant reductions for all groups.<sup>21</sup>

The Barry et. al (2008) followed a cross-sectional qualitative study design, where by the investigators interviewed health care practitioners (counselors) treating opioid dependent patients, inquiring into the influence of chronic pain on patients response to MMT.<sup>20</sup> Barry et. al (2008) reported descriptive statistics of the counselors' patients, as well as their reported experiences with this population. Interviews revealed 60% of chronic pain patients report continued drug use to their counselors, and that 56% of chronic pain

patients attributed their continued substance use patterns to their attempts at pain reduction.<sup>20</sup>

Barry et. al (2009) report findings from a cross-sectional investigation assessing the influence of chronic pain on 293 MMT patients.<sup>19</sup> Barry (2009) investigated different indicators for methadone response including the reported consumption of prescription and non-prescription opioids in the last 7 days for the purpose of reducing pain.<sup>19</sup> Barry (2009) used a chi-square statistic to compare substance abuse in the last 7-days between chronic pain and non-chronic pain patients, where they found no statistically significant differences. The found rates of using: more than prescribed opioid medication (chi-square statistic: 0.25,  $p>0.05$ ), someone else's opioid medication (chi-square statistic: 1.21,  $p>0.05$ ), heroin (chi-square statistic: 0.15,  $p>0.05$ ), street methadone (chi-square statistic: 1.54,  $p>0.05$ ), more than prescribed non-opioid medication (chi-square statistic: 2.46,  $p>0.05$ ), more than prescribed benzodiazepine medication (chi-square statistic: 2.74,  $p>0.05$ ), and someone else's non-opioid medication (chi-square statistic: 3.38,  $p>0.05$ ) were not significantly different between patients reporting a life-time history of pain in comparison to patients reporting no history of pain.

### **2.5.6 Impact of Chronic Pain and Response to MMT Definitions and Measurements on Study Findings**

The measurements of chronic pain and substance use behaviour do not appear to bias the study findings in a particular direction. [Table 2.5.2b](#) provides a summary of the major findings and different measurements used across studies. The Trafton et. al (2004) and

Ilgen et. al (2006) studies emerged from the same patient population, with Ilgen's (2006) results corresponding to the 1 year follow-up data. As expected each study used the same measurements for pain and treatment response and also reported similar findings.<sup>21,22</sup> The outcome assessment timeframe, pain measurement tools, as well as definitions and response varied even within the studies reporting similar associations (Table 2.5.2b). When comparing the studies reporting no significant findings<sup>7,19,21</sup> to those showing chronic pain as an important predictor or poor treatment response.<sup>20-22</sup>

### **2.5.7 Methodological Quality Assessment**

Using the Newcastle Ottawa Scale to evaluate risk of bias across individual studies, we found limited variation between studies (Table 2.5.7), with the majority of studies having the same weaknesses. These weaknesses include 1) the inadequate assessment or discussion of missing data, 2) lack of objective measurements for exposure or outcome ascertainment, and 3) improper or lack of adjustment for important confounders (adjusting for duration in MMT) when comparing the impact of pain on response to opioid addiction treatment.

## 2.6 DISCUSSION

There is a disagreement in the evidence addressing the impact of chronic pain on methadone treatment outcomes. While some studies appear to be reporting a strong association between chronic pain and substance abuse among MMT patients,<sup>7,22</sup> other studies report no association.<sup>19,21</sup> In an effort to determine whether there truly is an association, or if the differences in observed are a result of differences in methodology, we have performed a systematic review to identify all studies investigating chronic pain and methadone response among opioid dependent patients. We have outlined the study design, investigative findings, and statistical measures of association used for all of the collected studies.

The results of this investigation emphasize the real lack of consensus existing in the research community as to whether chronic pain significantly impacts patient's treatment response characteristics such as substance abuse behaviour. Our findings are complicated by the fact that there are few studies assessing pain in patients with opioid dependence and each study that did use varying definitions of treatment response and measurements of pain. More explicitly, the Trafton (2004) and Ilgen (2006) studies used the Short-Form 3V6 questionnaire (SF3V6),<sup>21,22</sup> the Barry (2008) and (2009) used patients self reported pain (patient's reporting they have pain when asked),<sup>19,20</sup> and the Rosenblum (2003) study used the BPI pain measurement.<sup>7</sup> The variances in pain measurements across studies could have contributed to the differences in reported opioid abuse behaviour.

Reviewing the measurement of treatment response across studies further highlights discrepancies in the literature. While the Trafton et. al (2004),<sup>22</sup> Rosenblum et. al (2003),<sup>7</sup> and the Barry et. al (2008)<sup>20</sup> studies report significant treatment effects among patients with pain, whereby their substance use is increased, the Ilgen et. al (2006)<sup>21</sup> and Barry et. al (2009)<sup>19</sup> do not support such findings. The studies supporting the hypothesis that chronic pain impacts methadone treatment use self-reported measures of substance use over the time frame of 30 days<sup>22</sup> to 3 months.<sup>7</sup> In addition, the Rosenblum (2003) study reviewing substance use behaviour over a 3-month period reported only significant findings for drug “cravings,” among patients reporting pain.<sup>7</sup> Their results were inconclusive when determining whether patients with pain abuse substances at a higher rate. The Ilgen (2006) study reported no association between pain and treatment response, however this study used a 7-day time frame.<sup>21</sup> Duration of follow-up is a pertinent design feature for studies evaluation the methadone maintenance treatment patient response. As a chronic and remitting disorder, opioid dependence should be cataloged and analyzed over a broad timeframe. With a reported 2-year median length of treatment,<sup>23</sup> it seems inappropriate to determine the predictors of response using a time frame of 7-30 days.

While we have spent a considerable amount of time explaining reasons for the inconsistent findings reported across the literature, it is important to focus attention on the ways future studies can improve our confidence in the estimates. To start, future investigations should focus on prospectively collecting data on MMT patients, preferably collecting repeated measurements over time for both pain and substance use. Repeated measurements allow for an assessment of the change in pain and substance use behaviour.

We would be more confident if investigators can demonstrate a causal association, such that substance use behaviour changes in accordance with pain severity. Moreover, a dose-response relationship such as increasing pain severity corresponding to increasing opioid consumption would also demonstrate a more causal association. While many of the studies here chose to evaluate opioid consumption with different measurements, we would suggest the use of more objective measures such as urine toxicology screening to avoid social desirability bias. Due to the chronic and remitting nature of opioid use disorder, we would also suggest the evaluation of substance use behaviour over a broader time frame (2-3 months). As for the evaluation of pain, results from this review are important since we demonstrate the measurement of pain (BPI tool vs. self-report) is not the likely source of bias contributing to the inconsistencies reported in the literature. However, it will be important to assess the severity of pain in order to demonstrate a causal association (eg. Dose-response), thus selection of a measurement tool with items assessing pain on a continuum is preferable.

Future studies can also benefit by improving their statistical approaches to evaluating the impact of pain on substance use behaviours. Our methodological assessment of the current literature shed light on the statistical analysis methods utilized across studies assessing pain in the methadone setting, where we find the majority of studies relying on unadjusted estimates. Evaluation of an exposure such as pain prevents us from using a randomized design, limiting our methodological selection to the more bias prone observational designs. Randomized studies benefit from the equal distribution of prognostic variables across intervention/exposure groups. Acknowledging our inability to

assure the balance of confounding variables between our exposure populations (pain vs non-pain), statistical attention should be paid to adjustment through multi-variable regression analysis. Generation of a well-fit multi-variable regression model could benefit the majority of analyses discussed in this review, providing an opportunity to evaluate the impact of pain while adjusted for age, sex, duration on methadone treatment, methadone dose (mg/day), as well as socio-economic characteristics such as employment, income, and educational background. While many of these variables were discussed during each study's population description, none were properly adjusted for in a regression model or evaluated in later stratified analyses. This is concerning since many of these variables (socioeconomic characteristics, duration on treatment) are known to directly impact a patient's propensity for substance use.<sup>24-26</sup>

Lastly, future studies will also benefit by exploring the etiology of pain and the subsequent effect of this on treatment prognosis. Studies included in this review sought to establish the impact of chronic non-cancer pain on opioid use behavior, however none address the fact that the etiology of pain experienced by those with addiction is multifaceted. For instance, patients may experience hyperalgesic effects of methadone due to opioid induced hyperalgesia, whereby opioid exposure may increase the intensity of preexisting pain.<sup>27, 28</sup> Patients may also be experiencing withdrawal pain, pain from injury, recurrent pain from healed injury sites, as well as pain from ongoing central or peripheral pathology, all of which may have different effects on subsequent opioid use behavior.

## **2.7 CONCLUSION**

The field of addiction medicine is at a lack of consensus as to the real effect of chronic pain on treatment response among opioid dependent patients. The lack of a single “gold standard” measurement of treatment response and the lack of a consistent measurement of pain makes it difficult to summarize and compare the results of existing studies.

## **2.8 ACKNOWLEDGMENTS, FUNDING, AND AUTHOR CONTRIBUTION**

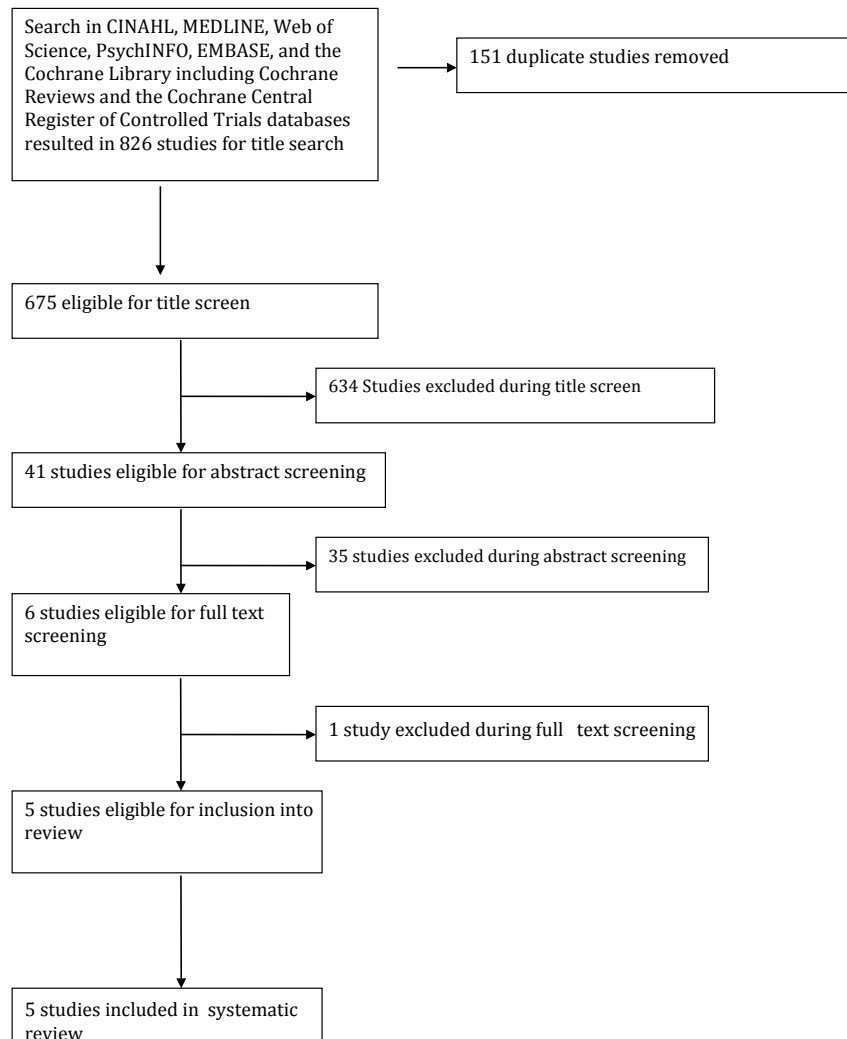
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BBD and ZS conceived the research question and designed the review protocol. BBD and MB completed the systematic review processes in duplicate, including the electronic literature search, study screening, and data abstraction. BBD, ZS, and LT designed the data-analysis plan for the chronic pain measurement validation in the clinical sample. BBD, MB, LT, ZS, CP, MV, JD, DCM, DD, GP, and AW contributed equally to writing and revision of the manuscript. All authors have approved the version of the manuscript being submitted.

## 2.9 FIGURES AND TABLES

**Figure 2.4.2:** Flow Diagram of Systematic Review Title, Abstract, and Full Text Screening

**Figure 1: Flow Diagram of Systematic Review Title, Abstract, and Full Text Screening**



**Table 2.4.1: Description of Electronic Search Strategies**

CINAHL Search Strategy	<ol style="list-style-type: none"> <li>1. (MH "chronic pain+")</li> <li>2. (MH "hyperalgesia")</li> <li>3. (MH "opioid induced hyperalgesia")</li> <li>4. (MH "methadone+")</li> <li>5. (MH "methadone maintenance treatment+")</li> <li>6. (MH "opioid substitution treatment")</li> <li>7. (MH "opioid addiction")</li> <li>8. (MH "substance related disorders")</li> <li>9. 1 OR 2 OR 3</li> <li>10. 4 OR 5 OR 6</li> <li>11. 7 OR 8</li> <li>12. 9 AND 10 AND 11</li> </ol>
MEDLINE Search Strategy	<ol style="list-style-type: none"> <li>1. methadon.mp OR methadone/</li> <li>2. limit 1 to humans</li> <li>3. opioid substitution treatment.mp/ OR opiate substitution treatment/</li> <li>4. limit 3 to humans</li> <li>5. substance-Related Disorders.mp OR substance-related disorders/</li> <li>6. limit 5 to humans</li> <li>7. chronic pain.mp. or Chronic Pain/</li> <li>8. limit 7 to humans</li> <li>9. 2 OR 4</li> <li>10. 9 AND 6 AND 8</li> </ol>
Web of Science Search Strategy	<ol style="list-style-type: none"> <li>1. Topic=("methadone" OR "methadone maintenance therapy")</li> <li>2. Topic=("opioid dependence" OR "addiction")</li> <li>3. Topic=("chronic pain " OR "pain")</li> <li>4. 1 AND 2 AND 3</li> </ol> <p>refined to original articles in substance use/psychiatry research area</p>
PsychINFO Search Strategy	<ol style="list-style-type: none"> <li>1. exp Drug Therapy/ or exp Methadone Maintenance/ or exp Heroin Addiction/</li> <li>2. exp Methadone/ or exp Drug Therapy/ or exp Drug Dependency/</li> <li>3. exp Drug Therapy/ or exp Methadone Maintenance/</li> </ol>

	<p>4. exp Drug Abuse/ or substance related disorder.mp. or exp Drug Dependency/                      5. substance abuse.mp. or exp Drug Abuse/                      6. chronic pain.mp. or exp Chronic Pain/                      7. 1 OR 2 OR 3                      8. 4 OR 5                      9. 7 AND 8 AND 6</p>
EMBASE Search Strategy	<p>1. methadone treatment/ or methadone/ or methadone plus naloxone/                      2. methadone/ or opiate addiction/ or substitute opioid therapy.mp                      3. opiate substitution treatment/ae [Adverse Drug Reaction]                      4. substance abuse/ or addiction/ or drug dependence/                      5. chronic pain.mp. or chronic pain/                      6. 1 OR 2 OR 3                      7. 4 AND 5 AND 6</p>
Cochrane Library (Cochrane Review and Cochrane Central Register of Controlled Trials) Search Strategy	<p>1. "methadone" OR "methadone maintenance treatment" OR "opioid substitution treatment"                      2. "substance abuse disorder" OR "opioid abuse" OR "substance-related disorder" OR "opioid addiction"                      3. "chronic pain" OR "pain" OR "hyperalgesia" OR "neuropathic pain" OR "pain"                      4. 1 AND 2 AND 3</p>

**Table 2.5.2a: Summary of Results of Studies Eligible for Inclusion into Systematic Review**

Author Name	Year	Journal Name	Study Design	Number of Participants (mean age)	% Male	Definition of Methadone Response	Statistical Analysis	Findings, Magnitude of Association, p-value
Trafton, J.A	2004	Drug and Alcohol Dependence	Cross Sectional	251 (49)	97	Propensity for misuse of substances with analgesic effects (number of days of drug use including opioids and heroin in the last 30 days and percentage of patients who injected drugs in the last 6 months)	ANOVA for first outcome (i.e. Days of Drug use in last 30 days) and chi square for percentage of patients who injected drugs in last 6 months)	ANOVA t-tests evaluating the differences in the mean number of days (out of 30) of illicit opioid use between the overall (1.6 days), pain (2.3 days), and non-pain (0.8 days) populations found a significant (p<0.03) difference between these groups.
Barry, D.T	2008	Journal of Addiction Medicine	Qualitative /Cross Sectional	25 (n/a)	28	Experiences Working with MMT patients, and Interest in receiving specialized training	Qualitative Study, reported descriptive statistics	60% of chronic pain patients of counselors reported continued drug use, 56% of chronic pain patients of counselors attributed the continued drug use to reasons for pain reduction
Ilgen, M.A	2006	Drug and Alcohol Dependence	Prospective Cohort Design	200 (49.5)	99	Looking at number of days of drug use out of the last 30 days for heroin and illicit prescription analgesics), comparing chronic pain and no chronic pain patients at intake and 1 year	Repeated Measures ANOVA	Presence of chronic pain did not greatly impact participants substance use behaviours, where patients reporting pain (intake[1]:2.5 days opioid use, 1-year[1]:0.3 days opioid use/I: 21.9 days heroin use, 1: 3.1 days heroin use), no-pain (I: 0.8 days opioid use, 1: 0.0 days opioid use/I: 23.0 days heroin use, 1: 3.5 days heroin use), and the overall population (I: 1.7 days opioid use, 1: 0.2 days opioid use/I: 22.4 days heroin use, 1: 3.3 days heroin use) showed similar rates of heroin use and only a mild difference in the rate of illicit opioid use across groups (p=0.012), where the observed treatment effect is marginal.
Rosenblum, A.	2003	JAMA	Cross Sectional	390 (43)	62	Correlates of Chronic Severe Pain (drug cravings, drugs used in the last 3 months and reason for using drugs)	OR used for all outcomes (i.e. Drugs used in the last 3 months, drug cravings, and reasons for using drugs)	Significant Association found for drug craving differences between chronic pain and non-chronic pain patients (p<0.05), no significant differences between the number of times of drug use in the last 3 months (p>0.05)
Barry, D.T	2009	American Journal of Addiction	Cross Sectional	293 (35.7 for chronic pain, 29.6 for non-chronic pain)	60	Consumption of prescription and non-prescription opioids in the last 7 days to reduce pain	Chi Square, no significance in substance abuse in the last 7 days between CP and non CP patients	Rates of using more than prescribed opioid medication (chi-square statistic: 0.25, p>0.05), someone else's opioid medication (chi-square statistic: 1.21, p>0.05), heroin (chi-square statistic: 0.15, p>0.05), street methadone (chi-square statistic: 1.54, p>0.05) were not significantly different between patients

								reporting a life-time history of pain in comparison to patients reporting no history of pain.
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**Table 2.5.2b: Definitions and Measurements of Chronic Pain and Treatment Response Across Studies**

Author Name	Year	Definition of Chronic Pain	Chronic Pain Measurement	Definition of Methadone Response	Measurement of Methadone Response	Findings
Trafton, J.A	2004	moderate to very severe pain (scale = none, mild, moderate, severe, very severe) experienced in the last 4 weeks	using the SF-3V6 (tested in veteran populations)	propensity for misuse of opioid substances (number of days of drug use including opioids and heroin in the last 30 days and percentage of patients who injected drugs in the last 6 months)	Addiction Severity Index, self-report	t-tests evaluating the differences in the mean number of days (out of 30) of illicit opioid use between the overall (1.6 days), pain (2.3 days), and non-pain (0.8 days) populations found a significant difference between these groups.
Barry, D.T	2008	pain lasting greater than 3 months	self-report	no single definition of methadone response, just reported experiences of staff working with MMT patients	self-report, questionnaire	higher percentage of chronic pain patients attributed continued opioid use for pain reduction
Ilgen, M.A	2006	moderate to very severe pain (scale = none, mild, moderate, severe, very severe) experienced in the last 4 weeks	SF-3V6 Quality of Life Index, self report on a scale, in last 4 weeks how much pain have you experienced (none, mild, mod, severe, very severe)	continued opioid abuse, looking at number of days of drug use out of the last 30 days for heroin and illicit prescription analgesics)	Addiction Severity Index, self-report	significant difference in the number of days of opioid use between the pain, non-pain, and over-all patient groups, this difference was not observed for heroin use
Rosenblum, A.	2003	pain that persisted more than 6 months of moderate to severe intensity or significantly interfered with daily activities	Brief Pain Inventory, adapted, 0-10 point scale and pain interference measured with BPI subscale	drug cravings, drugs used in the last 3 months, and reason for using drugs	self-report, questionnaire	higher rates of drug cravings among patients with pain, however no significant differences between patients with and without pain when evaluating drug use over the last 3 months (p>0.05)

Barry, D.T	2009	Presence of pain in the last 7 days – 3 months, and level of intensity on a 6 point scale (0-5 scale, 5 being unbearable)	self-report	consumption of prescription and non-prescription opioids in the last 7 days to reduce pain	self-report, questionnaire	rates of opioid misuse did not significantly differ between patients reporting a life-time history of pain in comparison to patients reporting no history of pain

**Table 6.4: Risk of Bias Assessment: Modified Newcastle Ottawa Scale for Methadone Patient Research**

<b>Risk of Bias</b>	<b>Criterion</b>	<b>Ilgen 2006</b>	<b>Trafton 2004</b>	<b>Rosenblum 2003</b>	<b>Barry 2009</b>
Selection Bias	Is the case definition adequate? (how well is chronic pain and/or methadone response defined)	⊕	⊕	⊕	⊕
	Was there a consecutive or obviously representative series of cases?	⊕	⊕	⊕	⊗
	Were controls selected from the community? (are cases and controls selected from the same methadone clinic populations)	⊕	⊕	⊕	⊕
	Definition of control: Were controls disease free?	⊕	⊕	⊕	⊗
Detection Bias	Comparability of cases and controls on the basis of the design or analysis: a) Study controls for duration of treatment when assessing response to MMT	⊗	⊗	⊗	⊗
	Ascertainment of exposure and outcome of interest included an objective measurement (i.e. use of urine toxicology screening and a validated pain measurement scale)	⊗	⊗	⊗	⊕
	Was there the same method of exposure ascertainment for cases and controls?	⊕	⊕	⊕	⊕
	Is there little missing data?	⊗	⊗	⊗	⊗

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## CHAPTER 3

### STUDY 2

#### **Evaluation of Clinical and Inflammatory Profile in Opioid Addiction Patients with Comorbid Pain: Results from a Multi-Centre Investigation**

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### 3.1 ABSTRACT

**Background:** Chronic pain is the most commonly reported comorbidity among patients with opioid addiction receiving methadone maintenance treatment (MMT), with an estimated prevalence ranging between 30 to 55%. Evidence suggests patients with comorbid pain are at high risk for poor treatment response including continued illicit substance use. Due to the important relationship between the presence of pain and illicit substance abuse within the MMT setting, it is imperative we target our efforts toward understanding the characteristics of this patient population.

**Methods:** The primary objective of this study was to explore the clinical and inflammatory profile of MMT patients reporting comorbid pain. This multi-centre study enrolled patients (n=235) on MMT for the treatment of opioid dependence. Clinical history, blood and urine data were collected. Blood samples were obtained for inflammatory markers serum levels (TNF- $\alpha$ , IL-1ra, IL-6, IL-8, IL-10, IFN- $\gamma$  and CCL2). The study objectives were addressed using a descriptive statistical summary and a multivariable logistic regression model constructed in STATA Version 12.

**Results:** Among participants eligible for inclusion (n=235), serum IFN- $\gamma$  and substance abuse behavior proved to be important delineating characteristics for the detection of comorbid pain. Analysis of inflammatory profile showed IFN- $\gamma$  to be significantly elevated among patients reporting comorbid pain (Odds Ratio: 2.02 95%CI: 1.17, 3.50; p=0.01). Patients reporting comorbid pain were also found to have an increase in positive

opioid urine screens (OR: 1.02 95% CI 1.00, 1.03;  $p=0.01$ ), indicating an increase in illicit opioid consumption.

**Conclusion:** MMT patients with comorbid pain were shown to have elevated IFN- $\gamma$  and higher rates of continued opioid abuse. The ability to objectively distinguish between patients with comorbid pain may help to improve the prediction of poor responders to MMT as well as identify treatment approaches such as anti-inflammatory medications as a safe alternative for MMT patients with comorbid pain.

## 3.2 INTRODUCTION

Attention towards improving treatments for opioid dependence is increasing in conjunction with efforts to control the abuse of opioids. These efforts are seriously challenged by the increase in opioid prescriptions worldwide, where the global population of opioid users is now estimated to be 21.9 million people.<sup>1</sup> Methadone—a synthetic opioid—is the most common treatment of opioid dependence.<sup>2</sup> It is given to alleviate the symptoms of withdrawal and prevent relapse.<sup>2</sup> Studies examining patients on methadone maintenance treatment (MMT) report chronic pain as a common comorbid disorder, with prevalence ranging from as low as 37%<sup>3</sup> in some studies to as high as 55.3% in others.<sup>4</sup> Chronic pain is both prevalent and concerning for patients with opioid addiction. Patients with comorbid chronic pain report a higher incidence of continued opioid abuse (COA).<sup>3,5,6</sup> Concomitant use of illicit opioids in combination with MMT poses a serious risk of abnormal cardiac conductivity,<sup>7,8</sup> overdose,<sup>9,10</sup> and death.<sup>9</sup> MMT patients with comorbid chronic pain are thought to be in the highest risk category for such adverse events due to the larger amount of illicit opioid consumption chronic pain patients report.<sup>3,5,6</sup> Such reported outcomes in combination with the high reported prevalence of pain dictate the need for further investigation into the characteristics and treatment effects of pain in patients with opioid use disorder. Determining the important delineating features of pain among MMT patients will help clinicians to develop a stronger understanding of the clinical profile and risks associated with comorbid pain.

Inflammatory profile serves as a recent development in the search for objective measures of pain, and possibly a source of discrimination between patients with and without chronic pain. Both cytokines and chemokines operate as neuromodulators, regulating neuroinflammation and neurodevelopment.<sup>11</sup> The deregulation of cytokines and chemokines is associated with both neuroinflammation and neurodegeneration,<sup>12,13</sup> and any increase in neuroinflammation can result in neuropathic pain as well as inflammation.<sup>14-16</sup> Proinflammatory cytokines and chemokines have been noted to also provoke hyperalgesia.<sup>17,18</sup> One such study demonstrated a dose response relationship between elevating cytokine level (IL-1 $\beta$ , IL-2, IL-6, IFN- $\gamma$ , TNF- $\alpha$ ) and chronic pain severity.<sup>18</sup> However this study was restricted by a small sample size (94 patients with pain, 6 healthy controls), where most cytokines failed to reach significance after adjusting for multiple testing.<sup>18</sup>

Due to the important relationship between the presence of pain and illicit substance abuse as well as the overwhelming presence of pain within the methadone setting, it is imperative we target our efforts toward understanding the characteristics of this patient population. Understanding pain is important not only in preventing adverse health outcomes for patients, it is vital for reducing social expenditure on treatments that may stand ineffective for specific subpopulations. The studies examining the characteristics of chronic pain are small in number and marked by inconsistent findings. There are an equal number of studies reporting a positive association between chronic pain and continued opioid abuse (COA)<sup>3,5</sup> as those reporting no significant findings.<sup>19,20</sup> As well, we have yet to properly identify the mechanisms of pain among MMT patients. These shortcomings

prompted us to commence a sizable investigation of MMT patients to address our primary research objective: to explore the clinical and inflammatory profile of MMT patients reporting comorbid pain. We addressed our objective using data collected for the GENetics of Opioid Addiction (GENOA) research collaborative.<sup>21</sup> GENOA is a multi-centre cross-sectional investigation, accomplished through the partnership between McMaster University and the Canadian Addiction Treatment Centres (CATC).<sup>21</sup>

## **3.3 METHODS**

### **3.3.1 Overview of GENetics of Opioid dependence (GENOA)**

Data have been collected for this study from the GENOA research collaborative between the Canadian Addiction Treatment Centres (CATC) – the largest MMT network of opioid dependence treatment centres in North America – and the Population Genomics Program in the Faculty of Health Science at McMaster University. The detailed methodology of the GENOA investigation has been described previously.<sup>21</sup> The GENOA study is a multi-centre cross-sectional analysis, which includes clinical data from four sites (methadone clinics) in southern Ontario. Participants were enrolled in the study between June and December of 2011. The Hamilton Integrated Research Ethics Board approved this study.

The study inclusion criteria, were: men and women, age  $\geq 18$  years, ability to provide informed consent, willingness to provide a blood sample, and receiving methadone for opioid dependence treatment. All study participants were diagnosed with opioid dependence according to DSM-IV criteria, based on clinical interviews at the time of entry into treatment with methadone. This study will focus on the data collected from 235 MMT patients ([Figure 3.3.1](#)), investigating the relationship between self-reported comorbid and methadone response. Information on participant's physical comorbidities was gathered from face-to-face clinical interviews performed by trained OATC nurses. The presence of chronic and/or comorbid pain was determined by asking patients to respond to the following question: “are you currently experiencing or have been diagnosed with chronic pain?” The use of this question to define chronic pain cases has

been validated against the Brief Pain Inventory in a previous study.<sup>22</sup> Results from the validation suggest simply asking patients whether they have pain shows an 88.8% specificity, 84.4% PPV and C-statistic of 0.69.<sup>22</sup> COA was determined through the assessment of weekly urinalysis for illicit opioids testing. Pain was also examined in relationship to the following inflammatory markers: TNF- $\alpha$ , IL-1ra, IL-6, IL-8, IL-10, IFN- $\gamma$ , and CCL2 serum. Evidence shows that different anticoagulants (such as EDTA present in blood collection tubes) influence absolute cytokine levels in various manners,<sup>23-25</sup> as such serum levels were used in preference to plasma.

Interviewers obtained weight and height measurements from all participants. Information on social demographic factors, medical history, methadone dose, methadone treatment duration, family history of drug use, and psychiatric disorders were obtained during the interview process. All participants received the Mini International Neuropsychiatric Interview (M.I.N.I.) drug and alcohol modules. Blood samples were taken for serum inflammatory markers level. Participant blood specimens were processed within 2 hours and stored on site in – 20 degrees Celsius freezers then shipped monthly to the Hamilton research lab and stored in liquid nitrogen until the time of analysis.

### **3.3.2.0 Laboratory Analyses**

Laboratory measures include urine toxicology screens to measure illicit opioid abuse, and Bio-Plex<sup>TM</sup> Cytokine Assay (Bio-Rad)<sup>26</sup> to measure serum inflammatory markers.

**3.3.2.1 Urinalysis:** Qualitative and semi-quantitative urinalysis was conducted using iMDx<sup>TM</sup> Prep Assay.<sup>27</sup> The iMDx<sup>TM</sup> Prep Assays are intended for the measurement of

drugs-of-abuse as well the identification of adulteration in human urine samples on the iMDx™ Analyzer and used in drug rehabilitation clinics and physician offices by trained users. OATC clinics require patients to provide weekly urine samples as part of routine clinical care. While participants are also tested for cocaine, THC, and benzodiazepines, we are primarily interested in the patient's use of opioids. Using the iMDx™ Prep Assays we are able to differentiate between specific types of opioids such as naturally occurring opioids (heroin), prescribed synthetic opioids, as well as methadone.<sup>27</sup> In this investigation opioid use is an indicator for methadone response. Since methadone is not used for the treatment of benzodiazepine or cocaine addiction, a patient's continued use of these substances does not indicate a methadone treatment failure. Urine toxicology screening was used to determine whether opioids (natural and synthetic) were present in the participants' urine.

Participants provided urine samples at supervised facilities; there were no missing urine samples from study participants. COA was determined by calculating the percentage of positive opioid urine screens provided by participants (number of positive opioid urine screens / total number of opioid urine screens). High COA percentage is indicative of a high number of positive opioid urine screens, or alternatively a higher rate of illicit opioid consumption. We chose to include a measure of continued opioid abuse that adjusts for the entire duration of methadone treatment. Opioid dependence is a remitting, relapsing disorder and as such, restricting the measurement of response to such a short time frame of the patient's overall treatment course is limited.

### **3.3.2.2 Serum Inflammatory Markers Methods: Bioplex assay**

Serum samples were collected from participants using BD Vacutainer tubes and allowed to clot for 30 minutes. Samples were centrifuged at 1,500g for 15 minutes at room temperature and serum frozen in liquid nitrogen until further analysis.

Samples were thawed only once and 50 microliter removed to a 96 well plates. Serum cytokine levels were determined using the Bioplex assay (Bio-Rad Laboratories, Hercules, CA) measuring IL-6, IL-8, IL-1ra, TNF- $\alpha$ , IFN- $\gamma$ , IL-10, IL-1B, and CCL2, and standard curves generated as per manufacturer's instructions. The Bioplex Manager 6.0 software was used for data analysis. Cytokine measurements were expressed as pg/ml.

While IL-1B was originally tested for in all participants, more than 50% of the samples were inconclusive. With such a high proportion of data missing we chose not to include IL-1B in any analyses.

### **3.3.3 Statistical Analysis**

STATA Version 12 was used to complete all analyses. All study data have been quality checked and entered into Research Electronic Data Capture (RedCap) database at the Population Genomics Program, McMaster University.

Multiple imputation using chained equations was employed to adjust for missing data. Age, sex, COA, chronic pain and methadone dose (mg/day) were the variables selected to aid in the MI prediction of missing values. When running analyses of inflammatory biomarkers, if the value was below detectable range, the lowest value before detection

cut-off was imputed. All data were tested for normal distribution, where log transformations were made when necessary. All outlier data were removed before performing the primary analyses. To adjust for outlier variables, box plots were constructed for all predictors included in each model using STATA version 12, these being methadone dose, duration on MMT, age, BMI, and all inflammatory biomarkers. The box plots resulted in the identification of ten outlier observations across predictors ( $n_{\text{participants}} = 10$ ). The inflammatory biomarkers proved to have an overwhelming number of outlier observations due to their wide distribution, limiting our ability to adequately remove them from the sample (Figure 13.3). However, we acknowledge how sensitive inflammatory profiles are and that currently no normal range has been established in the MMT patient population.

We determined the appropriateness of our sample size ( $n=235$ ) to address our primary analysis, the multivariable logistic regression of chronic pain. With response to treatment (COA) as our primary independent variable, in addition to eleven other a priori defined covariates, we determined our model could withstand the addition of 20 covariates under the assumption that model stability is maintained with 10 – 12 observations per covariate. Within this model we have added twelve covariates, allowing for 20 observations per covariate in our sample of 235.<sup>28</sup> Reporting of this study follows the Strengthening of Reporting of Observational Studies in Epidemiology (STROBE) guidelines.<sup>29</sup>

Primary Analysis:

All demographic characteristics are summarized using descriptive statistics, reporting means and SD for continuous values and percentages for dichotomous values. All demographic characteristic data are presented by pain status. A multi-variable logistic regression model (RM) was constructed to address our primary objective, determining the clinical and inflammatory profile of patients reporting comorbid pain, where self-reported pain was the binary dependent variable. This model included multiple covariates identified as or trending towards significance during the univariate analysis (age, IFN-Gamma, response to treatment [COA]). The model also adjusted for important confounding variables such as age, presence of inflammatory medications, sex, presence of infectious disease, as well as methadone dose (mg/day).

## 3.4 RESULTS

### 3.4.1 Demographic Characteristics of GENOA Participants

The recruitment process led to a completed sample of 249 participants eligible for this study. Any participants reporting prescribed opioids in their current medication list were removed from any analyses, leaving us with a sample of 235 MMT patients. A flow diagram of participant screening and selection is presented in [Figure 3.3.1](#).

Among participants eligible for inclusion into the analyses (n=235), 40.42% were female with the mean age of 36.82 (Standard deviation [SD] 10.36) years and mean body mass index [BMI] of 26.59 (SD 5.46). Participants self-reported the following comorbidities; 0.43% HIV, 22.98% hepatitis, 5.11% liver disease, 24.68% chronic pain, 2.13% epilepsy, 23.40 % other, with a total of 58.40% of participants reporting at least one of the aforementioned comorbidities. When asked to indicate any “other” physical comorbidities, participants responses included: diabetes (n=8), cardiac functioning abnormalities and stroke history (n=7), hypertension (n=3), high cholesterol (n=1), neurological deficit (n=2), Crohn’s disease (n=4), asthma (n=8), renal functioning problems (n=2), gall stones (n=3), fibromyalgia (n=1), thyroid abnormalities (n=3), arthritis (n=5), respiratory problems (n=2), allergies (n=3), hernia (n=1), gout (n=1), spondylitis (n=1), and endometriosis (n=1). Reporting of these “other” comorbidities did not vary between patients with and without pain. All participants’ demographic information presented by pain status is summarized in [Table 3.4.1](#).

### **3.4.2 The Clinical and Inflammatory Profile of Methadone Maintenance Patients With Comorbid Pain**

The demographic characteristics summarized in [Table 3.4.1](#) suggest that participants reporting pain are similar in demographic and clinical profile to participants without pain. We find age, methadone dose (mg/day), sex, treatment duration (months), and onset age of opioid abuse to be relatively the same across patient groups ([Table 3.4.1](#)). A distinct aspect of clinical profile for patients with pain is noted in the significantly different treatment response rates across groups. Another distinction between patients with and without pain is their inflammatory profile, where we found participants with pain to have elevated IFN- $\gamma$ , trending toward significance.

We chose to construct a multi-variable logistic regression model to further assess these associations using patient reported pain as our outcome of interest. Regression models allow the assessment of association between factors while also adjusting for other important confounders. Using results from the univariate analysis to guide or selection of covariates, we included COA (treatment response) and IFN- $\gamma$  as our primary independent variables. We adjusted this model for presence of inflammatory medications, sex, presence of infectious disease, as well as methadone dose (mg/day). The results from the multi-variable regression model are summarized in [Table 3.4.2](#). Results suggested IFN- $\gamma$  to be significantly elevated among patients reporting chronic pain, while adjusting for important covariates (Odds Ratio: 2.02 95% CI: 1.17, 3.50;  $p=0.01$ ). The results also suggest patients reporting comorbid pain have an increase in positive opioid urine screens (OR: 1.02 95% CI 1.00, 1.03;  $p=0.01$ ), indicating an increase in illicit opioid consumption.

## **3.5 DISCUSSION**

### **3.5.1 Summary of Findings**

Considerations of pain in the clinical setting for patients on MMT for opioid dependence is complicated by the inconsistent findings reported across studies. While some studies appear to be reporting a strong association between chronic pain and substance abuse among MMT patients,<sup>3,5</sup> other studies report no association.<sup>19,20</sup> There is also limited research on the inflammatory characteristics of pain patients within MMT. Results from this investigation provide a thorough evaluation of the clinical and inflammatory characteristics of opioid dependent patients with pain, where we show 1) response to MMT is significantly influenced by the presence of pain, and 2) MMT patients reporting chronic pain show elevated levels of IFN- $\gamma$ .

### **3.5.2 The Context of Comorbid Pain and Opioid Abuse in the Current Literature**

MMT patients with severe pain are known to have increased methadone dose,<sup>4</sup> and an increased rate of illicit substance use.<sup>4</sup> Findings from this study are consistent with some of the literature,<sup>3,5</sup> where response to treatment was highly associated with chronic pain status. When determining the source of contention across studies examining pain and opioid abuse we took a closer look at the differences in measurement and definition of response to MMT. While in this study we chose to use the percentage of opioid positive urine screens as an objective proxy outcome measure for response to methadone treatment, other studies report response to treatment as the number of days of illicit heroin

or opioid abuse in the last month,<sup>5,20</sup> or the percentage of patients that report using illicit opioids in the month.<sup>3,6,19</sup> In addition, a number of studies rely on different measurement for response such as self-reported,<sup>3,6,19</sup> and some studies go so far as using validated tools to assess the severity of substance abuse behavior.<sup>5,20</sup>

In comparison to our investigation, the majority of clinical studies assess response to treatment over a very short time frame (seven days to three months).<sup>3,20,30</sup> It is known that opioid dependence is a chronic relapsing disorder, with the average methadone treatment duration being two years. As such, capturing “response,” over a short time frame of a patient’s overall treatment course appears limited. Determining response to MMT by reviewing the patient’s entire duration on MMT appears as a more adequate approach to characterizing the course and patient response to methadone. In this study, we looked at the number of positive opioid urine screens as a percentage of the total number of screens in an effort to adjust for these duration effects, which may explain why our results may differ from studies basing treatment response on a shorter time frame (i.e seven to nine days).<sup>20</sup>

Similar to the measurement of response, the measurement chronic pain also varies across studies. This variation may also be a source of discrepancy in the reported findings of the current literature. The measurement of pain varies from validated pain measures in some studies<sup>3,20</sup> to the use of self-reported pain in others.<sup>6,19</sup> Even studies selecting “validated” pain measures such as the Brief Pain Inventory (BPI),<sup>3</sup> should be interpreted with caution,

for no pain measurement tool has undergone specific psychometric testing or predictive/criterion validation within the MMT patient population.

### **3.5.3 Inflammatory Profile and Comorbid Pain**

Our results have shown IFN- $\gamma$  to be elevated among MMT patients reporting comorbid pain. The role of IFN- $\gamma$  in pain can be inferred from animal studies where IFN- $\gamma$  is noted to induce pain.<sup>31</sup> Tsuda et al (2009) found that the IFN- $\gamma$  receptor (IFN- $\gamma$ ) mediates spinal microglia activation, ultimately leading to neuropathic pain.<sup>31</sup> When the spinal microglia is activated they increase pain processing inside the dorsal horn to an important level that triggers neuropathic pain.<sup>32-35</sup> This is one of the mechanisms by which inflammation causes and propagates pain.

Our findings are consistent with other studies, where IFN- $\gamma$  is elevated during periods of pain.<sup>18,36</sup> In one investigation, 21 patients with lumbar degenerative disc disease were compared against 3 controls, for inflammatory profile differences, where they identified immunoreactivity of IFN- $\gamma$  in patients with axial back pain.<sup>36</sup> Another study, examining 94 chronic pain patients and six healthy volunteers found pro-inflammatory cytokines such as IL-1 $\beta$ , IL-2, IL-6, IFN- $\gamma$ , TNF- $\alpha$  correlated with increasing pain intensity.<sup>18</sup> In addition, proinflammatory cytokines have been demonstrated to directly oppose opioid actions, where one study demonstrated that an increase in morphine and methadone administration is directly linked to an increase in spinal glial activation as well as elevated cytokine level.<sup>37</sup>

To date no study has explored the association between comorbid pain and inflammatory profile within the MMT patient population. This investigation showed the significant association between elevated IFN- $\gamma$  and the presence of chronic pain. The importance of these results rests on our understanding of treatment strategies for patients with concurrent opioid dependence and chronic pain. The ability to objectively distinguish between patients with comorbid pain through the identification of IFN- $\gamma$  may be able to help distinguish treatment approaches such as anti-inflammatory medications as a safe alternative to opioid analgesics in this patient population.

### **3.5.4 Strengths and Limitations**

A major limitation of this study is the use of self-reported chronic pain. The true prevalence of pain could have been under or overestimated. Without the use of a validated pain assessment for opioid dependent patients receiving MMT, the reported results should be subject to cautious interpretation. However, in a recent study we have validated the use of patient reported pain in comparison the BPI assessment, where results suggest simply asking patients whether they have pain shows an 88.8% specificity, 84.4% PPV and C-statistic of 0.69.<sup>22</sup> Such results indicate that the use of patient reported pain very closely identifies the same population as the BPI assessment. In addition, we should note discount the use of more objective markers for reported pain. This study found elevated inflammatory markers, supporting the case for both the use of objective pain indicators and consideration of anti-inflammatory agents as adjunct therapy for MMT patients.

The use of a cross-sectional design is an additional limitation of this study, which precludes us from making any assumptions as to the causal pathway of inflammation.

Elevated inflammatory markers within the pain subset may be a result of injecting drug use behavior—known to cause cellulitis<sup>38</sup> and endocarditis<sup>39</sup>—and could lead to patients to resume injecting opioids for the purpose of reducing pain. Consequently, the pain itself may also cause the inflammation. While we can be confident our analyses have been properly designed to adjust for high-risk behavior and infectious disorders, due to the cross-sectional nature of the data we are unable to adequately flush out the mechanism of inflammation.

### **3.6 CONCLUSION**

While our study shows a significant association between pain and poor response to MMT, it also proves important in determining an objective measure of inflammation for MMT patients with comorbid pain. We determined that pain is significantly associated with an increase in positive opioid urines screens, as well as a substantial elevation of IFN- $\gamma$ . In an effort to adequately manage patients at an increased risk for methadone overdose and poor response, future research should determine the therapeutic impact of using anti-inflammatory analgesics to prevent the use of illicit opioids and reduce pain in opioid dependent patients on MMT.

### **3.7 ACKNOWLEDGMENTS, AUTHOR CONTRIBUTIONS, AND FUNDING**

We report no competing interests for this investigation. This work was supported by CIHR Drug Safety and Effectiveness Network (DSEN) grant (grant number: 126639).

The funders had no role in study design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript. Dr. Zainab Samaan, Brittany B. Dennis and Dr. Lehana Thabane were responsible for the development of the question and research protocol for this study.

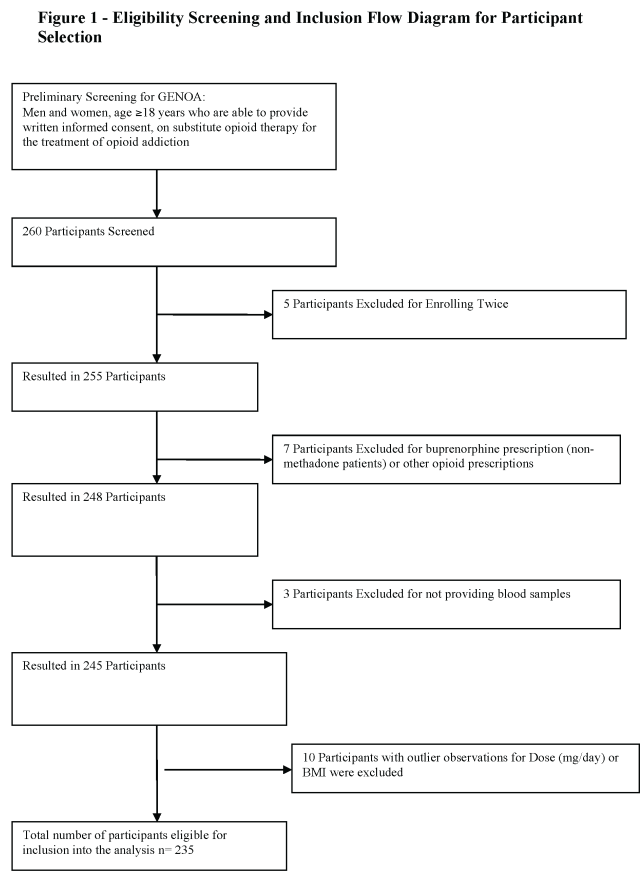
Brittany B. Dennis was responsible for all statistical analyses performed in this investigation. Dr. M. Constantine Samaan designed and performed all laboratory analyses for inflammatory profile. All authors contributed equally during manuscript development. Zainab Samaan had full access to data from this investigation and she is accountable for the reliability of the data and the accuracy of all analyses performed

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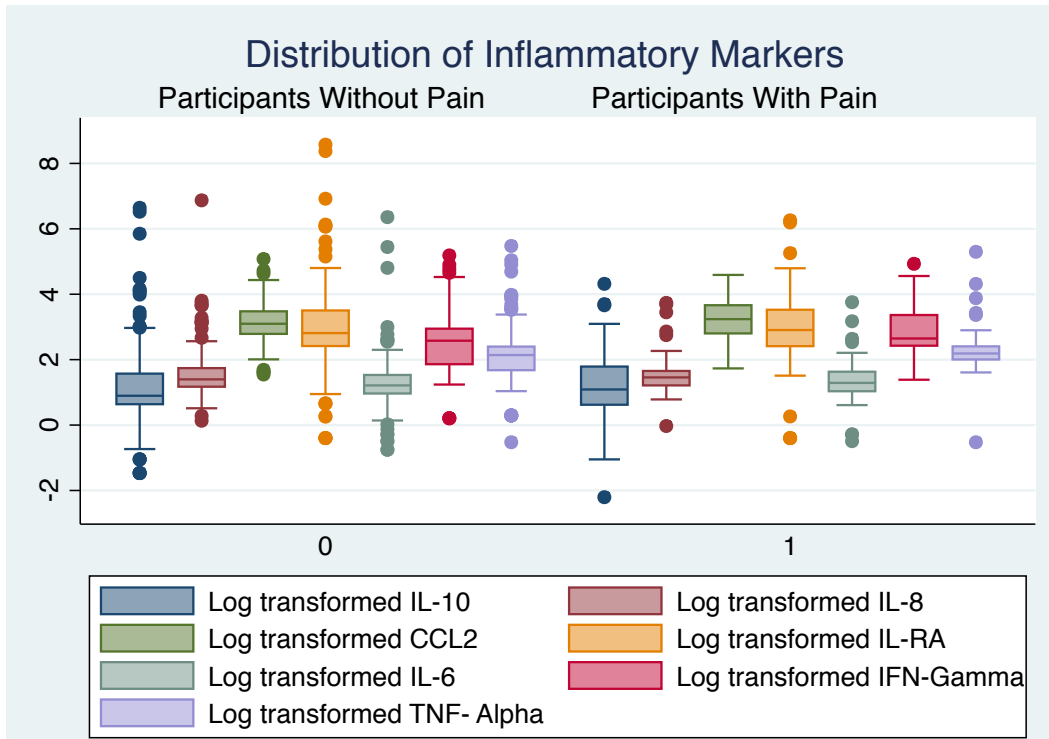
would like to also thank the McMaster University undergraduate students who contributed a great deal of time in helping with data entry and cleaning. These students include Sindooraa Iyer, Leen Naji, Anuja Bhalerao, Herman Bami and Andrew Kamphuis.

### 3.8 FIGURES AND TABLES

**Figure 3.3.1 Patient Flow Diagram**



**Figure 3.3.3** Distribution of Inflammatory Biomarkers



Cytokine data provided in this figure was originally measured in pg/mL using participant serum, the distribution here is provided

**Table 3.4.1 Participant Demographic Characteristics (n=235)**

	<b><u>Comorbid Pain, n=58 (SD)</u></b>	<b><u>No Comorbid Pain, n=177 (SD)</u></b>	<b><u>P-Value Univariate Analysis</u></b>
<b><u>Demographic Characteristics</u></b>			
<b>Female (%)</b>	41.38	40.11	0.90
<b>Mean Age in Years</b>	39.45 (10.29)	35.95 (10.26)	0.02
<b>Mean BMI</b>	27.46 (5.08)	26.31 (5.56)	0.15
<b>Mean Methadone Dose in mg/day</b>	84.64 (51.51)	85.74 (50.14)	0.76
<b>Mean Response to MMT (Mean % Opioid Positive Urine Screens)</b>	23.99 (27.14)	15.82 (20.11)	0.02
<b>Duration on MMT in Months</b>	41.31 (38.99)	38.25 (42.79)	0.61
<b>Mean Onset Age of Opioid Abuse</b>	23.21 (11.28)	23.16 (8.61)	0.98
<b>Patients with HIV (%)</b>	0.00	0.56	Unable to Determine
<b>Patients with Hepatitis (%)</b>	29.31	20.90	0.22
<b><u>Inflammatory Profile</u></b>			
<b>IL-10</b>	1.15 (1.14)	1.16 (1.28)	0.86

<b>IL-8</b>	1.55 (0.67)	1.56 (0.76)	0.97
<b>CCL2</b>	3.25 (0.60)	3.14 (0.57)	0.26
<b>IL-ra</b>	2.96 (1.30)	2.96 (1.33)	0.92
<b>IL-6</b>	1.35 (0.72)	1.30 (0.85)	0.62
<b>IFN- <math>\gamma</math></b>	2.78 (0.89)	2.55 (0.89)	0.08
<b>TNF- <math>\alpha</math></b>	2.25 (0.77)	2.20 (0.80)	0.69

a) All inflammatory biomarker concentrations have been log transformed for this table (originally measured as pg/mL)

b) MMT = Methadone Maintenance Treatment, IL- Interleukin, BMI: Body Mass Index = kg/m<sup>2</sup>

c) These are the results for the 235 participants eligible for study inclusion, outliers identified for BMI and methadone dose were removed for regression models (n=10)

**Table 3.4.2 Clinical and Inflammatory Characteristics of Comorbid Pain: A Multi-variable Logistic Regression Model (N=235)**

<b>Covariates</b>	<b>Odds Ratio</b>	<b>95% Confidence Interval</b>	<b>P-Value</b>
Age (years)	1.03	0.99, 1.06	0.08
Sex	1.08	0.56, 2.07	0.82
Response to MMT (% positive opioid urine tests)	1.02	1.00, 1.03	0.01
Infectious Disease Status	1.40	0.65, 3.00	0.38
Methadone Dose (mg/day)	1.00	0.99, 1.01	0.94
Presence of Inflammatory Medications	1.26	0.41, 3.92	0.69
TNF-Alpha	0.69	0.37, 1.30	0.25
IFN-Gamma	2.02	1.17, 3.50	0.01
IL-6	1.18	0.60, 2.32	0.63
IL-ra	0.84	0.51, 1.37	0.49
CCL2	1.60	0.88, 2.88	0.12
IL-8	0.73	0.43, 1.21	0.22
IL-10	1.01	0.69, 1.48	0.97

a) Sex is interpreted as female, in reference to males

b) Infectious Disease Status was a binary measure of the presence of HIV and/or Hepatitis

c) MMT: methadone maintenance treatment

d) All cytokine measurements have been log transformed and the original measurements were in pg/mL

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## CHAPTER 4

### Study 3

#### **Brief Pain Inventory Fails to Identify Prognostically Relevant Pain in Opioid Addiction Patients Receiving Methadone Treatment**

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## 4.1 ABSTRACT

**Background:** Chronic pain is implicated as a risk factor for illicit opioid use among patients with opioid addiction treated with methadone. However, there exists conflicting evidence that supports and refutes this claim. These discrepancies may stem from the large variability in pain measurement reported across studies. We aim to determine the clinical and demographic characteristics of patients reporting pain and evaluate the prognostic value of different pain classification measures in a sample of opioid addiction patients.

**Methods:** This study includes participants from the Genetics of Opioid Addiction (GENOA) prospective cohort study. We assessed the prognostic value of different pain measures for predicting opioid relapse. Pain measures include the Brief Pain Inventory (BPI) and patients' response to a direct pain question all study participants were asked from the GENOA case report form (CRF) "are you currently experiencing or have been diagnosed with chronic pain?" Performance characteristics of the GENOA CRF pain measure was estimated with sensitivity and specificity using the BPI as the gold standard reference. Prognostic value was assessed using pain classification as the primary independent variable in an adjusted analysis using 1) the percentage of positive opioid urine screens and 2) high-risk opioid use ( $\geq 50\%$  positive opioid urine screens) as the dependent variables in a linear and logistic regression analyses respectively.

**Results:** Among participants eligible for inclusion (n=444) the BPI was found to be highly sensitive, classifying a large number of GENOA participants with pain (n=281 of the 297 classified with pain, 94.6%) in comparison to the GENOA CRF (n=154 of 297 classified with pain, 51.8%). Participants concordantly classified as having pain according to the GENOA CRF and BPI were found to have an estimated 7.79% increase in positive opioid urine screens (Estimated coefficient: 7.79; 95%CI 0.74, 14.85; p=0.031) and a four times greater odds (Odds Ratio [OR]: 4.10 p=0.008; 95%CI: 1.44, 11.63) of engaging in a “high risk” level of illicit opioids use. The prognostic relevance of pain classification was not maintained for the additional participants classified by the BPI (n=143 discordant).

**Conclusion:** These results suggest that while the BPI may be more sensitive in capturing pain among patients with opioid addiction, this tool is of less value for predicting the impact of pain on illicit opioid use for opioid addiction patients on methadone maintenance treatment. The GENOA CRF showed high predictive ability, whereby patients classified according to the GENOA CRF are at serious risk for opioid relapse. Using the appropriate tool to assess pain in opioid addiction may serve to improve the current detection and management of comorbid pain.

## 4.2 INTRODUCTION

Morbidity and mortality incurred from opioid use outweighs the burden resulting from any other illicit substance and accounts for 9.2 million disability adjusted life-years (DALYs)—a 73% increase since 1990.<sup>1</sup> The global prevalence is rising and recent estimates propose 26 to 36 million people abuse opioids.<sup>2</sup> Without treatment patients with opioid addiction incur a substantial risk for serious comorbidities such as HIV,<sup>3</sup> hepatitis,<sup>3</sup> infective endocarditis, and mortality.<sup>4,5</sup>

Front-line treatments for opioid addiction include opioid substitution therapy (OST), whereby patients are prescribed long-acting synthetic opioids to reduce symptoms of craving and withdrawal under clinical supervision.<sup>6</sup> Methadone, buprenorphine, and are among the cadre of OSTs used globally, of which methadone is the oldest and most commonly prescribed treatment.<sup>7,8</sup> Methadone has been shown to reduce illicit opioid use<sup>9-11</sup> and criminal behaviour,<sup>11</sup> as well as improve adjunct therapy (e.g. counselling) compliance,<sup>10</sup> with higher doses providing the greatest benefit.<sup>12-15</sup> Even when compared against other OSTs, methadone proved more effective at reducing illicit opioid use.<sup>13,16,17</sup>

Despite the demonstrated benefit of methadone maintenance treatment (MMT), some patients continue to abuse opioids or drop out of methadone treatment altogether.<sup>18,19</sup> Lower methadone dose,<sup>20</sup> unemployment,<sup>20</sup> poly-substance use,<sup>21</sup> as well as the presence of physical or psychiatric comorbidity are among a number of risk factors that adversely affect OST compliance and outcomes.<sup>22-24</sup> Given the sharp rise in global opioid

prescriptions<sup>25</sup> more attention is being directed to chronic pain as an important and prevalent comorbidity. Chronic pain is commonly reported among patients receiving methadone for opioid addiction with estimates ranging from 24-55%.<sup>26-28</sup> Chronic pain is suggested to impact psychiatric symptoms, social functioning, as well as methadone pharmacokinetics.<sup>28-30</sup> Due to the long-term exposure to opioids some studies argue chronic pain mediates the effect of methadone by inducing a hyperalgesic state among patients,<sup>31,32</sup> which may in part explain the higher rates of opioid abuse reported among patients with comorbid pain.<sup>28</sup> However, there remains an uncertainty when assessing the impact of pain on opioid use behaviour within the addiction setting. While some studies report chronic pain to be a significant risk factor for substance abuse,<sup>26,28,33</sup> other studies report no association.<sup>34,35</sup> These discrepancies might stem from the large variability in pain measurement reported across studies.<sup>26,28,33-35</sup> The majority of studies both supporting and refuting chronic pain as a significant risk factor for substance abuse rely on the Brief Pain Inventory (BPI) to assess pain in opioid addiction patients, though the definitions and cut-offs used to classify pain with the BPI vary greatly.<sup>26,27,36-40</sup> The validity of a measurement tool applies exclusively to the population the tool is created for and tested within.<sup>41</sup> While the BPI is commonly cited as a validated tool to assess the presence of pain,<sup>26,27,36-40</sup> it has yet to undergo a reliability assessment within opioid addiction patients.

Whether it be uncertainty concerning the prognostic value of the BPI for assessing pain in opioid addiction patients, the stigma of drug-seeking behaviour, or the under treatment of pain in the addiction setting, there is a lack of consensus as to the real impact of pain on

illicit substance use behaviour in MMT patients. Addressing the discrepancies reported across the literature may improve the current management of comorbid pain. How well does the BPI work to classify pain among opioid addiction patients? Is there a pain measure that better predicts opioid relapse in this population? Are there specific characteristics associated with comorbid pain in opioid addiction patients, or that explain the differences in pain classification? Answering these questions will; 1) clarify the prognostic values of the BPI in opioid addiction patients, 2) resolve whether pain is a risk factor for important treatment response outcomes, and 3) provide a profile of the clinical, demographic, and social characteristics of patients with comorbid pain. We aim to evaluate these questions using evidence gathered from a prospective cohort study of 444 MMT patients.

### **4.3 OBJECTIVES**

1. Evaluate the prognostic value of different pain classification measures in a sample of opioid addiction patients
  - a. Provide performance characteristics of the simple self-reported pain measure (sensitivity, specificity, positive predicted value [PPV] and negative predicted value [NPV]) using the BPI as the gold-standard reference measure
  - b. Estimate the prognostic significance of each pain classification measure using opioid relapse confirmed by urine toxicology screening as an indicator of response to MMT
  - c. Confirm the association between continued opioid abuse and the presence of chronic pain using different measures of pain
2. Determine the clinical and demographic characteristics of patients reporting pain reported by different pain classification measures
  - a. Exploring employment history, medical comorbidities, psychiatric comorbidity, pain severity and interference, sexual functioning, criminal activity, HIV risk behaviour, and domestic conflict

## **4.4.0 METHODS**

### **4.4.1 GENetics of Opioid Addiction (GENOA) Prospective Cohort Study**

This study included participants from an investigation known formally as Genetics of Opioid Addiction (GENOA). GENOA is a research collaborative between the Population Genomics Program at McMaster University and the Canadian Addiction Treatment Centres (CATC). Methods of the GENOA pilot study are published elsewhere.<sup>42</sup> GENOA expanded out of the cross-sectional pilot design and is now conducting an ongoing 12-month prospective cohort study. Modifications were made to address the challenges noted during the cross-sectional stage.<sup>42</sup> These modifications include the addition of 13 new recruitment sites across southern Ontario as well as a validated addiction severity, psychiatric comorbidity, and pain assessment. Baseline measures include the collection of demographic characteristics such as educational background, employment, marital status, addiction treatment history (e.g. number of previous treatments), source of opioid use, methadone dose (mg/day), as well as a full medical history. Information has been collected on physical comorbidities include HIV, hepatitis C, diabetes, liver disease, epilepsy, chronic pain, as well as any other chronic disorders. Participants are followed up by onsite nursing staff every 3-months. Follow-up assessments include urinalysis and demographic questionnaires.

Eligibility criteria include: patients  $\geq 18$  years on methadone for opioid addiction treatment meeting DSM-IV criteria for opioid dependence (assessed by clinical interviews during admission to MMT), and able to provide informed consent. The

Hamilton Integrated Research Ethics Board (HiREB) approved this study (HiREB Study ID 11-056). This study adheres to the STROBE guidelines.<sup>43</sup>

#### **4.4.2 Measures**

We employed the M.I.N.I. International Neuropsychiatric Interview version 6.0<sup>44</sup> to assess for psychiatric comorbidities and the Maudsley Addiction Profile (MAP) instrument to assess addiction severity across personal, physical, and social functioning domains.<sup>45</sup> We used the Brief Pain Inventory (BPI) to capture pain severity and interference. This tool has been validated in the assessment of pain in patients with and without neuropathic etiology.<sup>46,47</sup> The BPI uses the primary question, “throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches), have you had pain beyond these everyday kinds of pain?” to determine whether patients are currently experiencing any pain. Participants answering yes to this question are prompted to completed follow-up questions to assess pain severity and interference. Participants completing the full BPI assessment were defined as a positive pain case. Participants were also asked directly whether they have a history of pain, whereby those responding yes to the question, “are you currently experiencing or have been diagnosed with chronic pain?” were classified as positive pain case according to the GENOA case report form (CRF). Participant substance use behaviour was assessed using weekly urine specimens, which are collected as part of CATC routine clinical care. Qualitative and semiquantitative urine analysis using iMDx™ Prep Assay [NOVX Systems novxsystems.com] were performed on all samples to assess for illicit opioid, cocaine, benzodiazepine, and marijuana use. The iMDx™ Prep Assays assess urine pH and

creatinine levels to identify when urine samples have been tampered with. Trained CATC clinical staff performs all adjudication of urinalysis results. The prep assays used in CATC clinics can discern specific types of opioids such prescribed synthetic medications (e.g. oxycontin), naturally occurring opioids (heroin), and methadone.<sup>48</sup>

#### **4.4.3.0 Statistical Analysis**

Baseline demographic characteristics including employment history, physical comorbidity, sexual activity, criminal activity, psychiatric comorbidity, injecting behaviour, domestic conflict, and MAP domain scores are reported by pain classification. Pain classification categories include participants concordantly classified as having pain by GENOA CRF and BPI, participants concordantly classified as not having pain by GENOA CRF and BPI, as well as those discordantly classified as having pain by the BPI but not GENOA CRF. The participants classified as having pain according to the GENOA CRF but not the BPI are considered false positive classifications. These additional participants captured by the GENOA pain measure are likely a product of measurement error (random error) or differential misclassification. While this subgroup of participants is small (n=16), we chose to exclude them from later analyses examining the predictive validity of pain classification for illicit opioid consumption.

Continuous measures are summarized using means and standard deviations (SD), while dichotomous measures are reported by percentage. To evaluate the differences in the clinical and demographic characteristics between groups based on pain classification we performed a univariate logistic regression with pain classification as the dependent variable. Baseline demographic characteristics were then evaluated independently as

covariates in the logistic regression models. For example, characteristics such as age, sex, and employment status would be individually evaluated in a cross-sectional association with pain classification. We did not use this as a univariate analysis to inform the selection of covariates for the construction of a multi-variable regression model to evaluate prognostic significance. We performed these cross-sectional analyses to determine the clinical and demographic profile of patients classified by different pain measures. The odds ratio and corresponding p-values are reported in the baseline demographic characteristics table.

Performance characteristics of the GENOA CRF pain measures were estimated using sensitivity, specificity, PPV, and NPV. The performance characteristics were calculated using the BPI as the “gold standard” measure. We recognize pain is a subjective experience and while there is no standard “gold standard” measure of identifying this phenomenon we aimed to demonstrate the performance characteristics of a new pain classification measure in relation to the BPI since it is the most commonly used tool among studies determining the impact of pain in patients receiving OST.<sup>26,27,36-40</sup> We determined the prognostic significance of pain classification using multi-variable regression analysis to estimate an association between pain measure and illicit opioid consumption. We quantified the effect of pain on illicit opioid consumption with a multivariable linear regression using the percentage of positive opioid urine tests at three-month follow-up as the dependent variable. All analyses adjusted for age (in years), sex, duration on MMT (in months), number of opioid urine screens, and infectious disease

status (presence of HIV or hepatitis C). All participants on prescribed opioid medications for pain were removed from any analysis evaluation illicit opioid use behaviour (n=18).

The association between pain and different risk categorizations of opioid use behaviour were assessed using multivariable logistic regression. Independent models were constructed using high and moderate risk categorizations of the percentage of positive opioid urine tests provided over the three-month period following the pain assessment as the dependent variable. Participants with  $\geq 50\%$  positive opioid urine screens were categorized as high-risk and deemed non-responsive to MMT. This cut off was selected in accordance with previous research suggesting regular use of heroin and other opioids is significantly predictive of mortality among methadone maintenance patients thus indicating a treatment failure.<sup>49</sup> To demonstrate “high risk” opioid use behaviour participants would need to exhibit minimum of six weeks of continued opioid abuse to have obtained  $\geq 50\%$  positive opioid urine tests and considered regular users of illicit opioids, indicating a clinically significant risk for treatment failure. Participants with 30% positive opioid urine screens will be considered at moderate risk. This categorization of high and moderate risk participants was used as the binary dependent variable in three logistic regression models. These models adjusted for age (years), sex, duration on MMT (months), number of opioid urine screens, and infectious disease status (presence of HIV or hepatitis C). The adjusted and unadjusted predicted probability for high-risk opioid use was evaluated for each pain classification. Adjusted predicted probability was estimated using the results from the multi-variable logistic regression models.

All covariates included in the regression models were assessed for multi-collinearity. Box-plots were constructed to identify outlier observations. Sensitivity analyses were performed for both regression analyses, removing outlier observations. All continuous variables were assessed for normal distribution, whereby proper transformations were applied when necessary.

#### *4.4.3.1 Determining the Percentage of Positive Opioid Urine Screens at Three-month Follow-up Assessment*

Due to the unequal number of urine tests administered among participants we evaluated the relationship between number of urine test administrations and the percentage of positive opioid urine tests at 3-months. Visual plots of the data ([Figure 4.4.3.1](#)) suggest no relationship between number of opioid screens and the percentage of positive tests. Thus, we chose against adjusting for the number of opioid urine tests administered.

An imputation of zero percent positive opioid urine screens was used for participants successfully completing the methadone program before the 3-month urine assessment period (n=2). For participants discharged from the MMT due to non-compliance with the treatment regime (e.g. providing urine samples, receiving daily methadone doses) an imputation of 100% positive opioid urine screens was used for the 3-month opioid urine assessment (n=1). We carried the baseline urine assessment forward (% of positive opioid urine screens at baseline) for participants lost to follow-up at three months due to moving to a non-CATC treatment program (n=10).

## 4.5 RESULTS

Among the 460 MMT patients recruited in the GENOA investigation, 444 patients completed both the GENOA CRF and BPI. [Figure 4.5](#) summarizes the participant inclusion process. Demographic and diagnostic performance characteristics are presented using data from participants completing both pain measures during the baseline assessments (n=444). Demographic and clinical characteristics are presented by pain classification and summarized in [Table 4.5a](#). The mean age of all participants included in this study was 38.4 years (SD 11.0).

Findings from the classification of pain using the BPI and GENOA CRF suggest the BPI captures pain in a larger number of participants. Those classified as having pain according to the GENOA CRF are almost completely captured within the larger sample of patients classified according to the BPI ([Figure 4.5b](#)). Among all participants classified as having pain according to one or both of these measures (n=297), there is 46.4% concordance between measures (n=138). There is 53.6% discordance between the BPI and GENOA CRF, whereby 5.5% (n=16) patients are classified as having pain according to the GENOA CRF but not the BPI and 48.1% (n=143) of patients are classified as having pain according to the BPI but not the GENOA CRF. [Figure 4.5b](#) displays the concordance and discordance of pain classification using these two measures.

Assessment of the clinical and demographic characteristics of participants based on pain classification revealed differences between the concordant and discordant groups ([Table 4.5a](#)). Participants classified as having pain according to the GENOA CRF and the BPI

were found on average to be older (Odds Ratio [OR]: 1.05, 95%CI 1.02, 1.07;  $p < 0.0001$ ), with higher severity of physical symptoms based on MAP scoring (OR: 1.07, 95%CI 1.03, 1.11;  $p < 0.0001$ ), lower involvement in criminal activity (OR: 0.28, 95%CI 0.10, 0.78;  $p = 0.015$ ), and with a lower rate of post traumatic stress disorder (OR: 0.40, 95%CI 0.15, 1.06;  $p = 0.065$ ).

Evaluation of the diagnostic performance characteristics suggest the GENOA CRF pain classification to be highly specific (90.2%, 95% Confidence Interval [CI]: 84.5, 94.4), indicating patients classified as having no pain according to the GENOA pain classification are unlikely to have pain. Accordingly, these results also suggest the BPI to be highly sensitive, classifying a much larger number of GENOA participants with pain ( $n = 281$ , 63.3%;  $n = 444$  for participants with BPI measures) in comparison to the GENOA CRF classification ( $n = 150$ , 33.4%;  $n = 460$  for GENOA CRF measure). Results from the diagnostic performance statistics also suggest the GENOA CRF classification to have high positive predicted value (PPV=89.6, 95%CI: 83.7, 93.9), indicating the GENOA CRF has a very low false positive rate. Diagnostic performance tests are summarized in Table 4.5b.

To demonstrate the prognostic significance the GENOA pain measure we evaluated the predictive performance of pain classification using concordant (classified as having pain according to GENOA CRF & BPI) and discordant (classified as having pain according to BPI but not GENOA CRF) categorizations. GENOA is an active study with ongoing recruitment, rendering a portion of the recently recruited participants ( $n = 143$ ) ineligible for follow-up at this time. Results from these analyses are performed in a reduced sample

of 278 participants ([Figure 4.5a](#)). The models adjusted for age (years), sex, duration on MMT (months), and infectious disease status (presence of HIV or hepatitis C). Evaluation of the percentage of positive opioid urine specimens collected over the three month period following the pain assessments suggests participants concordantly classified as having pain according to the GENOA CRF and BPI were found to have an estimated 7.79% increase in positive opioid urine screens (Estimated coefficient: 7.79; 95%CI 0.74, 14.85;  $p=0.031$ ). Patients classified as having pain according to both measures were also found to have a four times greater odds (Odds Ratio [OR]: 4.10  $p=0.008$ ; 95%CI: 1.44, 11.63) of consuming a “high risk” level of illicit opioids ( $\geq 50\%$  positive opioid urine screens over 3-month period following pain assessment).

The prognostic relevance of pain classification was not maintained for the additional participants classified by the BPI ( $n=143$  discordant), whereby pain classification is no longer predictive of positive opioid urine screens (Estimated coefficient: 1.78; 95%CI - 4.66, 8.21;  $p=0.588$ ) or a “high-risk” level of opioid consumption BPI (OR: 1.08, 95%CI: 0.35, 3.29;  $p=0.898$ ). Results from these analyses are summarized in [Tables 4.5c](#) and [Table 4.5d](#). Similar findings were observed when evaluating the prognostic relevance of the GENOA classification in comparison to the BPI across moderate risk opioid use outcomes, however the observed predictive significance of the GENOA CRF classification was slightly diminished (OR: 2.13; 95%CI: 0.93, 4.90  $p=0.075$ ).

The adjusted and unadjusted predicted probability for high-risk opioid use was evaluated for each pain classification. Again, we find those participants classified by the GENOA

CRF and BPI were found to have a high-predicted probability (17%) for high-risk opioid consumption. There were no differences in the predicted probability for high-risk abuse between the additional participants classified by the BPI and those without pain. These results are summarized in [Figure 4.5c](#).

## 4.6 DISCUSSION

Findings from this study emphasize the prognostic impact of different pain classification measures for patients with opioid addiction. While the BPI may be the most commonly used measure to assess pain among MMT patients,<sup>26,27,36-40</sup> results from this study suggest the BPI holds poor prognostic value for distinguishing patients at high risk for opioid abuse. The BPI classifies a large number of patients with comorbid pain, however simpler evaluations such as the question “are you currently experiencing or have been diagnosed with chronic pain?” demonstrate stronger prognostic significance for distinguishing patients at high risk for continued opioid abuse. The BPI showed high sensitivity when compared against the simpler pain classification question used in the GENOA CRF, however the additional participants identified by the BPI classification weakened the predictive ability of the measure. Classification of pain based on the BPI alone biased the results to suggest participants with pain are not at risk for engaging in problematic opioid consumption behaviour. However, the subgroup of patients within the BPI classified concordantly by both measures were shown to be a serious risk for engaging in concerning levels of illicit opioid consumption. In light of the findings we are likely to question the validity of the results of previous studies using BPI to classify pain among MMT patients.

Numerous studies evaluating the effect of pain on response to MMT use the BPI to classify pain citing its previous validation as justification.<sup>26,27,36,39,40</sup> However, this

suggestion is problematic since the validity of a measurement scale apply exclusively to the population the tool is developed for and tested within.<sup>41</sup> To our knowledge no previous reliability estimates are reported for the BPI within opioid addiction population. For instance, neither the psychometric properties such as internal consistency nor the test-retest reliability have been reported for a population of addiction patients. The BPI was originally generated and validated within a population of cancer and rheumatoid arthritis patients,<sup>50</sup> resting our confidence in the BPI's ability to distinguish pain on the assumption that there are strong similarities between the addiction population and the population the tool was created within, of which we have serious concerns.

Contention in the literature may stem directly from the use of pain classification measures with limited prognostic value. Among studies evaluating the association between comorbid pain and illicit opioid use,<sup>26-28,33,36,39,40,51</sup> those measuring pain using the BPI report no effect of pain on illicit opioid consumption.<sup>26,27,36,39,40</sup> To the contrary, studies reporting a significant effect of pain on opioid abuse behaviour did not classify pain using the BPI.<sup>28,33</sup> The BPI may indeed appropriately identify participants with comorbid pain, however its classification casts a net so wide it loses prognostic value. Findings from this study demonstrate pain is related to how people progress through treatment at an etiologic level. Thus, the BPI may be capturing domains that are not associated with prognostically relevant pain. The alternative explanation may be that the simpler measure captures a specific subgroup of patients who self-identify as having pain. These patients may experience significant pain such that it has become a core part of their identify and possibly a core part of the reason they abuse drugs.

As the most common complaint among drug seeking patients with substance use disorder, chronic pain can be a challenging symptom to ascertain and treat.<sup>52</sup> High-intensity comorbid pain among patients with a history of addiction is a significant risk factor for opioid misuse.<sup>53</sup> Patients catastrophizing pain are also found to have higher rates of opioid abuse.<sup>54</sup> Distinguishing between drug seeking patients and those with real pain is challenging. However emerging research suggests patients with comorbid pain are often not seeking additional opioids when discussing pain with their physician but instead want a diagnosis for their pain and their clinician to guide them through the fragmented management of chronic pain.<sup>55</sup>

Pain is a subjective phenomena, as such the measurement and classification of pain is sensitive to the population being assessed. Thus, it could be claimed the GENOA CRF pain classification is capturing a specific group of “drug seeking” patients. However, findings from a previous study of independent sample of 235 patients with opioid addiction treated with MMT using the same pain measure as the GENOA CRF found patients reporting pain to have significantly elevated Interferon-Gamma (IFN- $\alpha$ ), indicating a biological distinction between patients classified according to the GENOA CRF.<sup>28</sup>

Major studies evaluating pain among addiction patients emphasize the need for future research to replicate their findings as well as develop validated questions for assessing treatment response.<sup>26,36</sup> The current study provides evidence to suggest the selection of pain measure may be driving previous findings. To our knowledge this is the first study to

demonstrate the effect of pain on opioid consumption over a 3-month follow-up using a prospective cohort design. Precautions were taken to ensure we employed objective measurements, this includes electing to use urine toxicology screening over self-report to assess opioid consumption. Using the CATC network of clinics guarantees all participants receive care according to a standardized treatment protocol, which includes weekly physician visits and urine samples, as well as dosing and tapering procedures. For participants without 3-month data due to 1) switching clinics, 2) treatment failure, or 3) successful treatment completion we imputed missing data based on the participant's treatment response history. For instance, participants terminated from the MMT program due to non-compliance (e.g. not willing to provide urine, serious comorbid substance use), we imputed 100% positive opioid urine to reflect a high-risk patient. Over the total number of individuals with imputed data is small (n=13) and thus may have no effect on the results. However, we caution the interpretation of these result since they are still reflective of participants already maintained on an OST, which can largely differ from patients who drop out of MMT or never seek treatment altogether. Employing an observational study design in addition to using multiple centres to capture differing SES population increases our confidence that these results reflect the treatment prognosis for the larger population of opioid addiction patients receiving methadone treatment. Additionally, demographic characteristics of GENOA participants are consistent with those reported in previous population based studies.<sup>56</sup>

## 4.7 CONCLUSION

Acknowledging chronic pain is predictive of high-risk opioid use will improve relapse prevention management, prevent opioid overdose, as well as encourage clinicians to target appropriate adjunct therapies to patients with comorbid addiction and pain conditions. Findings from this study suggest the most common pain measure –the BPI— is not only time consuming to administer, it fails to classify distinguish prognostically relevant. Directly inquiring into patients’ history of pain using question such as, “are you currently experiencing or have been diagnosed with chronic pain?” will distinguish patients at high-risk for dangerous opioid consumption behaviour. Healthcare providers often report dissatisfaction with managing pain due to the lack of training in addiction treatment. Providing clinicians with information on the distinguishing risk factors for high-risk opioid consumption is imperative for enhancing the management of addictive disorders. It is also important we identify measures that are no longer useful for evaluation of pain impact on substance use behaviour.

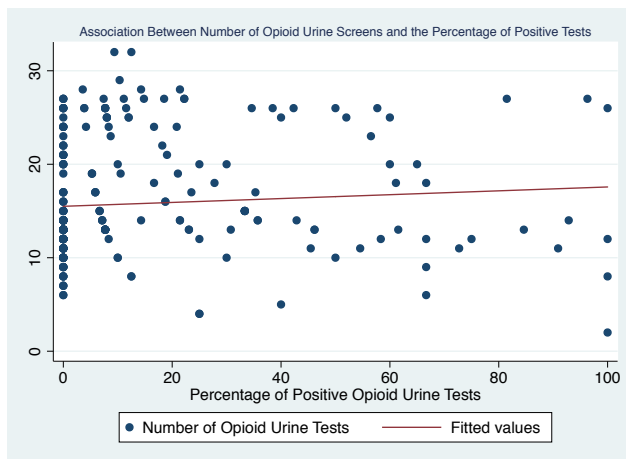
## **4.8 ACKNOWLEDGMENTS, FUNDING, AND AUTHOR CONTRIBUTIONS**

We report no competing interests for this investigation. This work was supported by the Chanchlani Research Centre, Peter Boris Centre for Addictions Research, and the CIHR Drug Safety and Effectiveness Network (DSEN) grant (grant number: 126639). The funders had no role in study design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript. Dr. Zainab Samaan, Brittany B. Dennis and Dr. Lehana Thabane were responsible for the development of the question and research protocol for this study. Brittany B. Dennis was responsible for all statistical analyses performed in this investigation. All authors contributed equally during manuscript development. Zainab Samaan had full access to data from this investigation and she is accountable for the reliability of the data and the accuracy of all analyses performed

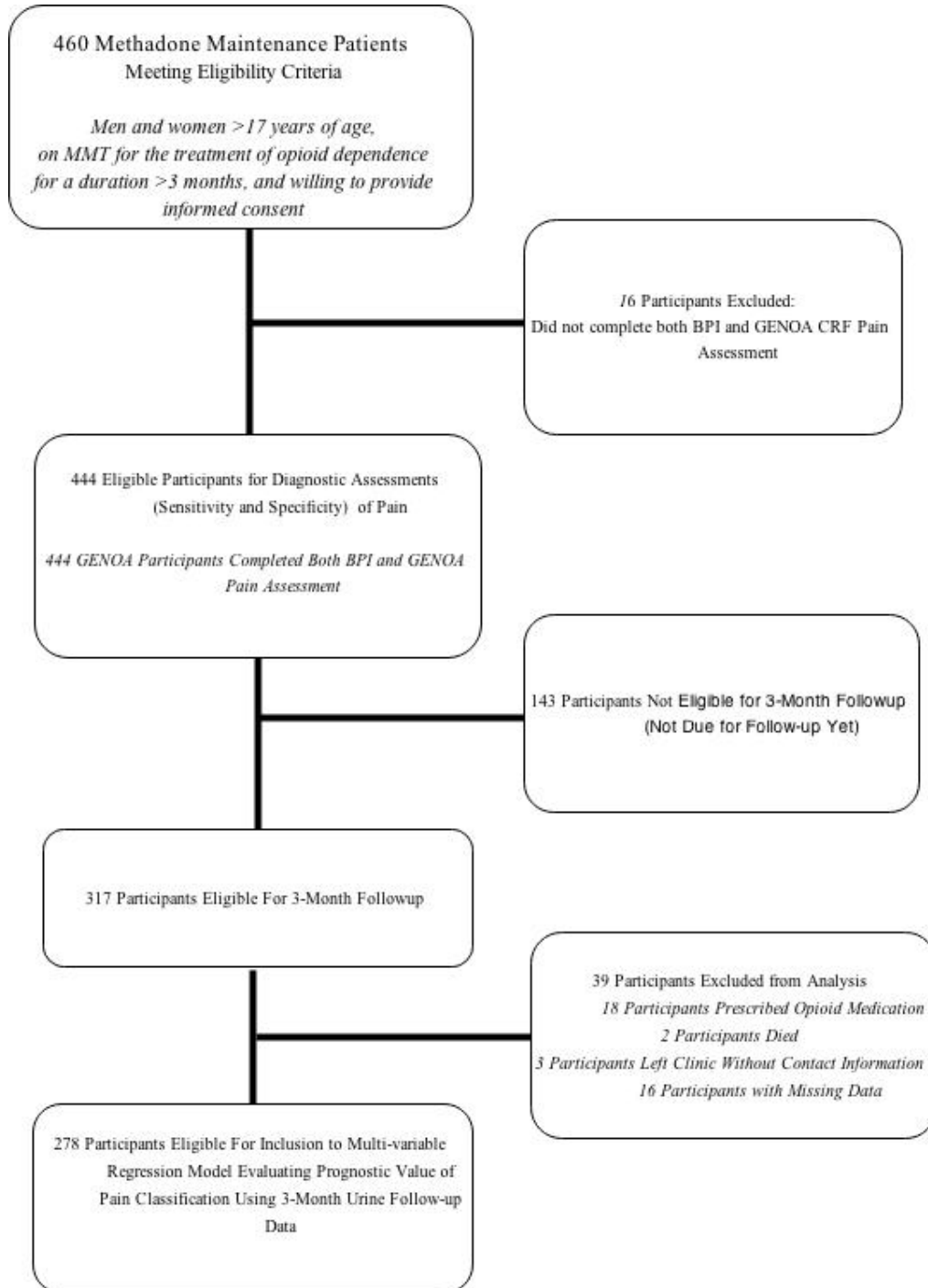
We would like to sincerely thank everyone who contributed to the completion of this Project. This project would not have been possible without the great collaboration cemented between GENOA and the OATC network of clinical sites. We would extend our sincere appreciation to all the participants from the OATC facilities who generously donated their time, information and samples, without them this study would not be possible. We would like to extend our gratitude to the OATC clinical staff for all their great efforts in patient recruitment and data collection. We would like to thank Jacqueline Hudson for her great dedication as the research coordinator on the GENOA team.

## 4.9 FIGURES AND TABLES

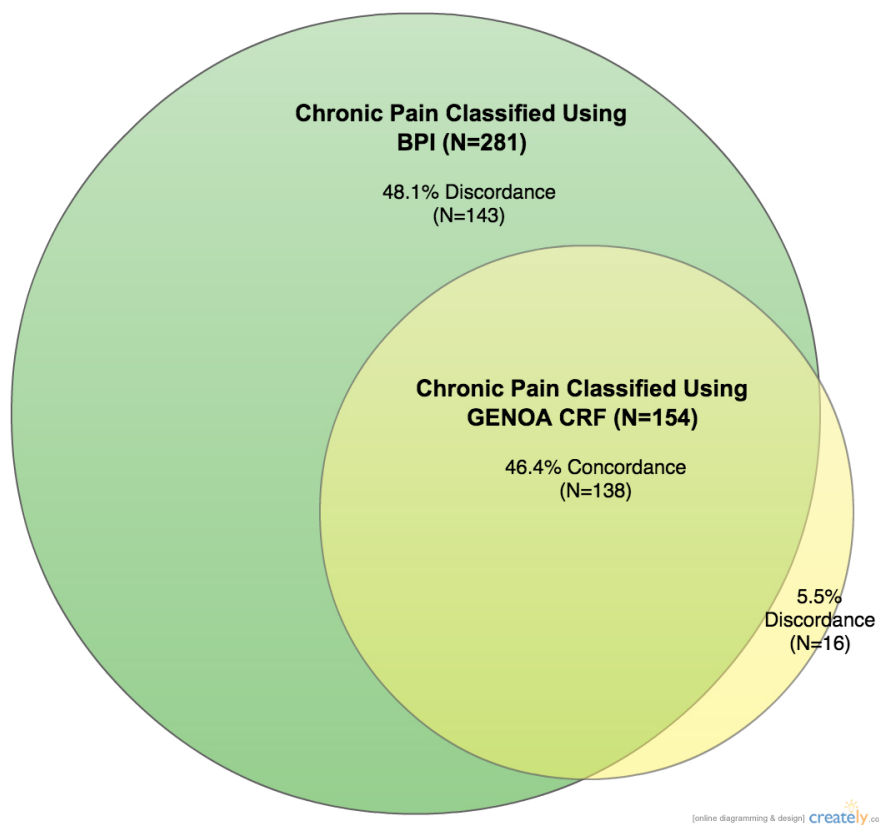
**Figure 4.4.3.1 Association Between Number of Urine Tests and Number of Positive Tests**



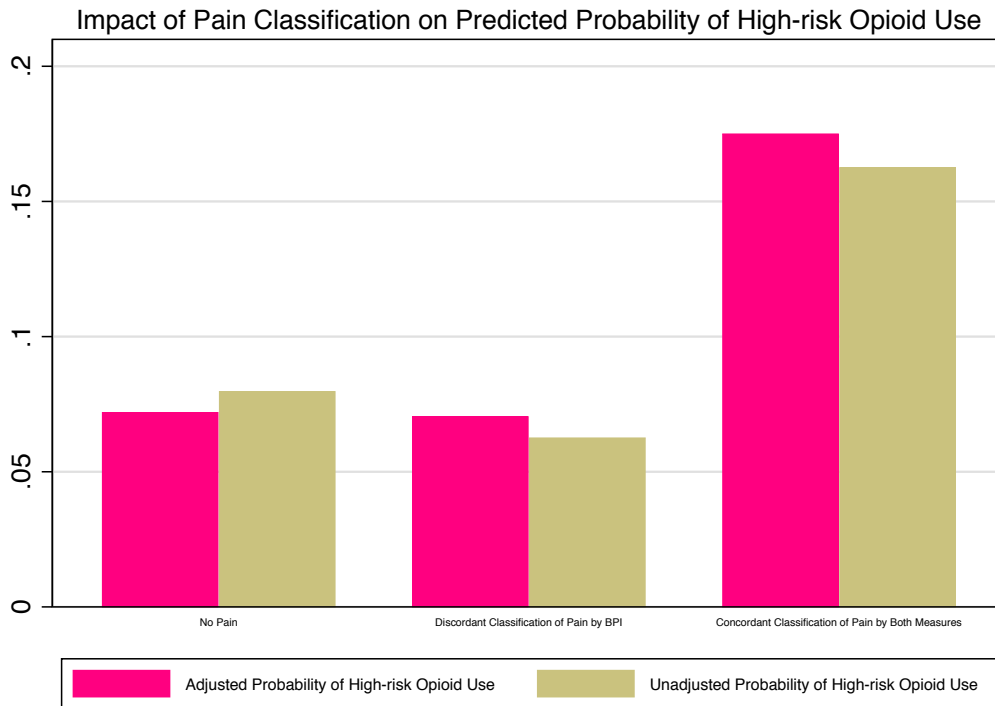
**Figure 4.5a Participant Flow Diagram of the Participant Inclusion Process**



**Figure 4.5b Classification of Pain in the GENOA Sample**



**Figure 4.5c Impact of Classification on Predicted Probability of High-risk Opioid Use**



**Table 4.5a Baseline Demographic Characteristics of Methadone Maintenance Patients (results reported for participants completing both GENOA CRF and BPI pain classification n=428)**

	Participants Classified as Having Pain by BPI and GENOA CRF (n=138)	Participants Classified as Having Pain by BPI but Not GENOA CRF (n=143)	Participants Classified as Having No Pain (n=147)	Logistic Regression Model Using Pain Classification as the Dependent Variable		
				Unadjusted Odds Ratio, P-Value		
				Concordant Classification (n=285) <sup>a</sup>	Discordant Classification (n=290) <sup>b</sup>	Comparison of Concordant and Discordant (n=281) <sup>c</sup>
Mean Age (SD)	42.7 (10.6)	37.4 (10.3)	34.8 (10.4)	1.1, p<0.0001	1.0, 0.037	1.0, p<0.0001
Sex (% Female)	46.7	47.6	46.3	1.0, 0.939	1.1, 0.825	1.0, 0.888
Marital Status (% Participants Married or Common Law)	33.3	31.2	32	1.1, 0.807	1.0, 0.889	1.1, 0.704
Employed	28.3	37.3	42.9	0.5, 0.011	0.8, 0.338	0.6, 0.107
Smoking Status (% Participants Smoking)	97.1	93.6	92.5	2.7, 0.095	1.2, 0.726	2.3, 0.174
<b>Family History of Addiction</b>						
Father	37	44.1	40.1	0.9, 0.582	1.2, 0.499	0.7, 0.226
Mother	32	31.5	32	0.9, 0.987	1.0, 0.927	1.0, 0.940
Brother	26.1	25.2	22.4	1.2, 0.474	1.2, 0.586	1.0, 0.861
Sister	18.8	18.8	17.7	1.1, 0.801	1.1, 0.793	1.0, 0.993
<b>Comorbid Medical Disorders</b>						
HIV	0.7	0.6	0.7	1.1, 0.964	1.0, 0.984	1.0, 0.980
Epilepsy	3.6	2.1	2	1.8, 0.425	1.0, 0.973	1.8, 0.448
Hepatitis C	26.8	21	20.4	1.4, 0.204	1.0, 0.905	1.4, 0.252
Liver Disease	9.4	1.4	4.8	2.1, 0.131	0.3, 0.120	7.3, 0.010
Diabetes	6.5	5.6	4.1	1.6, 0.361	1.4, 0.550	1.2, 0.745
<b>Illicit Drug Use (Mean Percent of Positive Urine Screens During Baseline Assessment)</b>						
Opioids	18.5 (30.8)	14.5 (24.3)	14.7 (26.7)	1.0, 0.283	0.9, 0.939	1.0, 0.240

Cannabis	28.6 (41.9)	35.7 (45.0)	30.6 (41.6)	1.0, 0.776	1.0, 0.489	1.0, 0.298
Cocaine	13.9 (27.8)	15.5 (28.6)	13.5 (25.6)	1.0, 0.972	1.0, 0.536	0.9, 0.641
Amphetamine	7.9 (24.3)	3.2 (16.9)	2.0 (9.5)	1.0, 0.105	1.0, 0.622	1.0, 0.174
Ecstasy	7.8 (24.5)	3.4 (17.2)	1.7 (9.2)	1.0, 0.108	1.0, 0.516	1.0, 0.208
<b>Mean Scoring for BPI Intensity and Interference Scales</b>						
Composite Pain Intensity Scoring (SD)	20.1 (7.6)	15.2 (8.0)	/	/	/	
Composite Pain Interference Scoring (SD)	39.8 (17.9)	25.8 (18.5)	/	/	/	
<b>Maudsley Addiction Profile Scoring</b>						
Mean Physical Symptoms Score (SD)	19.3 (7.1)	15.8 (7.5)	12.1 (6.5)	1.2, p<0.0001	1.1, p<0.0001	1.1, p<0.0001
Mean Psychological Symptoms (SD)	14.1 (8.4)	13.4 (8.9)	11.4 (8.4)	1.02, 0.008	1.02, 0.046	1.0, 0.513
<i>MAP Health Risk Behavior</i>						
Number of Days of Injecting Drug Use	2.8 (7.6)	1.9 (5.9)	2.8 (7.4)	0.9, 0.926	1.0, 0.398	1.0, 0.448
Number of Time of Sharing Equipment for Injecting Drug Use	0	0.01 (0.1)	0.2 (1.2)	n/a	0.6, 0.527	/
Number of Sexual Partners Without a Condom	0.5 (0.6)	0.6 (0.5)	0.8 (0.7)	0.6, 0.056	0.6, 0.066	0.9, 0.768
<i>Personal and Social Functioning</i>						
Conflict Scoring Partner	20.1 (33.1)	15.8 (28.9)	16.1 (25.1)	1.0, 0.358	1.0, 0.932	1.0, 0.356
Conflict Scoring Family	11.7 (25.6)	15.5 (30.0)	10.4 (21.9)	1.0, 0.666	1.0, 0.126	1.0, 0.312
Conflict Scoring Friends	6.7 (19.5)	4.6 (16.0)	2.7 (10.3)	1.0, 0.073	1.0, 0.294	1.0, 0.387
<i>Criminal Activity</i>						
Percentage of Participants Reporting Any Criminal Behavior	3.6	11.9	12.2	0.3, 0.012	0.9, 0.926	0.3, 0.015
Mean Number of Days Selling Drugs (SD)	0.3 (2.6)	0.9 (4.9)	0.6 (3.7)	0.9, 0.451	1.0, 0.490	1.0, 0.200
Mean Number of Days Committing Fraud (SD)	0	0	0	/	/	/
Mean Number of Days Shoplifting (SD)	0	0.2 (1.9)	0.2 (1.4)	/	1.0, 0.981	/

Mean Number of Days of Theft of Property (SD)	0.1 (0.9)	0	0	/	/	/
Mean Number of Days of Theft from Vehicle (SD)	0	0	0.03 (0.3)	/	/	/
Mean Number of Days of Theft of a Vehicle (SD)	0	0	0	/	/	/
<b>Percentage of Participants with Psychiatric Disorders Diagnosed by MINI<sup>d</sup></b>						
Major Depressive Disorder (including current, past, or recurrent)	37.7	44.6	42	0.8, 0.478	1.1, 0.669	0.8, 0.266
Current Bipolar Disorder	1.6	3.1	1.4	1.1, 0.901	2.2, 0.379	0.5, 0.462
Generalized Anxiety Disorder	18.1	25.9	13	1.5, 0.303	2.3, 0.013	0.6, 0.196
Anorexia	0	0	0	/	/	/
Bulimia	0.8	2.3	2.2	0.4, 0.394	1.1, 0.941	0.3, 0.366
Alcohol Dependence	4.1	6.9	5.8	0.7, 0.532	1.2, 0.706	0.6, 0.333
Alcohol Abuse	6.6	11.5	8.7	0.7, 0.520	1.4, 0.441	0.5, 0.175
Post Traumatic Stress Disorder	4.9	11.2	3.6	1.4, 0.606	3.5, 0.019	0.4, 0.065
Suicidal Ideation	29.5	33.1	31.9	0.9, 0.679	1.1, 0.835	0.8, 0.542
Antisocial Personality Disorder	14.8	23.8	18.1	0.8, 0.467	1.4, 0.250	0.6, 0.071

Results not reported for 16 participants not captured by BPI (assuming measurement error)

<sup>a</sup> results from the univariate logistic regression evaluating the differences between those classified as having pain according to both the BPI and GENOA CRF and those classified as having no pain, pain classification is the dependent variable

<sup>b</sup> results from the univariate logistic regression evaluating the differences between those classified as having pain according to the BPI but NOT the GENOA CRF and those classified as having no pain, pain classification is the dependent variable

<sup>c</sup> results from the univariate logistic regression evaluating the differences between those classified as having pain according to the BPI but NOT the GENOA CRF and those classified as having pain according to both the BPI and GENOA CRF, pain classification is the dependent variable

<sup>d</sup> the number of participants from each group evaluated with the MINI are not reflective of the number of participants listed at the top of the table, for participants completing the MINI there were 121 concordantly classified as having pain according to both GENOA CRF and BPI, 130 discordant participants (classified as having pain according to BPI but not GENOA CRF), and 138 witho

**Table 4.5b Summary of Performance Characteristics of Chronic Pain Classifications (N=444)**

Performance Tests (BPI as Gold Standard)		95% Confidence Interval
Prevalence of Chronic Pain According to BPI (Gold Standard Reference)	63.0%	59.0, 67.8
Sensitivity	49.1%	43.0, 55.0
Specificity	90.2%	84.5, 94.3
ROC area (Sensitivity + Specificity)/2	0.70	0.66, 0.73
Positive predictive value	89.6%	83.7, 93.9
Negative predictive value	50.7%	44.8, 56.6

**Table 4.5c The Prognostic Significance of Pain Classification for Predicting Percentage of Positive Opioid Urine Screens - Results from Multi-variable Linear Regression (n=278)**

	<b>Estimated Coefficient</b>	<b>P-Value</b>	<b>95% Confidence Interval</b>
<b>Pain Classification (Reference: Participants Concordantly Classified Without Pain)</b>			
<i>Participants Concordantly Classified With Pain By Both Measures</i>	7.79	0.031	0.72, 14.85
<i>Discordantly Classified Participants (Classified as Having Pain According to BPI not GENOA CRF)</i>	1.78	0.588	-4.66, 8.21
<b>Age</b>			
<b>Age</b>	-0.15	0.296	-0.44, 0.13
<b>Methadone Dose (mg/day)</b>			
<b>Methadone Dose (mg/day)</b>	-0.11	0.002	-0.18, -0.04
<b>Sex</b>			
<b>Sex</b>	0.95	0.73	-4.45, 6.35
<b>Duration on MMT (months)</b>			
<b>Duration on MMT (months)</b>	0.00	0.903	-0.06, .06
<b>Infectious Disease Status (Positive for HIV or Hepatitis C)</b>			
<b>Infectious Disease Status (Positive for HIV or Hepatitis C)</b>	2.29	0.49	-4.23, 8.82

**Table 4.5d Impact of Pain Classification on High-Risk Opioid Use Behaviour (n=278)**

	<b>Odds Ratio</b>	<b>P-Value</b>	<b>95% Confidence Interval</b>
<b>Pain Classification (Reference Participants Concordantly Classified Without Pain)</b>			
<i>Participants Concordantly Classified With Pain By Both Measures</i>	4.10	0.008	1.44, 11.63
<i>Discordantly Classified Participants (Classified as Having Pain According to BPI not GENOA CRF)</i>	1.08	0.898	0.35, 3.29
<b>Age</b>			
	0.98	0.37	0.94, 1.02
<b>Methadone Dose (mg/day)</b>			
	0.99	0.026	0.98, 0.99
<b>Sex</b>			
	1.01	0.983	0.44, 2.30
<b>Duration on MMT (months)</b>			
	1.00	0.822	0.98, 1.01
<b>Infectious Disease Status (Positive for HIV or Hepatitis C)</b>			
	0.96	0.944	0.36, 2.62

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## CHAPTER 5

### Study 4 Part 1

#### The Impact of Chronic Pain on Opioid Addiction Treatment: A Systematic Review

#### Protocol

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### *Publications*

Dennis B, Bawor M, Paul J, et al. The impact of chronic pain on opioid addiction treatment: a systematic review protocol. *Systematic reviews*. 2015;4(1):49.

This publication is located in Appendix Item ii

## 5.1 ABSTRACT

**Background:** The consequences of opioid relapse among patients being treated with opioid substitution or antagonist treatment (OSAT) are serious and can result in abnormal cardiovascular function, overdose, and mortality. Chronic pain is a major risk factor for opioid relapse within the addiction treatment setting. There exist a number of opioid maintenance and antagonist therapies including methadone, naltrexone, buprenorphine, and levomethadyl acetate (LAAM), of which the mediating effects of pain on treatment attrition, substance use behaviour, and social functioning may differ across therapies. We aim to 1) evaluate the impact of pain on the treatment outcomes of addiction patients being managed with OSAT and 2) identify the most recently published opioid maintenance treatment guidelines from the United States, Canada, and the UK to determine how the evidence is being translated into clinical practice.

**Methods/Design:** The authors will search Medline, EMBASE, PubMed, PsycINFO, Web of Science, Cochrane Database of Systematic Reviews, ProQuest Dissertations and theses Database, Cochrane Central Register of Controlled Trials (CENTRAL), World Health Organization International Clinical Trials Registry Platform Search Portal, and the National Institutes for Health Clinical Trials Registry. We will search [www.guidelines.gov](http://www.guidelines.gov) and the National Institute for Care and Excellence (NICE) databases to identify the most recently published OST guidelines. All screening and data extraction will be completed in duplicate. Provided the data are suitable, we will perform a multiple

treatment comparison using Bayesian meta-analytic methods to produce summary statistics estimating the effect of chronic pain on all OSATs. Our primary outcome is substance use behaviour, which includes opioid and non-opioid substance use. We will also evaluate secondary endpoints such as treatment retention, general physical health, intervention adherence, personal and social functioning, as well as psychiatric symptoms.

**Discussion:** This review will capture the experience of treatment outcomes for a sub-population of opioid addiction patients and provide an opportunity to distinguish the best quality guidelines for OSAT. If chronic pain truly does result in negative consequences for opioid addiction patients it is important we identify which OSATs are most appropriate for chronic pain patients as well as ensure the treatment guidelines incorporate this information.

**Systematic review registration:**

PROSPERO CRD42014014015

## 5.2 INTRODUCTION

Chronic non-cancer pain is a serious comorbidity impacting the lives of over 95 million people, an estimated 30.7% of the US population.<sup>1</sup> Chronic pain is defined as pain lasting longer than three months or past the standard time for tissue to heal.<sup>2</sup> Front-line treatments include the prescription of long-acting opioids, although there is minimal evidence to suggest opioids provide any long-term relief for chronic pain.<sup>3</sup> Trends in current prescribing practice suggest the rise in prescription opioid use<sup>4</sup> has been paralleled by a concerning increase in opioid related deaths, addiction, and medication diversion.<sup>5-9</sup> Opioids are highly liable for misuse, which is evident from the reported incidence of addiction, ranging from 3.2-27% among the chronic pain population.<sup>10</sup>

While methadone is employed in the management of chronic pain, its most common use is in the treatment of opioid addiction,<sup>11</sup> known formally as methadone maintenance treatment (MMT). Under the supervision of addiction specialists, methadone (a synthetic opioid) is prescribed to alleviate the symptoms of withdrawal and prevent relapse.<sup>11</sup> Within the addiction population being treated with methadone, chronic non-cancer pain is the most commonly reported comorbidity, with an estimated prevalence ranging from 37-55.3%.<sup>12-14</sup>

The intersection between pain management, opioid dependence, and addictive behaviour inflates the challenges of treating both addiction and chronic pain. In addition to psychiatric disturbance and inadequate social support, chronic pain is known to be one of the greatest risk factors for opioid relapse within the methadone setting.<sup>15,16</sup> These

effects are argued to be the result of opioid induced hyperalgesia, characterized as a status of heightened nociceptive sensitization caused by opioid exposure.<sup>17</sup> This effect has been demonstrated repeatedly, where by patients with non-cancer chronic pain taking methadone showed increased hyperalgesic response (assessed by cold presser test but not stimulus) in comparison to their placebo matched controls.<sup>17,18</sup>

The risk for abnormal cardiovascular function,<sup>19,20</sup> overdose,<sup>21,22</sup> and mortality<sup>21</sup> is highest among patients abusing opioids in combination with MMT. Classifying chronic pain as a risk factor for continued opioid abuse<sup>12,15,16,23</sup> calls to question which addiction treatment is most appropriate for patients with comorbid pain. There exist a number of opioid maintenance and antagonist therapies including methadone, buprenorphine, naltrexone, and levomethadyl acetate (LAAM), of which the mediating effects of pain on treatment attrition, substance use behaviour, and social functioning may differ across therapies.

Is chronic pain an important mediating factor when evaluating patient response to opioid addiction treatment? Which opioid maintenance or antagonist therapy is best for improving physical, psychiatric, and substance use behaviour outcomes in patients with opioid addiction and chronic pain? We aim to evaluate these questions using evidence gathered from all studies evaluating chronic pain in the opioid addiction patient population. The lack of current summary of evidence evaluating the mediating effects of pain suggests our current effort to combine the evidence will serve to 1) distinguish the best therapy for opioid addiction patients with comorbid pain, and 2) enable clinicians to tailor treatments based on an important and highly prevalent risk factor.

### **5.2.1 Objectives**

We aim to 1) evaluate the impact of comorbid chronic non-cancer pain on all opioid addiction treatment outcomes reported in the literature including treatment retention, illicit substance-use behaviour, as well as physical and psychiatric symptoms, 2) determine how different opioid maintenance and antagonist treatments compare in their effectiveness for patients with comorbid chronic non-cancer pain, 3) provided the data are suitable, combine the evidence from direct and indirect comparisons using network meta-analysis, and 4) identify the most recently published opioid maintenance or antagonist treatment guidelines from the United States, Canada, and the UK to determine how the evidence is being translated into clinical practice for addiction management.

### **5.2.2 Research Questions**

**1.1** Among patients with opioid addiction being treated with (or randomized to) opioid substitution or antagonist treatment (OSAT): 1) does chronic non-cancer pain interfere with the effect of OSAT, and 2) which OSAT is best for improving treatment response for patients with comorbid chronic non-cancer pain? We will evaluate response across multiple outcome domains including: substance use behaviour, physical health, psychiatric symptoms, as well as personal and social functioning.

**1.2** Do the most recently published United States, Canadian, and United Kingdom OSAT clinical practice guidelines capture and properly translate the evidence obtained from the studies evaluated in this review?

## 5.3 METHODS

### 5.3.1 Systematic Review Methods

#### 5.3.1.1 *Inclusion and Exclusion Criteria*

To be included in this review, the study must evaluate the impact of chronic pain on patient's response to opioid addiction treatment. The study must have provided a comparison of response to treatment outcomes (e.g. continued opioid abuse, general physical health) between patients with and without chronic pain. We also require the studies to have evaluated patients on an OSAT for opioid addiction. We will not place any restrictions on the types of OSAT or measurement of chronic pain. All study designs will be accepted into this review, (i.e. randomized controlled trials, observational studies or qualitative studies). No restrictions were placed on socioeconomic, geographic, or ethnic backgrounds of participants for this review.

To be eligible for inclusion, all studies must be primary (original research in patients with pain, no secondary reporting), completed (no interim analyses will be allowed in this review), and performed in a human population.

#### 5.3.1.2 *Outcome Measures*

The primary outcome in this review is illicit opioid use, which can be measured in various ways including urine toxicology screening or self-report. We anticipate many definitions and measurements of opioid use. For example, some studies measure opioid use behaviour as the number of days of opioid use in the last month, while others report

the mean number of positive opioid urine screens, or days until opioid relapse. We will accept any definition or measurement of illicit opioid use, provided the study performs an analysis comparing opioid use behaviour based on patients' chronic pain status. We will also abstract data on all other efficacy end-points including non-opioid substance abuse, general physical health, psychiatric symptoms, personal and social functioning, intervention adherence (e.g. treatment retention, drop out rate), resource utilization (e.g. hospital admissions) as well as treatment preference. However, short-term outcomes (initial dosing, initial response in a period of <3 weeks or early detoxification response) will not be evaluated.

#### *5.3.1.3 Data Sources and Search Strategy*

We will perform an electronic search using the Medline, EMBASE, PubMed, PsycINFO, Web of Science, Cochrane Database of Systematic Reviews, ProQuest Dissertations and theses Database, Cochrane Central Register of Controlled Trials (CENTRAL), World Health Organization International Clinical Trials Registry Platform Search Portal, and the National Institutes for Health Clinical Trials Registry. In addition, the reference lists of all Cochrane reviews addressing this topic will be reviewed. We will use the Cochrane reviews to validate our own searches of databases and ensure we have captured the relevant articles in our field. This supplementary search will be applied to Cochrane reviews since they are considered the gold standard in systematic reviews.

We will use a comprehensive search strategy tailored for each database. Please refer to [Table 5.3.1.3](#) for an outline of the search strategy. We consulted a McMaster University Faculty of Health Science librarian as needed throughout the design and

investigation phases of the study. The search will be restricted to human studies. Our search will not be restricted to the published literature. We acknowledge that studies in the unpublished literature may not be subject to the same scrutiny as the investigations published in peer-reviewed journals. However, the unpublished literature meeting the inclusion criteria will still be subject to the same rigorous risk of bias assessment as all studies included in this review. To ascertain the gray literature we will perform a search using the ProQuest Dissertations and theses Database. The title, abstract, and full text screening will be performed in duplicate by two independent reviewers (Dennis, B and Bawor, M).

#### *5.3.1.4 Selection of Studies*

Two independent reviewers will screen titles and abstracts and potentially eligible full text articles using predefined inclusion criteria. Any disagreements or variability between reviewers will be resolved by discussion. If discussion does not lead to a resolution, a third author (Samaan, Z) will be consulted and have the final judgment over the disputed article. We will calculate and report the kappa statistic for each stage (title, abstract, full-text) of screening to display the level of agreement between reviewers.

This review will be reported in accordance with the PRISMA guidelines.<sup>24</sup> The review will include a flow diagram ([Figure 5.3.1.4](#)) of the article screening process.

#### *5.3.1.5 Data Abstraction*

The two authors (BD and MB) will independently extract data from the studies using a pre-established data extraction form (DEF), which is available upon request. All study information will be recorded onto the DEF and later entered onto an electronic Microsoft Excel sheet. The independent reviewers will extract all eligible studies in duplicate. Similar to the methods for disagreement resolution during the title and abstract screening, the independent reviewers will first discuss the disagreements they have during the data abstraction. When discussion does not lead to a resolution, a third reviewer (Samaan, Z) will provide the final decision over the disagreement.

Information extracted during the data abstraction will include author, date of publication, journal of publication, number of study participants, type of population (clinical, incarcerated, pregnant), eligibility criteria, OSAT(s), OSAT dose (by chronic pain status), definition of chronic pain, identification of primary outcome, definition of response outcome(s), measurement of chronic pain, measurement of response outcome(s), percentage/number of participants with chronic pain, statistical analysis performed, study findings, overall statistical findings, factors associated with treatment response (if reported), and authors conclusions.

#### *5.3.1.6 Assessment of Methodological Quality*

Two independent reviewers will assess the methodological quality of the studies in duplicate using a modified Newcastle Ottawa scale for case-control and cohort studies,<sup>25</sup>

the NIH National Heart, Lung, and Blood Institute: Quality Assessment Tool for Cross-Sectional Studies,<sup>26</sup> and the Cochrane Risk of Bias Tool<sup>27</sup> for randomized controlled trials. As mentioned above, any discrepancies between the independent reviewers will first be resolved by discussion, if discussion does not lead to an adequate solution a third reviewer (Samaan, Z) will be brought in with the responsibility of resolving the dispute.

All summary estimates obtained from meta-analysis will be subject to evaluation using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) guidelines.<sup>28</sup> Provided the data are appropriate, summary statistics derived for direct and indirect estimates using NMA will also be subject to assessment using the GRADE framework.<sup>29</sup>

### **5.3.2.0 Statistical Analysis Methods**

The results of this systematic review will be reported in a narrative and where possible, a combined statistical manner. Agreement levels between the independent reviewers will be measured using the kappa statistic. Provided there is little heterogeneity between studies, we plan to conduct a meta-analysis to derive a summary statistic representing the combined statistical result of multiple studies across our primary outcome (illicit opioid use behaviour) and secondary efficacy end-points. As described previously,<sup>30</sup> the lack of direct comparisons reported in the literature is a common problem when combining the evidence from studies evaluating OSATs. The majority of studies evaluate new therapies in direct comparison to methadone or placebo, leaving us to question the comparative effectiveness compared to other OSATs. To circumvent this

problem we are proposing using network meta-analysis (NMA) to provide the pooled effect estimates of chronic pains mediating effects on the primary outcome (illicit opioid use behaviour) for all OSTs.

Research methodologists highly caution against the pooling of studies with fundamentally different designs,<sup>31,32</sup> largely because of imbalanced susceptibility to selection bias non-randomized studies face.<sup>31</sup> Thus, we will combine the results of randomised and non-randomised studies in separate meta-analyses.

#### *5.3.2.1 Direct Comparisons*

We will perform a meta-analysis to pool results for our primary outcome as well as all secondary efficacy end-points. Findings abstracted from direct comparisons will be pooled together using a random-effect meta-analysis with Knapp-Hartung (KH) estimator.<sup>33</sup> All analyses will be performed using the metafor and rmeta packages in R.<sup>34</sup>

Dichotomous outcome(s) will be combined into a pooled odds ratio, where continuous outcomes (e.g. mean number of positive opioid urine screens evaluated by chronic pain status) will be pooled using the standardized mean difference. All direct comparisons will be weighted using the inverse of the variance.

Results from studies deemed eligible for inclusion into the meta-analysis will be presented in a forest plot, with the associated 95% confidence intervals presented. We will calculate and report the inconsistency index ( $I^2$ ) statistics and p-values as the measure of heterogeneity in the results of the studies and whether the actual observed

difference can be attributable to chance alone.<sup>35</sup> We will interpret the  $I^2$  statistic using the thresholds set forth by the Cochrane Collaboration, these include  $I^2$  of 0-40% (might not be important), 30-60% (moderate heterogeneity), 50-90% (substantial heterogeneity), and 75-100% (considerable heterogeneity).<sup>31</sup> The Egger's test will be used to assess for publication bias.

We anticipate a study's scoring on methodological quality assessment as well as differences in measurement selection (e.g. urine toxicology screening versus self-report) to be important factors accounting for heterogeneity between studies. The methodological quality of individual studies will be captured using the Cochrane Risk of Bias tool, Newcastle Ottawa Scale, and the NIH National Heart, Lung, and Blood Institute: Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies. Subgroup analyses will stratify on the basis of the study's performance on the risk of bias assessment. We will stratify our analyses on the basis of Cochrane risk of bias responses, whereby studies will be characterized as having an overall "high risk of bias" if at least one domain on the Cochrane risk of bias tool is rated as high risk. Thus, results of any study with  $\geq 1$  "high risk of bias" rating across domains will be considered at risk for confounding. For observational studies, we will need to address risk of bias according to the appropriate assessment tools, thus we will not be able to use Cochrane risk of bias across all studies. For cohort and case-control studies, any study with zero stars in  $\geq 1$  section will be considered high risk of bias based on the Newcastle Ottawa Scale. According to the Newcastle Ottawa Scale, receiving stars indicates a lower risk of bias. The lack of stars in any section indicates the study has not addressed a possible source of

confounding. For cross-sectional studies rated with the NIH tool, any study receiving a “fair” or overall “poor” quality rating will be classified as high risk of bias and included for subgroup analysis. We anticipate the studies with improper adjustment for important confounding variables to have high-susceptibility for confounded treatment effects.

We will also stratify our meta-analyses based on outcome measurement. A clear example of how measurement can influence the study results is noted with the measurement of opioid use, where some studies use urine toxicology screening to determine concomitant opioid abuse and other studies use self-report. Self-report is susceptible to social desirability bias, where some patients may be reluctant to report continued opioid abuse in an effort to maintain a positive standing with physicians and clinical staff. Thus, quality of measurement can contribute to large difference in the study findings.

Acknowledging the impact of publication status as a potential source of bias, we will perform sensitivity analysis to determine whether a study’s publication status impacts the observed effect estimates. Studies in the gray literature are not subject to the same level of scrutiny as those in peer reviewed journals. The peer review process leads to the identification of potential sources of confounding and allows authors to re-perform their analyses by properly adjusting for newly identified sources of error. Thus, some of the unpublished literature may present different treatment effects simply due to the lack of external evaluation. We will evaluate this potential concern by performing an additional sensitivity analysis, stratifying our meta-analyses by the articles publication status.

### *5.3.2.2 Combining Direct and Indirect Evidence: The Network Meta-Analysis*

Provided the data are suitable for NMA, we propose building a Bayesian hierarchical model using maximum likelihood estimation to derive summary statistics for binary outcomes. This model will introduce a random effect representing the variation in effect estimates resulting from the comparison itself. Any variation in the random effect will be considered “inconsistency”.<sup>36</sup> This method allows for treatment heterogeneity, sampling variability, and inconsistency<sup>36</sup> while also applying maximum likelihood estimation.<sup>36</sup>

Due to the fragility of the NMA, we propose selecting the best evidence for inclusion into the model. Thus, only evidence from randomized trials with  $\geq 200$  people in the comparison will be selected for inclusion into the NMA model. We set this sample size requirement to adjust for the high susceptibility of type I error in studies evaluating multiple treatment outcomes.

We will use node splitting to identify inconsistency,<sup>37,38</sup> a method that identifies loops with large inconsistency. The inconsistency will be taken into consideration during the interpretation of the results. We will also use the deviance information criterion (DIC) to estimate how parsimonious the data are.<sup>37</sup>

Findings from the NMA will be presented using probability statements of treatment effects as well as a ranking of these probabilities, which illustrates each interventions probability of ranking first.<sup>39</sup> We will also graphically display the probability ranks using the surface under the cumulative ranking (SUCRA) line.<sup>39</sup>

### **5.3.3 Methods for Evaluating the Clinical Guidelines**

To identify the most recently published North American guidelines on opioid maintenance treatments we will search [www.guidelines.gov](http://www.guidelines.gov). We will search using the terms “opioid use disorder, opioid dependence, opioid addiction, and opioid substitution treatment.” We will also search the National Institute for Health and Care Excellence (NICE) database to identify the most recently published guidelines used by the National Health Service in the UK. We will use pilot tested data-abstraction forms to extract data on: the recommendations made by each guideline, the strength of the recommendation, the evidence cited by the guideline for each recommendation, whether the guideline developers interpreted any clinical subgroup effects with caution, and whether the guideline discussed the impact of pain on poor treatment response. We will also quantitatively appraise the quality of the guidelines using the Appraisal of Guidelines for Research & Evaluation II (AGREE) Instrument, a validated tool used for guideline assessment.<sup>40,41</sup> We will use this tool to assess the transparency in the development of guideline recommendations for chronic pain subpopulations. However, the use of the AGREE II will be unjustified if no formal recommendations are made for managing this population.

## 5.4 DISCUSSION

Understanding the impact of comorbid disorders on addiction treatment outcomes is essential for enhancing evidence-based practices within the field of mental health and addiction. This investigation will focus on determining the role that chronic non-cancer pain has on the patient's experience of opioid addiction treatment. Acknowledging the complexity of comorbid pain management within the addiction treatment setting, we aim to understand the extent to which chronic pain is related to negative health outcomes including functional disability, physical difficulty, mental health problems such as depression and anxiety in the context of opioid addiction.<sup>10</sup> Determining the influence of chronic pain on response to OSAT will require a detailed assessment across several different patient important outcomes. This review will capture the experience of treatment for a substantive sub-population of opioid addiction patients. If chronic pain truly does result in negative consequences for opioid addiction patients, it is important we identify which OSAT is most appropriate for chronic non-cancer pain patients. We will also identify how current evidence is translated into practice by thoroughly reviewing international guidelines for OSAT. We aim to address how addiction treatment guidelines propose managing patients with comorbid pain. This objective provides an opportunity to distinguish the best quality guidelines and ultimately identify future areas for improvement.

## **5.5 ACKNOWLEDGMENTS, FUNDING, AND AUTHOR CONTRIBUTIONS**

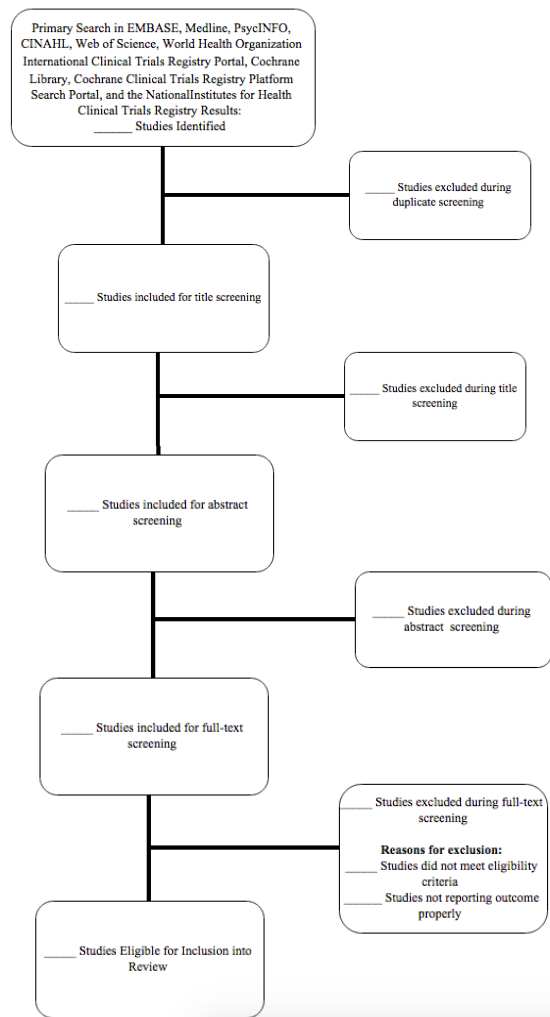
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The authors declare that they have no competing interests. BBD, MB, LT, ZS, JP, CP, MV, JD, DCM, DD, GP, and AW conceived the research question and designed the review protocol. JP provided guidance for the evaluation of pain measures in opioid dependent populations. BBD and MB performed the literature search, tested and revised the electronic search strategy, as well as designed and pilot tested the data extraction forms. BBD and LT designed the statistical analysis plan. BBD, MB, LT, JP, ZS, CP, MV, JD, DCM, DD, GP, and AW contributed equally to writing and revision of the manuscript. The final version of the protocol has been read and approved by all authors.

## 5.6 FIGURES AND TABLES

Figure 5.3.1.4 Flow Diagram of Article Screening Process

Figure 1: Flow diagram of the article screening process



**Table 5.3.1.3 Electronic Search Strategy for the Identification of Relevant Studies Across Multiple Databases**

<p><b>MEDLINE</b> Search = _____</p>	<ol style="list-style-type: none"> <li>1. substance related disorders.mp. or Substance-Related Disorders/</li> <li>2. opioid related disorders.mp. or Opioid-Related Disorders/</li> <li>3. Opioid-Related Disorders/ or Methadone/ or Analgesics, Opioid/ or Heroin Dependence/</li> <li>4. 1 or 2 or 3</li> <li>5. methadone.mp. or Methadone/</li> <li>6. Opiate Substitution Treatment/ or Naloxone/ or Buprenorphine/ or Opioid-Related Disorders/ or Narcotic Antagonists/</li> <li>7. buprenorphine.mp. or Buprenorphine/</li> <li>8. naltrexone.mp. or Naltrexone/</li> <li>9. Substance Abuse Treatment Centers/ or Heroin/ or Heroin Dependence/ or Opioid-Related Disorders/ or Randomized Controlled Trials as Topic/ or Methadone/</li> <li>10. opioid substitution treatment.mp. or Opiate Substitution Treatment/</li> <li>11. Buprenorphine/ or Analgesics, Opioid/ or Opioid-Related Disorders/ or Methadone/ or Heroin Dependence/</li> <li>12. 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12</li> <li>13. chronic pain.mp. or Chronic Pain/</li> <li>14. 4 and 13 and 4</li> <li>15. limit 15 to humans</li> </ol>
<p><b>Web of Science</b> Search = _____</p>	<ol style="list-style-type: none"> <li>1. Topic=("methadone" OR "methadone maintenance therapy" OR "naltrexone" OR "suboxone" OR "buprenorphine" OR "heroin assisted treatment")</li> <li>2. Topic=("opioid dependence" or "addiction")</li> <li>1. Topic=("chronic pain" OR "pain" OR opioid induced hyperalgesia")</li> <li>2. 1 AND 2 AND 3</li> </ol>
<p><b>EMBASE</b> = _____</p>	<ol style="list-style-type: none"> <li>1. methadone treatment/ or methadone.mp. or methadone/ or methadone plus naloxone/</li> <li>2. heroin dependence/ or maintenance therapy/ or methadone/ or opiate addiction/ or diamorphine/ or methadone treatment/</li> <li>3. buprenorphine/ or buprenorphine.mp.</li> <li>4. naltrexone.mp. or morphine sulfate plus naltrexone/ or naltrexone/</li> <li>5. opioid substitution treatment.mp. or opiate substitution treatment/</li> <li>6. methadone/ or diamorphine/ or heroin dependence/</li> <li>7. levomethadyl acetate.mp. or levacetylmethadol/</li> <li>8. 1 or 2 or 3 or 4 or 5 or 6 or 7</li> <li>9. substance related disorder.mp. or addiction/</li> <li>10. naltrexone/ or buprenorphine/ or opioid addiction.mp. or methadone/</li> <li>11. 9 or 10</li> <li>12. chronic pain.mp. or chronic pain/</li> <li>13. 8 and 11 and 12</li> <li>14. limit 13 to human</li> </ol>
<p><b>PsychINFO</b> Search = _____</p>	<ol style="list-style-type: none"> <li>1. exp Drug Therapy/ or exp Methadone Maintenance/ or exp Heroin Addiction/</li> <li>2. exp Methadone/ or exp Naloxone/ or exp Drug Therapy/ or exp Drug Dependency/ or buprenorphine.mp.</li> <li>3. naltrexone.mp. or exp Naltrexone/</li> <li>4. exp Heroin Addiction/ or exp Drug Rehabilitation/ or exp Drug Dependency/ or exp Clinical Trials/</li> <li>5. exp Drug Therapy/ or exp Methadone Maintenance/</li> <li>6. 1 or 2 or 3 or 4 or 5</li> </ol>

	<ol style="list-style-type: none"> <li>7. exp Drug Abuse/ or substance related disorder.mp. or exp Drug Dependency/</li> <li>8. substance abuse.mp. or exp Drug Abuse/</li> <li>9. 7 or 8</li> <li>10. chronic pain.mp. or exp Chronic Pain/</li> <li>11. 6 and 9 and 10</li> </ol>
<p><b>Cochrane Library:</b> Cochrane Review and Cochrane Central Register of Controlled Trials = _____</p>	<p><b>Search title, abstract, keywords:</b></p> <ol style="list-style-type: none"> <li>1. "methadone" OR "naltrexone" OR "buprenorphine" OR "opioid substitution treatment" OR "levo-methadyl acetate" OR "heroin assisted treatment" OR "heroin substitution treatment"</li> <li>2. "substance abuse disorder" OR "opioid abuse" OR "substance-related disorder" OR "opioid addiction"</li> <li>3. "chronic Pain" OR "pain" OR "hyperalgesia" OR "neuropathic pain"</li> </ol>
<p><b>Clinical Trials Registry</b> through National Institutes for Health = _____</p>	<p>"methadone" OR "suboxone" OR "Buprenorphine" OR "substitute opioid therapy" OR "naltrexone" OR "heroin assisted treatment" OR "heroin adjustment therapy" AND "opioid addiction" AND "chronic pain", with additional criteria including: Completed studies, all trials had to be listed as Phase 3, 4</p>
<p><b>World Health Organization International Clinical Trials Registry Platform Search Portal</b> = _____</p>	<p>““opioid addiction” OR “opioid substitution treatment” OR “opioid maintenance treatment” OR “methadone maintenance treatment”” AND “chronic pain”</p>
<p><b>ProQuest Dissertations and theses Database</b> = _____</p>	<p>“opioid addiction” OR “opioid dependence” AND “pain” OR “Chronic Pain”</p>

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## CHAPTER 6

### Study 4 Part II

#### **Impact of Chronic Pain on Treatment Prognosis for Patients with Opioid Use Disorder: A Systematic Review and Meta-analysis**

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## 6.1 ABSTRACT

**Background:** A number of pharmacological interventions exist for the treatment of opioid addiction. Evidence evaluating the effect of pain on substance use behaviour, attrition rate, and physical or mental health amongst these therapies has not been well established. We aim to evaluate these effects using evidence gathered from a systematic review of studies evaluating chronic non-cancer pain (CNCP) in opioid addiction patients.

**Methods:** We searched the Medline, EMBASE, PubMed, PsycINFO, Web of Science, Cochrane Database of Systematic Reviews, ProQuest Dissertations and theses Database, Cochrane Central Register of Controlled Trials, World Health Organization International Clinical Trials Registry Platform Search Portal, and National Institutes for Health Clinical Trials Registry databases to identify articles evaluating the impact of pain on addiction treatment outcomes for patients maintained on opioid substitution or antagonist therapy (OSAT).

**Results:** Upon screening 3540 articles, fourteen studies with a combined sample of 3128 patients fulfilled the review inclusion criteria. We did not identify any studies evaluating patients on an opioid antagonist therapy. Results from the meta-analysis suggest pain has no effect on opioid relapse (Pooled Odds Ratio[pOR]:0.70, 95%CI 0.41,1.17:  $I^2=0.0$ ), and a protective effect for reducing illicit non-opioid consumption (pOR: 0.57, 95%CI 0.41, 0.79:  $I^2=0.0$ ). Studies evaluating illicit opioid consumption using other measures demonstrate pain to increase risk for opioid relapse. Pain is significantly associated with the presence of psychiatric disorders (pOR: 2.18; 95%CI 1.6, 2.9:  $I^2=0.0\%$ ).

**Conclusion:** CNCP may increase risk for opioid relapse and poor psychiatric functioning.

Qualitative synthesis of the findings suggests major methodological differences in the design and measurement of pain and treatment response outcomes are likely impacting the effect estimates.

## 6.2 INTRODUCTION

Despite impacting the lives of over 95 million people,<sup>1</sup> there are a limited number of effective treatments for chronic non-cancer pain (CNCP).<sup>2</sup> CNCP is characterised as a significant pain lasting longer than the standard healing time and that is not directly caused by malignancy.<sup>3</sup> While there is limited evidence to support the effectiveness of opioids for providing long-term pain relief,<sup>2</sup> they remain the most commonly used intervention.<sup>4</sup> This is concerning due the global rise in opioid-related medication diversion, morbidity, and mortality.<sup>5-9</sup> Patients prescribed opioids also incur a substantial risk for addiction and the incidence of opioid addiction is estimated to affect up to 27% of the CNCP population.<sup>10</sup> There exist a number of interventions for opioid addiction, of which methadone is the oldest and most commonly employed.<sup>11</sup> Methadone maintenance treatment (MMT) is an opioid substitution therapy (OST) prescribed to alleviate withdrawal symptoms and stabilize patients seeking to abstain from illicit opioid consumption.<sup>11</sup>

CNCP is the most commonly reported comorbid disorder among patients receiving OST, impacting 37-55.3% of patients receiving substitution therapy.<sup>12-14</sup> CNCP is also one of the strongest predictors for relapse within the OST setting.<sup>15,16</sup> Studies identifying predictors for adverse outcomes among patients treated with methadone found patients reporting pain to have higher incidence of opioid abuse and abnormal psychiatric symptoms.<sup>15,16</sup> Patients who continue to abuse opioids while on OST have an increased

risk for cardiovascular abnormalities,<sup>17,18</sup> overdose,<sup>19,20</sup> and death,<sup>19</sup> emphasizing the importance of distinguishing the risk factors for continued opioid abuse.

While many trials evaluate the effectiveness of OSTs for patients with addiction,<sup>21-54</sup> to our knowledge none provide an analysis or discussion as to the mediating effects of pain on substance use behaviour, treatment retention, or other patient important outcomes. Even among the oldest and most commonly employed OST –MMT— there exists conflicting evidence that both implicates and refutes the role of chronic pain as a risk for opioid relapse.<sup>12,16,55-57</sup> The management of patients with opioid addiction poses many challenges. Efforts to combine the evidence evaluating important risk factors for adverse outcomes in the management of opioid addiction will prove critical for enhancing our understanding of this complex disorder that is impacted by large variability in treatment effectiveness and prognosis.

A number of OSTs exist including MMT, levomethadyl acetate (LAAM), buprenorphine/naloxone, morphine, as well as heroin. However the impact of pain on the effectiveness of these therapies among outcomes such as attrition rate, substance use behaviour, and physical or mental health has not been well established leaving many questions unanswered: Are patients with pain responding poorly to opioid maintenance treatment? Is there evidence demonstrating superiority of any OST in the subpopulation of addiction patients with comorbid pain? We will attempt to answer these questions using evidence gathered from a systematic review of all studies evaluating CNCP in the opioid addiction patient population. Findings from this review will serve to provide consensus in establishing whether CNCP is an important risk factor for patients on OST, distinguish

the best available OST treatment for patients with CNCP, and provide an evidence-based knowledge synthesis to enable clinicians managing opioid-dependent and CNCP patients to evaluate risk factors for poor prognosis and tailor treatments accordingly.

## **6.3 OBJECTIVES AND RESEARCH QUESTION**

### **6.3.1 Objectives**

We aim to: 1) evaluate the impact of CNCP on substance use behaviour, physical health, psychiatric symptoms, as well as personal and social functioning; 2) determine whether any OST demonstrates superiority or shows significant benefit for patients with opioid addiction reporting comorbid pain; 3) provided the data are suitable, combine the evidence from direct and indirect comparisons using network meta-analysis, and; 4) identify the most recently published opioid maintenance treatment guidelines from the United States (US), Canada, and the United Kingdom (UK) to determine how the evidence is being translated into clinical practice for managing chronic pain associated with opioid addiction.

### **6.3.2 Research Question(s)**

**1.** Among patients with opioid addiction being treated with (or randomized to) opioid substitution treatment (OST):

**2.** Does CNCP impact OST outcomes?

**3.** Which OST is most effective for improving treatment response in patients with comorbid

CNCP?

*Treatment response will be defined by improvements in substance use behaviour, physical health, psychiatric symptoms, as well as personal and social functioning.*

4. Do the most recently published Canadian, American, and United Kingdom OST clinical practice guidelines capture pain as an important factor in opioid addiction and properly translate the evidence obtained from the studies evaluated in this review?

## 6.4 METHODS

### 6.4.1 Systematic Review

The methods of this systematic review are published<sup>58</sup> and registered with PROSPERO (ID: CRD42014014015). Briefly, we performed a systematic review to identify all studies evaluating the impact of chronic pain on different treatment outcomes within the opioid addiction patient population. We searched Medline, EMBASE, PubMed, PsycINFO, Web of Science, Cochrane Library, ProQuest Dissertations and theses Database, Cochrane Clinical Trials Registry, World Health Organization (WHO) International Clinical Trials Registry Platform Search Portal, and National Institutes for Health (NIH) Clinical Trials Registry databases. We searched the Cochrane Library to identify relevant systematic reviews of the topic. Independent reviewers later hand-searched reference lists from these reviews for any missed studies. We screened the title, abstract, and full-text articles in duplicate. We report the kappa statistic to demonstrate the level of agreement between reviewers.<sup>59</sup>

To be included in this review studies were required to assess the impact of pain on any of the following treatment outcomes: physical, psychological, or social outcomes for patients receiving opioid agonist or antagonist substitution therapy for opioid addiction. Study participants were required to be on a maintenance therapy for the opioid addiction. The initial search included studies evaluating patients on antagonist therapy, however no studies assessing antagonist therapy were identified. Studies evaluating patients on OST for the treatment of pain and not opioid addiction (e.g. methadone for pain) were not

eligible for this review. While our search did not place any language or time restrictions on retrieved articles, the search was restricted to human studies. All studies were subject to risk of bias assessment according to the appropriate quality assessment tools. We evaluated observational studies using two risk of bias tools, cross-sectional studies using the National Institutes of Health (NIH) National Heart, Lung, and Blood Institute: Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies<sup>60</sup> and cohort studies using the Newcastle Ottawa Scale.<sup>61</sup> We evaluated randomized trials using the Cochrane risk of bias tool.<sup>62</sup> We assessed the strength of the evidence summarized in this review using Grading of Recommendations Assessment, Development and Evaluation (GRADE).<sup>63</sup>

Independent reviewers performed full-text extraction in duplicate using pilot tested data extraction forms. We extracted from each study the following information: author, date of publication, journal of publication, number of study participants, type of population (clinical, incarcerated, pregnant), eligibility criteria, type of OST(s), OST dose (by chronic pain status), definition of chronic pain, identification of the study primary outcome, definition of treatment response outcome(s), measurement of chronic pain, measurement of response outcome(s), percentage/number of participants with chronic pain, statistical analysis performed, study findings, overall statistical findings, factors associated with treatment response (if reported), and authors' conclusions.

A flow diagram detailing the article selection process as well as detailed tables reporting the key methods and conclusions of studies deemed eligible for this review are reported in accordance with the meta-analysis of observational studies in epidemiology

(MOOSE) and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guidelines.<sup>64,65</sup>

#### **6.4.2 Guideline Assessment**

To identify Canadian and American opioid maintenance treatment guidelines we searched [www.guidelines.gov](http://www.guidelines.gov) with the terms “opioid dependence, opioid addiction, and opioid substitution treatment.” To identify the most recently published UK guidelines we searched the National Institute for Health and Care Excellence (NICE) using key words “opioid addiction,” “methadone,” “buprenorphine” “naltrexone,” and “opioid dependence.” We extracted specific information including year of publication, guideline objectives, any information on pain population subgroups, evidence cited by guideline for managing patients with comorbid pain, and any cautions regarding specialized populations.

We intended to evaluate each guideline using the rigor of development and applicability domains from the Appraisal of Guidelines for Research & Evaluation II (AGREE) Instrument. AGREE II is a validated instrument used for the quality assessment of clinical guidelines.<sup>66,67</sup> In its entirety the tool has 23 items organized across six quality domains.<sup>66</sup> Our major objective using these guidelines is to distinguish the best quality guidelines by assessing how evidence is being incorporated into guideline development. As such we only assessed these guidelines on the basis of the rigor of development and applicability domains.

#### **6.4.3.0 Statistical Analysis**

While we originally intended to perform a network meta-analysis (NMA) to statistically combine the results for direct and indirect OST comparisons, the lack of studies a) evaluating different OSTs, b) performing head to head comparisons, and c) evaluating similar outcomes prevented us from successfully completing the NMA. Thus, we summarize the results of all direct comparisons in this review narratively and statistically where appropriate.

#### *6.4.3.1 Qualitative Summary*

Due to the large variations in the definition and measurement of outcomes reported across studies we chose to provide a qualitative summary for each outcome. We provide a detailed summary of all results according to broader themes that appropriately capture the behaviour or attribute of interest. For instance, substance use behaviour can capture a wide array of specifically defined and measured outcomes. Whether it is the number of days of crack/cocaine use over the past month, or the percentage of participants reporting non-opioid substance abuse, the broader category of illicit substance use adequately captures this behaviour. We have chosen a list of categories generated from a larger systematic review of OST effectiveness (Dennis et. al, unpublished 2015) which organized outcomes collected from 60 trials into broader domains proposed by commonly used addiction severity indices (i.e., the Addiction Severity Index [ASI]<sup>68</sup> and Maudsley Addiction Profile [MAP]).<sup>69</sup> The identified outcome domains included: physical health, psychiatric health and symptoms, abstinence and substance use behavior, personal and social functioning, global quality of life and addiction severity assessments (including global addiction severity measure scores),

intervention adherence, acceptance of intervention, and resource utilization (e.g. hospital admission).

A summary of findings table is presented to demonstrate the impact of pain across each outcome domain. The additional “Findings” column details our conclusions based on the available evidence. To reach a valid conclusion we decided a priori on the following criterion:  $\geq 50\%$  of the studies for a single intervention (methadone, buprenorphine) must demonstrate a harmful or beneficial effect of pain on the outcome. If less than 50% of the studies demonstrate such an effect we concluded there was not enough evidence.

#### *6.4.3.2 Quantitative Summary*

We conducted meta-analyses using a random-effects model to address the following outcomes: illicit opioid use, illicit substance use, and presence of psychiatric illness. Each of these outcomes were measured as binary variables, whereby the studies provided the number/percentage of participants who reported using opioids, other substances, or a history of psychiatric illness. Since each of our outcomes used for the meta-analysis were dichotomous, we present the summary estimates as pooled odds with 95% confidence intervals. We employed the Mantel-Haenszel method for pooling the results of binary variables, this method provides the option to estimate between study variation by assessing each study’s final results to a Mantel-Haenszel fixed effect meta-analysis estimate. The results for each meta-analysis are presented in separate forest plots. Due to the small number of studies included in each meta-analysis (maximum of 3), we chose

not to assess for publication bias using Egger's plot. We used the inconsistency index ( $I^2$ ) statistic to determine the level of heterogeneity in the results of the studies, using the  $I^2$  values of 0-40% (might not be important), 30-60% (moderate heterogeneity), 50-90% (substantial heterogeneity), and 75-100% (considerable heterogeneity) as the categorizations set forth by the Cochrane Collaboration.<sup>70</sup>

As discussed in the published protocol, we anticipated the studies' quality assessment to important risk of bias assessment items (items assessing adjustment for confounding) as well as differences in measurement selection to be important factors contributing to heterogeneity between studies.<sup>58</sup> Our a priori hypotheses for heterogeneity between studies have been previously summarized in detail.<sup>58</sup> However, the number of studies eligible for inclusion in the meta-analysis was small enough ( $n \leq 3$ ) that the use of subgroup analyses would be deemed inappropriate.

## 6.5 RESULTS

### 6.5.1 Study Characteristics

Upon searching seven databases and three clinical trial registries we reviewed 3540 unique articles. Independent reviewers screened the title (Kappa[K]:0.51, SE 0.04; 95%CI 0.43,0.58), abstract (K:0.41, SE:0.09; 95%CI 0.24,0.58), and full text articles (K:0.77, SE 0.12; 95%CI 0.53,1.0) with moderate agreement. We identified 14 articles eligible for inclusion into this review.<sup>12-16,55,71-78</sup> [Figure 6.5.1a](#) provides a flow diagram detailing the screening process at each stage of the literature search.

Across a combined population of 3128 patients, the included studies evaluated the impact of pain on different treatment response outcomes for high-dose methadone ( $\geq 60$  mg/day), low-dose methadone ( $< 60$  mg/day), high-dose levoacetylmethadol (LAAM) ( $\geq 85$  mg/day), low dose LAAM ( $< 85$  mg/day), high-dose buprenorphine ( $\geq 16$  mg/day), low-dose buprenorphine ( $< 16$ mg/day), high-dose Suboxone® (buprenorphine  $\geq 16$  mg/day + naloxone), and low-dose Suboxone® (buprenorphine  $< 16$  mg/day + naloxone). The studies used a range of epidemiologic designs including cross-sectional, randomized controlled trial, and prospective cohort. Details of the design characteristics of individual studies are summarized in [Figure 6.5.1](#). While the majority of studies used the BPI<sup>12-14,71,75,76,78</sup> to measure pain ([Figure 6.5.1b](#)), the definitions and cut-offs used to determine pain varied greatly ([Figure 6.5.1](#)). Some studies provide unclear descriptions of both the measurement and definition of pain.<sup>15,74</sup>

Using the outcome domain categorizations described earlier, we found the majority of studies evaluated the effects of pain on abstinence from illicit opioids and other substance use related outcomes. [Figure 6.5.1c](#) provides a summary of all outcome domains with the corresponding number of studies reporting each outcome.

### **6.5.2 Risk of Bias Assessment**

The risk of bias assessment was performed using three instruments<sup>60-62</sup> across cross-sectional, cohort, and randomized studies. Results from the quality assessment are summarized in supplementary in supplementary Appendix iii [Tables S1-S3](#). The majority of studies suffer from a high risk of bias due to the lack of reporting on important issues such as follow-up, missing data, and blinding (Tables S1-S3). The majority of studies used a cross-sectional design (k=10) to assess the association between the presence of pain and OST treatment outcome, while only half of the studies (k=5) established a “dose response” relationship between pain severity and treatment outcome, suggesting an increase in the intensity of the exposure (pain) is associated with an increase in opioid consumption. (Table S1 in supplementary appendix iii).

### **6.5.3.0 Abstinence and Substance Use Behaviour**

#### *6.5.3.1 Illicit Opioid Use*

Among the 14 studies included in this review, 12 evaluated the impact of chronic pain on illicit opioid use behaviour. The measurements, definitions, and statistical methodology used to evaluate opioid use are described in [Table 6.5.3.1](#). The majority of studies

measured opioid use behaviour using urine toxicology screening (Table 6.5.3.1).<sup>13,14,16,73-75,77,78</sup> However some studies relied on a self-report tool generated for the study, or the Addiction Severity Index (ASI) to determine the frequency of opioid use.<sup>12,55,71,76</sup> We were unable to combine the results of the majority of studies evaluating the same intervention (e.g. methadone) because of the large variations in defining illicit opioid use behaviour. While some studies report the number of patients using illicit opioids (separated by pain status),<sup>12-14,16,71,73,74,76,77</sup> others choose to report the number of days of illicit opioid use,<sup>55</sup> as well as the percentage or mean percent of positive opioid screens reported by chronic pain status.<sup>16,75</sup> Of the 12 studies evaluating illicit opioid use behaviour, only two reported a significant effect of pain on opioid consumption,<sup>16,55</sup> whereby both studies were performed in MMT patients and use different measures to assess opioid use behaviour. Despite differences in measurements and interventions (e.g. methadone, buprenorphine), the majority of studies report no effect of pain on illicit opioid use.<sup>12-14,71,73-77</sup>

Studies eligible for inclusion in the meta-analysis defined opioid use behaviour as a binary outcome, categorizing participants as having engaged in illicit opioid consumption if  $\geq 1$  urine test in a designated time period preceding the survey was positive.<sup>13,16</sup> While not originally reported in the Dennis et. al (2014) paper, the authors provided data for the purposes of this review.<sup>16</sup> Of the 235 methadone patients assessed in the Dennis et. al (2014) study, 79.7% of the patients reporting pain and 81.3% of those without pain were found to have  $\geq 1$  positive opioid urine screen (Dennis et. al 2014, unpublished). The meta-analysis presented in the [Figure 6.5.3.1](#) forest plot provides the pooled odds ratio

using a random-effects model. Findings from the meta-analysis suggest there is no effect of pain on illicit opioid consumption (Pooled Odds Ratio [pOR]:0.70, 95% CI 0.41,1.17;  $I^2=0.0$ ). For the studies evaluating the impact of pain on opioid consumption among buprenorphine maintained patients, neither study reported a significant effect.<sup>73,74</sup>

#### *6.5.3.2 Illicit Substance Use (other than opioids)*

Seven studies assess the impact of pain on non-opioid illicit substance use,<sup>12,14,55,71-73,75</sup> of which the definition and measurement of what constitutes illicit substance use varied substantially. While some studies assess the number of participants reporting any illicit substance use (cocaine, benzodiazepine, cannabis) within the last week,<sup>71</sup> month,<sup>14</sup> or 3 months,<sup>12,75</sup> others chose to evaluate the predictors of illicit substance use behavior,<sup>73</sup> number of days of substance use in the previous month,<sup>55</sup> or the percentage of participants reporting any substance misuse at baseline.<sup>72</sup> The stark heterogeneity in defining and measuring illicit substance use precluded the majority of studies from inclusion in the meta-analysis. Two studies measuring substance use as the percentage of participants reporting substance use by pain status were pooled in the meta-analysis. Findings from the meta-analysis are presented in [Figure 6.5.3.2](#), where the presence of pain is shown to be protective against illicit non-opioid substance use (pOR: 0.57, 95%CI 0.41, 0.79;  $I^2:0.0$ ). These odds of reporting non-opioid illicit substance use are reduced by 43% in participants with comorbid pain.

The findings from individual studies revealed participants with pain report higher rates of marijuana,<sup>55</sup> benzodiazapine<sup>75</sup> and sedative<sup>55</sup> use. However, no differences were found when evaluating psychoactive substance use among participants based on pain

classification.<sup>14,71,72</sup> Trafton et. al (2004) assessed the impact of pain on the number of days of reported substance use in the previous month (measured using Addiction Severity Index),<sup>55</sup> reporting no significant differences in the number of days of reported use between patients with and without pain for alcohol, heroin, and cocaine.<sup>55</sup> However, Trafton et. al (2004) found a significant difference in the number of days as well as lifetime (years) reported use of opiates and marijuana, suggesting participants with pain were more likely to report using these substances.<sup>55</sup> Trafton et. al (2004) also found participants with pain to have a longer duration of lifetime history of sedatives use (pain: 2.4 years, no pain: 0.8 years).<sup>55</sup> Trafton et. al (2004) report no significant differences in health risk behaviours such as injecting or needle sharing between the pain and no pain groups.<sup>55</sup>

Bounes et. al (2013) evaluated the differences in illicit substance use (urine toxicology and self-report) at baseline between pain and no pain groups, however they present only the raw data and report no significant differences between groups for stimulants, hallucinogens, or cannabis use.<sup>72</sup> It appears however that cannabis use is reported at a higher rate in patients with pain (28%) in comparison to patients without pain (15%).<sup>72</sup> Barry et. al (2009) reported similar findings, suggesting, “the pain groups reported comparable levels of psychoactive substance use, illegal drug use and non-medical use of prescription drug in the past week.”<sup>71</sup> However, no specific percentages of substance use were reported per group. Dhingra et. al (2013) did not report the observed differences between pain groups, however they did suggest that neither urine drug screen (UDS) nor self-reported drug use on the ASI was statistically associated with clinically significant

pain in the univariate analysis.<sup>14</sup>

Dunn et. al (2014) report the mean percent of positive urine screens for opiates, benzodiazepine, and cocaine use, finding patients reporting pain to have a significantly higher rate of benzodiazepine use (mean % positive pain 7, mean % positive no pain 3;  $p=0.01$ ).<sup>75</sup> However, when evaluating the difference between the number of participants with  $\geq 1$  drug urine screen positive, they found 50 of 90 patients without pain and 52 of 137 patients with pain to be using illicit substances.<sup>75</sup> This second measurement was used in the [Figure 6.5.3.2](#) meta-analysis.

#### **6.5.4 Intervention Adherence**

Among the five studies evaluating the impact of pain on treatment retention,<sup>12,72,76-78</sup> one reported a significant effect.<sup>72</sup> Among patients treated with low-dose methadone and low-dose buprenorphine, Bounes et. al (2013) found retention was lower among patients reporting pain (crude OR: 0.44, 95%CI:0.22, 0.87).<sup>72</sup> Among patients treated with methadone and buprenorphine, Neumann et. al (2013) found no significant differences between retention rates among patients on buprenorphine (50% retention) and methadone (46.4% retention).<sup>77</sup> While retention was reported as an outcome in the remaining three studies,<sup>12,76,78</sup> none reported details of retention by pain status.

#### **6.5.5 Intervention Acceptance**

Three studies evaluated the impact of pain on intervention acceptance.<sup>15,72,77</sup> Jamison et. al (2000) summarized participants views towards methadone treatment, determining

whether participants with pain believe they are given enough methadone or are bothered by their dependence on OST.<sup>15</sup> Jamison showed participants with pain 1) did not believe they were given a high enough dose of methadone and 2) were extremely bothered by their dependence on methadone.<sup>15</sup> Neumann et. al (2013) chose to report the number of participants who crossed over to a different OST during the course of the trial, showing no significant differences in the rate of cross-over by pain status. Bounes et. al (2013) report the percentage of participants augmenting prescribed doses of opioid maintenance treatment and found no significant differences between patients with and without pain.<sup>72</sup>

#### **6.5.6 Resource Utilization**

Trafton et. al (2004) provided an analysis of resource utilization to evaluate the impact of pain on physical disability benefit collection, psychiatric disability benefit collection, and the number of hospitalizations reported over the lifetime.<sup>55</sup> Trafton (2004) reported a significant difference in the percentage of patients reporting physical disability claims (25% general population, 14% no pain, 35% pain,  $p < 0.001$ ) and lifetime hospitalizations (3.9% general population, 2.9% no pain, 4.9% pain,  $p = 0.002$ ).<sup>55</sup>

#### **6.5.7 Personal and Social Functioning**

Two studies assessed the impact of pain on personal and social functioning.<sup>15,55</sup> While measured and defined differently, both studies showed the presence of chronic pain to be associated with poor personal and social functioning.<sup>15,55</sup> Jamison et. al (2000) evaluated the differences in employment, family support, and family conflict among patients

reporting pain.<sup>15</sup> Jamison et. al (2000) found 17.1% of participants with pain reported employment, in comparison to the 32.3% without pain.<sup>15</sup> In addition, Jamison et. al (2000) found patients with pain (27%) were more likely to report better family support than patients without pain (21.%).<sup>15</sup> The differences between groups were tested using  $X^2$ , of which both were statistically significant.<sup>15</sup>

Trafton et. al (2004) evaluated personal and social functioning by examining the participant reported vitality and social functioning using the SF-36V.<sup>55</sup> Trafton (2004) found participants reporting pain to be much less likely to report vitality (35%) and social functioning (45%), in comparison to participants without pain, of which 53% and 76% reported vitality and social functioning respectively.<sup>55</sup> These results were statistically significant.

### **6.5.8 Physical Health**

Of the eight studies assessing the impact of pain on physical health outcomes including adverse events, symptoms related to physical functioning, and the presence of physical comorbidity,<sup>12-16,55,76,77</sup> seven studies showed a significant association between the presence pain and worsening physical health.<sup>12-16,55,76</sup> Measures for physical health outcomes varied and include; the presence of chronic illness as diagnosed by physician<sup>13</sup> or self-report,<sup>12,14-16,76,77</sup> inflammatory profile differences by pain status measured using serum levels for inflammatory biomarkers,<sup>16</sup> number of days of reported medical problems,<sup>55</sup> percent change in pain/functioning from baseline scores,<sup>77</sup> self-reported physical craving for opioids,<sup>12</sup> number of participants reporting adverse events by chronic

pain status,<sup>77</sup> as well as physical health measured by HRQL scores,<sup>14</sup> or SF-36V.<sup>55</sup> Of all the studies evaluating physical health outcomes, one did not provide the appropriate data to determine whether pain impacts physical health outcomes.<sup>77</sup> However, this same study found no differences in the physical health outcomes of pain patients randomized to low-dose methadone and low-dose suboxone.<sup>77</sup> The definitions, measurements, as well as reported findings for all health outcomes are detailed further in [Table 6.5.8](#).

### **6.5.9 Psychiatric Health and Symptoms**

Six studies report the association between pain and different psychiatric health outcomes,<sup>12,14,15,55,71,76</sup> of which all studies reporting a significant association between the presence of pain and 1) the presence of psychiatric disorders or 2) an increase in the severity of psychiatry symptoms. The investigation by Fox et. al (2013) found an increase in depressive symptoms among patients with pain at baseline. [Table S4 in Appendix iii](#) summarizes the findings from all studies evaluating psychiatric health outcomes including symptom severity or the presence of disorders. The majority of studies chose to present the prevalence of any psychiatric comorbidity stratified by pain status,<sup>12,15,55</sup> whereby patients reporting pain showed higher rates of psychiatric comorbidity than their non-pain counterparts.<sup>12,15,55</sup> Some studies did however evaluate psychiatric symptoms using different psychiatric symptom rating scales.<sup>14,71</sup> The studies evaluating the association between pain and specific psychiatric diagnosis (e.g. depression, anxiety)<sup>14,15,55,71</sup> showed participants reporting pain to have a significant increase in depressive symptoms,<sup>14,15,55,71</sup> anxiety,<sup>15,55,71</sup> somatization,<sup>71</sup> irritability,<sup>15</sup> suicidal ideation,<sup>55</sup> and violence.<sup>55</sup> Only one study reports no significant differences in the suicide attempt histories of pain and non-

pain patients.<sup>55</sup> Two studies provided suitable data for inclusion into a meta-analysis,<sup>12,15</sup> combining the results of studies assessing the percentage of participants reporting psychiatric comorbidity (including all diagnoses) by pain status as the outcome. Dennis et al (2014) provided additional data not originally reported in their study<sup>16</sup> on the prevalence of psychiatric comorbidity in patients with and without pain. This resulted in the inclusion of three studies into the meta-analysis evaluating the association between pain and psychiatric comorbidity in a combined sample of 788 participants (Figure 6.5.9). Findings from the meta-analysis suggest a significant association between chronic pain and psychiatric comorbidity (pOR: 2.18; 95%CI 1.6, 2.9, I<sup>2</sup>:0.0%, p=0.324), whereby in comparison to patients without pain the odds of reporting a psychiatric comorbidity is 2.18 times greater in patients reporting pain, suggesting a significant association between pain and psychiatric disorders.

#### **6.5.10 Summary of Included Studies**

The summary of findings specific to each intervention (e.g. methadone, buprenorphine) can be found in [Table 6.5.10](#). This table provides an outline of the number of studies evaluating each outcome, as well as those showing risk or benefit based on participants' exposure status. This table provides conclusions based on the evidence algorithm discussed previously, whereby  $\geq 50\%$  of the studies must demonstrate an effect. GRADE evidence profiles were constructed to assess our confidence in each meta-analysis estimate. Meta-analyses evaluating the impact of pain on illicit opioid use, illicit substance use, and psychiatric comorbidity were ranked very low, low, and low

respectively. The evidence profiles are summarized in Table S5 in Appendix iii.

### **6.5.11 Guideline Evaluation**

We identified three of the most recently published national guidelines for opioid addiction using the national guideline clearinghouse provided by [www.guideline.gov](http://www.guideline.gov), and the NICE database.<sup>11,79-81</sup> The guidelines provided minimal information about the effect of pain in the opioid addiction population.<sup>11,79-81</sup> While some guidelines provide suggestions to manage comorbid CNCP with non-opioid interventions<sup>11,79,80</sup> as well refer patients with severe pain to community specialists,<sup>11,80</sup> none provide any detail about the risk for psychiatric comorbidity, continued opioid abuse, poor physical, social, and personal functioning among patients with opioid addiction and comorbid pain.<sup>11,79-81</sup> The summary information including the detailed suggestions for managing patients with pain reported by the guidelines is described in Table 6.5.11. Due to the lack of formal recommendations for the management of patients with pain we were unable to assess each guideline using the rigor of development and applicability domains from the AGREE II. The rigor development and applicability domains are used to evaluate how evidence is being incorporated into guideline development. The available guidelines provide neither a formal assessment of the literature or identify major issues regarding the association between pain and treatment response in opioid addiction. The lack of formal recommendations for the management of pain during addiction treatment renders the application of tools to assess how evidence is being generated and used to inform recommendations for the management of pain in opioid addiction patients unjustified.

## 6.6. DISCUSSION

Findings from a systematic review of 14 studies including a combined sample of 3128 opioid addiction patients suggests comorbid pain is an important factor affecting the treatment course for patients on OST. Specifically, patients with CNCP were found to have higher rates of adverse physical, psychiatric, and personal/social functioning than patients without pain. However, these results were only demonstrated in studies evaluating methadone and LAAM.<sup>12-16,55,71,72,75</sup> Pain showed no effect on any of the outcomes evaluated for patients on buprenorphine or combination buprenorphine naloxone.<sup>72-74,76-78</sup> Results from this review also suggest the current treatment guidelines used for OSTs neither discuss the important impact of pain on treatment prognosis nor provide any formal recommendations for treatment management in this subpopulation. The guidelines only go so far as to suggest 1) managing with non-opioid medications, 2) consulting the specialized pain services for treatment, and 3) maintaining open communication with family physicians managing the patients' comorbid disorders. These suggestions are made in the supplementary sections of the guideline with no formal review process or evidence is cited to support their development. Guidelines may be restraining themselves from drawing any conclusions about the appropriate management of patients with comorbid pain because of the inconclusive nature of the evidence. However, the guidelines provide no discussion to suggest they have evaluated this topic.<sup>11,79-81</sup>

Findings from this review suggest the topic of pain among opioid addiction has gained

limited research exposure. Among the 3527 unique articles screened for inclusion, few studies (n=14) evaluated the prognostic impact of pain on physical, psychological, and social outcomes. In addition, the studies evaluating this topic suffered from a high risk of bias. The considerable methodological quality issues among the 14 included studies are presented in the individual risk of bias assessments (Tables S1-S3) and the GRADE evidence profiles (Table S5). The strength of the evidence generated by the three meta-analyses determining the impact of pain on illicit opioid use, illicit non-opioid substance use, and the presence of psychiatric comorbidity was downgraded to low, and very low. Many of the studies (k=5) were unable to demonstrate a dose-response relationship between pain severity and treatment response.<sup>14-16,74,75</sup> The evidence was downgraded due to a serious lack of reporting on important methodological study design features such as sample size calculations or power estimation,<sup>13-15,55,71,74,75</sup> blinding the outcome assessment,<sup>12-15,55,71,73-75</sup> as well as the management of missing data.<sup>13-15,55,71,73-75</sup>

Among the studies reporting an association between pain and treatment response outcomes such as illicit substance use behaviour (opioid and non-opioid),<sup>16,55,75</sup> poor physical health,<sup>12-16,55</sup> and psychiatric comorbidity,<sup>12,14,15,55,71</sup> a number of studies base their conclusions on relatively imprecise and unadjusted treatment effects. This is concerning since the majority of evidence stems from small sampled cross-sectional investigations. The experience of pain can be confounded by many variables including age, presence of other physical comorbidities, the use of adjunct pain therapeutics (e.g. gabapentin), as well as the duration on OST. Due to the hyperalgesic effects of some long-acting opioids, patients on OST may experience higher rates of pain.<sup>82</sup> Some of the studies included in

this review neither discuss these issues, nor adjust for important covariates.<sup>12,13,15,55,71,74</sup> In fact, many studies only adjust for variables they find significant in univariate analysis. At times this may be an inappropriate method since certain variables, while weak in a univariate analysis, may hold an important effect due to biological or other relevance to the outcome such as age or sex. Thus, variables of clinical significance known to impact treatment response such as age, sex, OST dose (mg/day), and duration on OST should always be considered in the analyses.

The definition and measurement of pain across studies requires further consideration. Half of the included studies use the BPI as a measure of pain, stating the BPI is a validated tool to assess the presence of pain. This is troubling since measurement tools are only validated in the population the tools was created and tested within<sup>83</sup> and to our knowledge this tool has never validated in an opioid addiction patient population. To state the psychometric properties such as internal consistency or test-retest reliability of a tool will be the same in a different population than the those the tool was developed in would be inaccurate. The properties of a reliable measurement tool rest in its ability to capture variance between patients, thus it becomes more difficult to distinguish between individuals of more homogenous populations.<sup>83</sup> Tools such as the BPI were originally generated and validated within a population of cancer and rheumatoid arthritis patients.<sup>84</sup> Although since then the BPI has been widely used in other populations with pain, to our knowledge no proper reliability assessment has been performed in patients with opioid addiction. Thus, the ability of the BPI to properly capture pain in OST patients remains questionable and requires formal validation in this population.

Assessment of the overall findings using [Table 6.5.10](#) emphasizes the lack of conclusive evidence demonstrating the impact of pain on therapeutic response. For instance, a number of studies suggest pain has no impact on treatment prognosis for patients on buprenorphine or combination buprenorphine/naloxone, however a number of outcomes were not evaluated for this intervention. Among patients on methadone –the intervention with the largest body of evidence— pain was found to increase the risk for adverse physical, psychiatric, as well as personal and social functioning. Though there is not enough evidence in this review to establish whether pain increases patients’ propensity to abuse opioids and other illicit substances. The meta-analysis assessing the impact of pain on non-opioid substance use (e.g. cocaine, benzodiazepine) suggests participants with pain have lower odds of abusing non-opioid substances. However, we will refrain from making firm conclusion based on this analysis since it relies on the findings from two studies,<sup>12,75</sup> which represent a fraction of the available evidence assessing this outcome.<sup>12,14,55,71,72,75</sup> The case is similar for opioid relapse, among the eight<sup>12-14,16,55,71,75,77</sup> studies assess opioid relapse using different definitions and measurements of opioid use (e.g. number of positive opioid urine screens, time until first opioid relapse), two studies are included in the meta-analysis, both of which suggest protective effects. Two studies precluded from the meta-analysis due to measurement variability actually report a risk association between the presence of pain and opioid use.<sup>16,55</sup> Evaluating the differences between the studies reporting a risk effect and those reporting a protective effect of pain on opioid use behaviour suggest the conservative definitions of opioid consumption using a binary categorization of opioid use based on one positive UDS will show a “protective”

association between pain and opioid consumption.<sup>13,16</sup> For studies evaluating opioid use behaviour as a continuous measure such as the mean number of positive opioid urine screens or the number of days of opioid use over the last month, the presence of pain is association with a “risk” association between pain and consumption.<sup>16,55</sup> Among the same group of participants, different classifications of opioid use behaviour can results in differences in the observed effects of pain.<sup>16</sup> Similar findings are noted among studies evaluating illicit non-opioid substance use, where again the evaluation of substance use behaviour as a continuous outcome such as the number of days of illicit substance use or the mean percentage of positive UDS suggests pain is a risk factor for increase illicit substance consumption.<sup>55,75</sup> Again, the evaluation of illicit substance consumption using a binary categorization of illicit substance use based on one positive UDS showed a “protective” association between pain and illicit substance use.<sup>72</sup> The fragility of these findings highlights the importance of an a priori selection for defining and measuring substance use outcomes (opioid or non-opioid). These results also emphasize the high susceptibility for selective reporting among studies evaluation pain and opioid addiction.

In absence of establishing the most effective therapy for managing opioid addiction patients with comorbid CNCP, it may be worthwhile to consider evidence assessing OAT in the general pain population. Bearing in mind patients can experience hyperalgesic effects from treatments such as methadone,<sup>85,86</sup> other OATs may deliver a more therapeutic effects within the pain subpopulation of addiction patients. For instance, recent evidence suggests patients converting from high-dose full opioid agonists (200–1,370 mg of morphine equivalents) to buprenorphine therapy for more than 60 days

exhibit significant improvements in pain severity and quality of life.<sup>87,88</sup> It is likely the unique pharmacologic properties of therapies like buprenorphine (being a partial mu-agonist) enhance the therapeutic effects of the medication, which may also inflate its effect in the pain subpopulation. In light of these findings, future efforts should focus on evaluating the effectiveness of buprenorphine for the chronic pain subpopulation of opioid addiction patients using a randomized study design.

## 6.7 CONCLUSION

Findings from this review suggests CNCP may increase the risk for poor physical, psychiatric, as well as personal and social functioning for opioid addiction patients on MMT or LAAM. Important outcomes such as resources utilization (e.g. hospitalization), intervention acceptance, and personal/social functioning are understudied. Additionally, we lack evidence on the majority of outcomes for the single formula buprenorphine and combination buprenorphine/naloxone treatments. We caution the interpretation of evidence from the meta-analyses since these results preclude a substantial portion of the evidence and are based on studies suffering from a high risk of bias. Qualitative synthesis of the findings suggests major methodological differences in the design and measurement of both pain and treatment response outcomes are likely impacting the observed effect estimates. Does pain really play an important role in mediating the effects of OST? Are patients with pain responding differently? Should patients with pain be managed differently? These questions have yet to be definitively answered. Further research is needed to confirm the association between pain and OST patient important outcomes before making any conclusions as to which treatment is superior for the pain subpopulation. We recommend future studies work to establish a larger sample with a demonstrated dose-response relationship between pain and treatment response. Current guideline neither address nor make any formal recommendations for managing patients with comorbid pain.

## **6.8 ACKNOWLEDGMENTS, FUNDING, AND AUTHOR CONTRIBUTIONS**

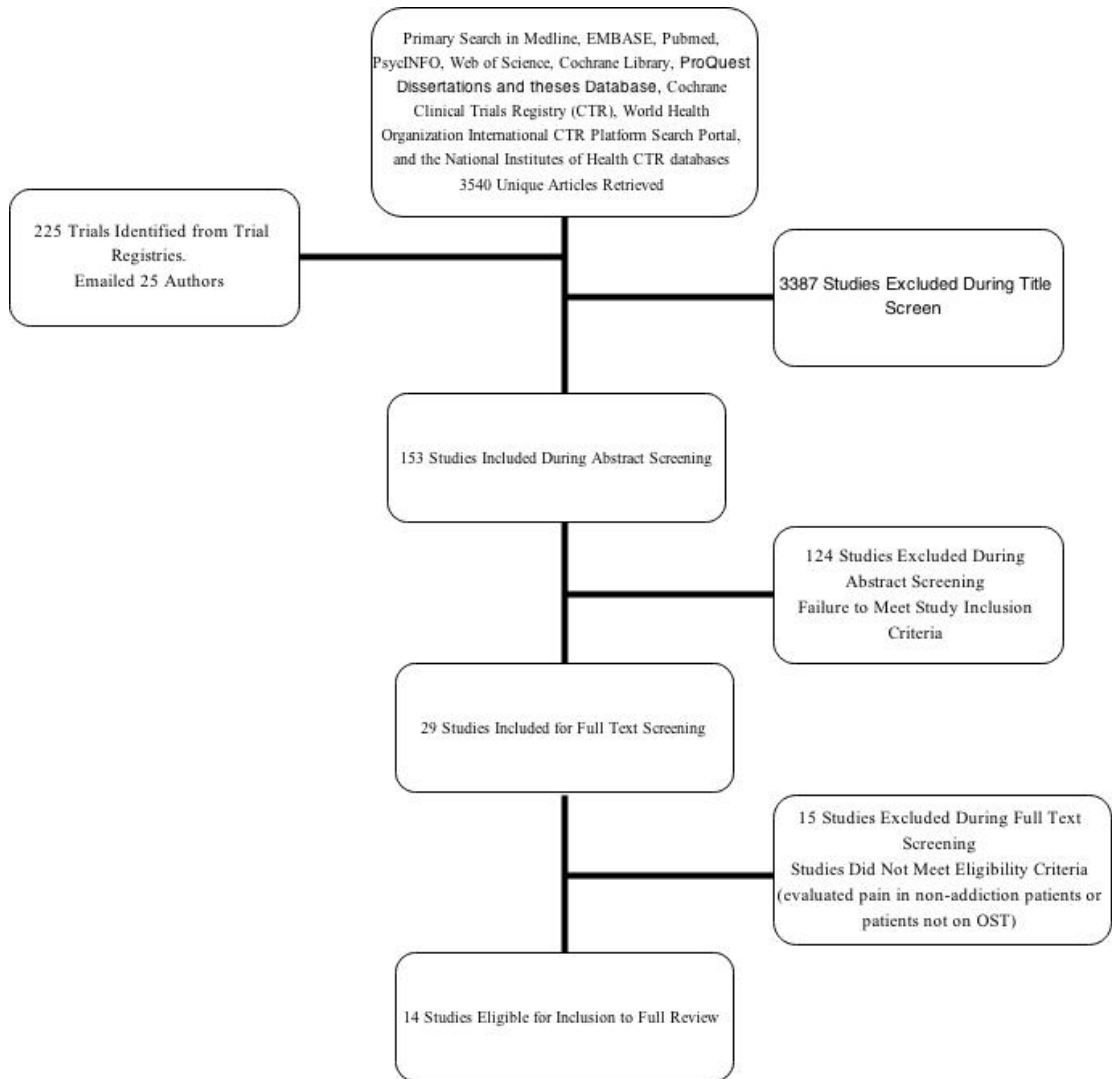
The study is supported by the Peter Boris Centre for Addictions Research and the CIHR Drug Safety and Effectiveness Network (DSEN) grant (grant number: 126639). The funders had no role in study design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript. This project would not have been possible without the great collaboration cemented between GENOA and the CATC network of clinical sites. We would also like to thank the funding agencies supporting individual researchers. Brittany B. Dennis and Monica Bawor are supported by the Intersections of Mental Health Perspectives in Addictions Research Training (IMPART) research fellowship funded through CIHR and British Columbia Center of Excellence for Women's Health. Brittany B. Dennis is also supported by the David L. Sackett Scholarship. Dr. Zainab Samaan, Brittany B. Dennis and Lehana Thabane conceived the research question and led the development of the study. Brittany B. Dennis, Monica Bawor, Leen Najji, Carol Chan, and Jaymie Varenbut were responsible for screening the titles, abstracts, and full-text articles. Brittany B. Dennis, Monica Bawor, Leen Najji, Carol Chan, and Jaymie Varenbut were responsible for full-text extraction. All authors contributed to the development of the research protocol, which is published in the journal *Systematic Reviews*. Brittany B. Dennis and Lehana Thabane are responsible for statistical analyses performed in this investigation.

Ph.D. Thesis – BB. Dennis; McMaster University – Health Research Methodology

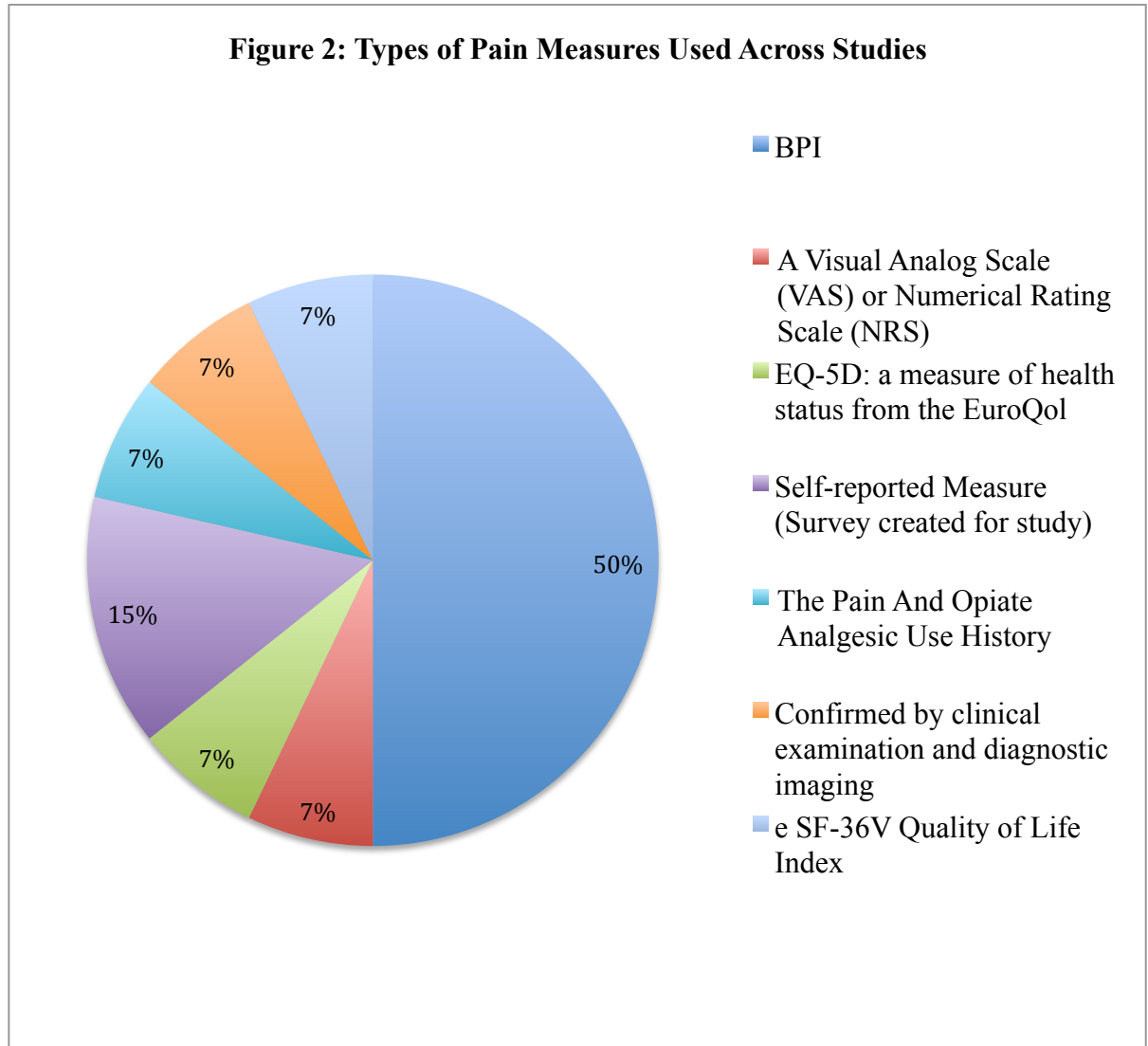
All authors (BBD, MB, LN, CC, JV, JP, MV, JD, GP, AW, DD, LT, ZS, CP, DCM) contributed equally to the interpretation of the data and writing the manuscript.

## 6.9 FIGURES AND TABLES

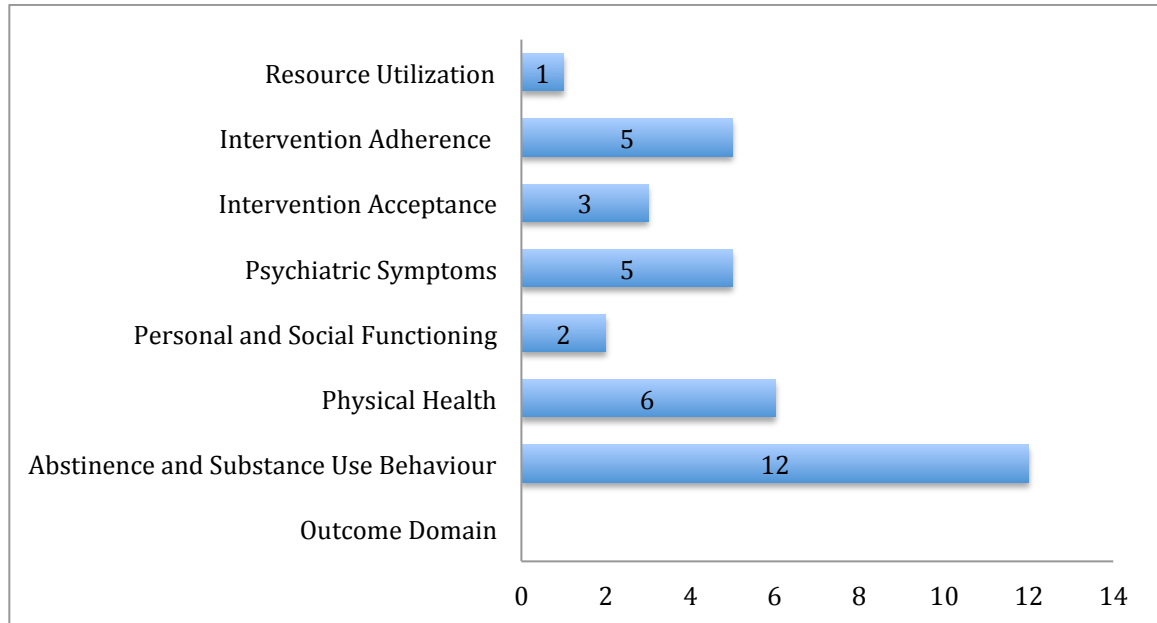
Figure 6.5.1a Flow Diagram of Study Selection Process



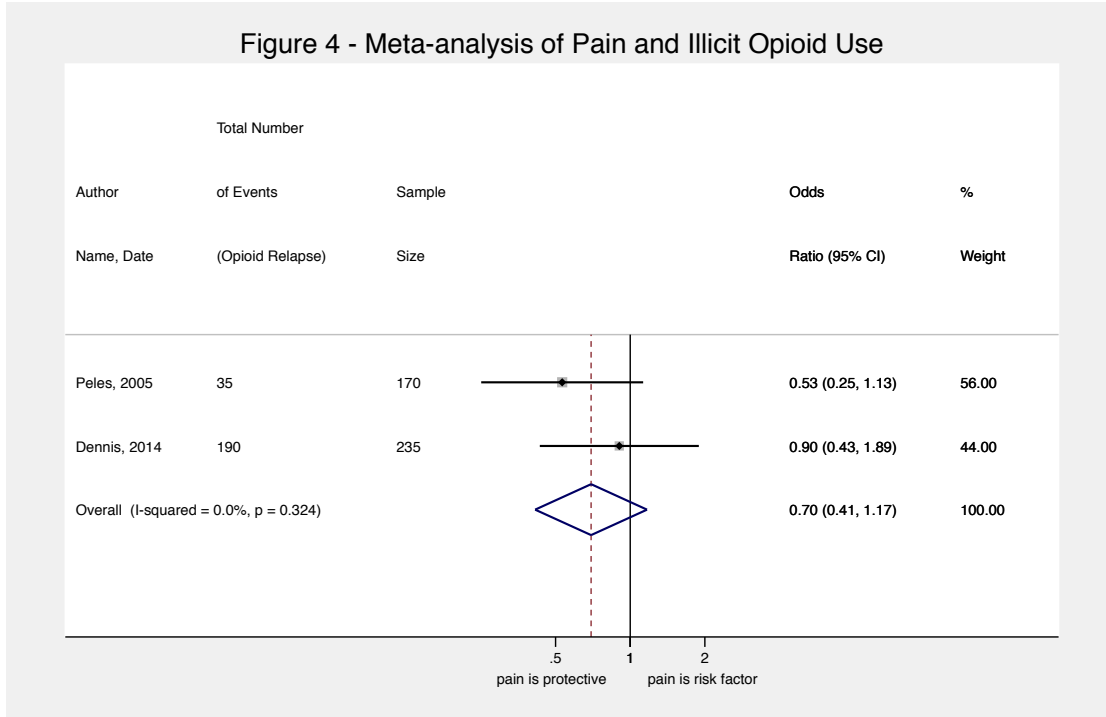
**Figure 6.5.1b Types of Pain Measures Used Across Studies**



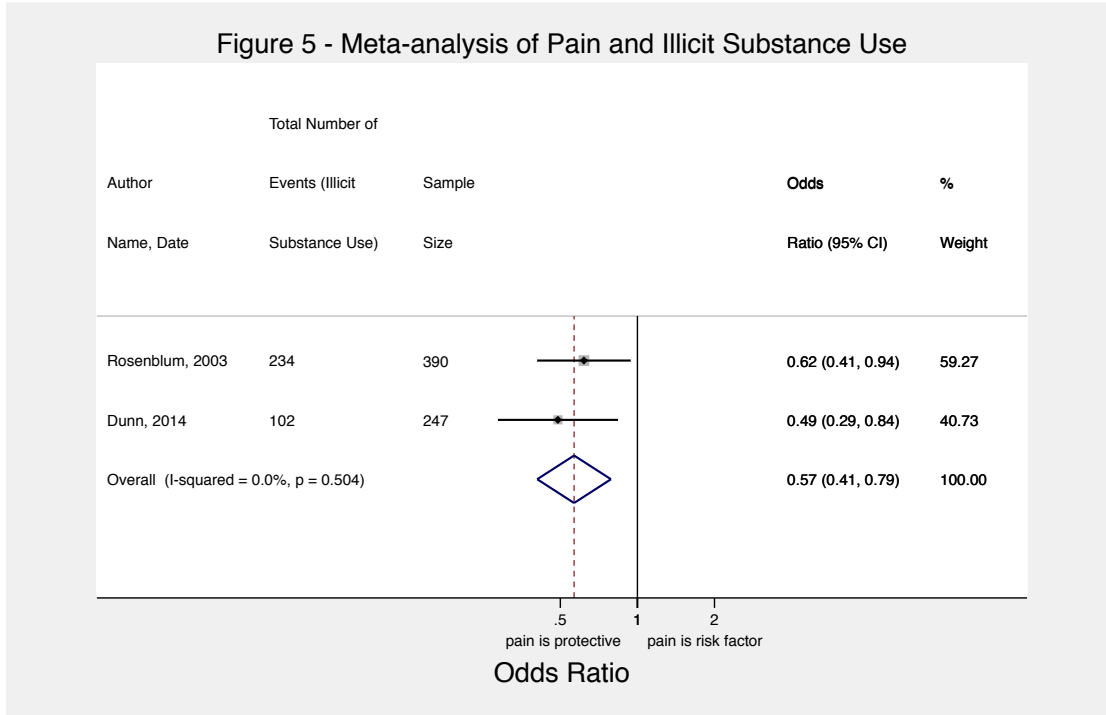
**Figure 6.5.1c Outcomes Evaluated Across Studies**



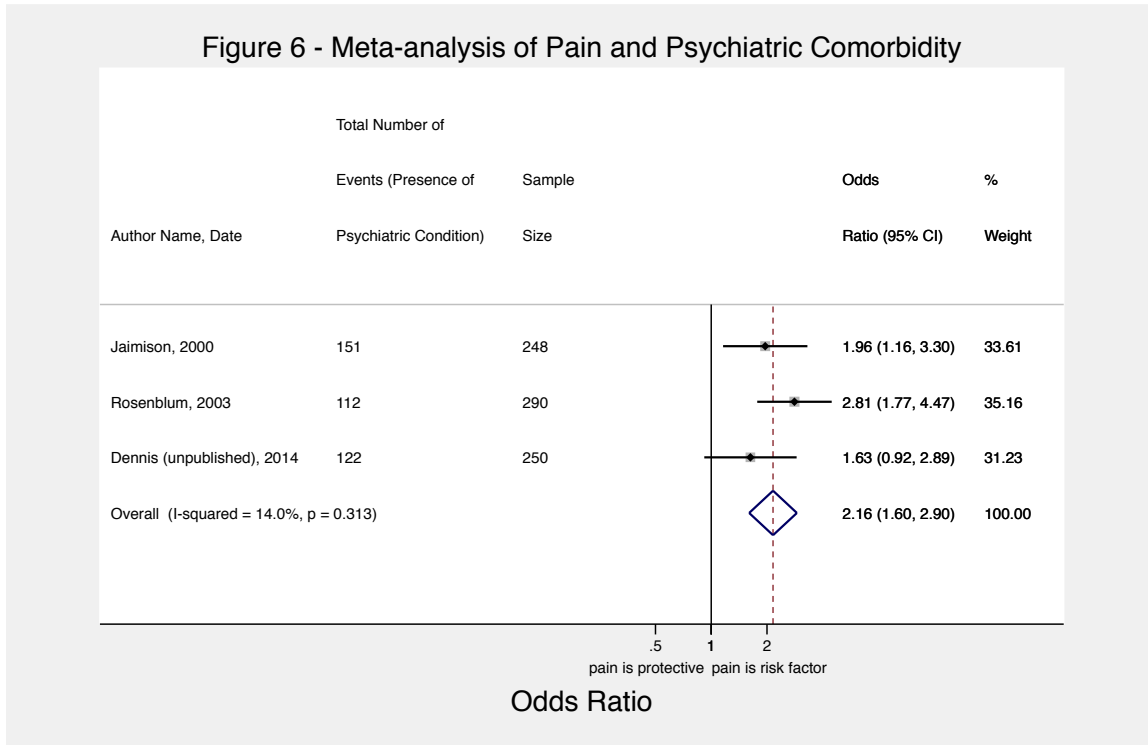
**Figure 6.5.3.1 Meta-analysis of Pain and Illicit Opioid Use**



**Figure 6.5.3.2 Meta-analysis of Pain and Illicit Substance Use**



**Figure 6.5.9: Meta-analysis of Pain and Psychiatric Comorbidity**



**Figure 6.5.1 Description of Study Design Characteristics**

Author Last Name	Year of Publication	Number of Participants	Study Design	Intervention(s) Evaluated	How was chronic pain measured?	How was chronic pain defined
Peles	2005	170	Cross-sectional	High-dose Methadone ( $\geq 60$ mg/day)	BPI	Current pain that lasted for at least 6 months
Dhingra	2012	489	Cross-sectional	High-dose Methadone ( $\geq 60$ mg/day)	BPI	“Clinically significant pain” was defined by an average pain intensity during the past week of $>5$ or an average pain interference score during the past week of $>5$ .
Barry	2009	150	Cross-sectional	High-dose Methadone ( $\geq 60$ mg/day)	BPI	Respondents’ answers to BPI items were used to classify them into one of three pain groups: a) “chronic severe pain” (i.e., pain lasting at least 6 months with moderate to severe pain intensity or significant pain interference, respondents who had pain lasting at least 6 months and who scored 5 or higher on the item pertaining to the worst pain intensity in the last 7 days or on any of the items relating to pain interference in the last 7 days were considered to exhibit chronic severe pain ; b) “some pain” (i.e., pain reported in past week but not CSP); and c) “no pain” (i.e., no pain reported in the past week and no CSP).
Bounes	2013	151	Cohort Study (Prospective or Retrospective)	Low-dose Methadone ( $<60$ mg/day), Low-dose Buprenorphine ( $<16$ mg/day)	A Visual Analog Scale (VAS) or Numerical Rating Scale (NRS) were used to assess and quantify the intensity of acute pain at the time of admission, after pain management, and just before hospital discharge.	Acute pain scores rated from 0 to 10 were obtained indiscriminately from one or the other measurement tool. Acute pain exposure was defined as a pain score greater than 0 at the time of admission on any of the rating scales.
Chakrabarti	2010	69	Cross-sectional	High-dose Suboxone® (buprenorphine $\geq 16$ mg/day + naloxone)	EQ-5D: a measure of health status from the EuroQol	Degree of pain 1 week before induction, measured as pain or discomfort experienced “today” and coded as 0 = no pain, 1 = some pain, or 2 = extreme pain

				mg/day + naloxone)	EuroQol	coded as 0 = no pain, 1 = some pain, or 2 = extreme pain
Dennis	2014	235	Cross-sectional	High-dose Methadone ( $\geq 60$ mg/day)	Self-report	Participants were categorized as having chronic and/or comorbid pain if they indicated they were currently experiencing or have been diagnosed with chronic pain
Dreifuss	2013	360	Cross-sectional	High-dose Suboxone® (buprenorphine $\geq 16$ mg/day + naloxone)	The Pain And Opiate Analgesic Use History	Not described
Dunn	2014	227	Cross-sectional	High-dose Methadone ( $\geq 60$ mg/day)	BPI	Chronic pain was defined as endorsing question 1 of the BPI, which asked, “Have you had pain other than everyday kinds of pain today?”
Fox	2012	82	Cohort Study (Prospective or Retrospective)	High-dose Buprenorphine ( $\geq 16$ mg/day), Low-dose Buprenorphine ( $< 16$ mg/day)	BPI	The Brief Pain Inventory (BPI) asked: “Please rate your pain during the last week by selecting the one number that best describes your pain on the average.” Participants were given a visual analog scale from 0 to 10, with 0 labeled as “no pain” and 10 as “pain as bad as you can imagine.” Similar to prior studies, participants reporting pain scores of $\geq 5$ at the initial interview were considered to have “baseline pain”; those reporting pain scores of $\geq 5$ at all follow-up visits were considered to have “persistent pain”
Jaimison	2000	248	Cross-sectional	High-dose Methadone ( $\geq 60$ mg/day), Low-dose Methadone ( $< 60$ mg/day)	Self-reported Measure (Survey created for study)	Not described
Neumann	2013	54	Randomized Controlled Trial	Low-dose Methadone ( $< 60$ mg/day), Low-dose Suboxone® (buprenorphine $< 16$ mg/day + naloxone)	Confirmed by clinical examination and diagnostic imaging	The diagnosis of a chronic pain condition originating from the spine or large joints was confirmed by clinical examination and the use of diagnostic imaging (e.g., radiographs, computed tomography scan, magnetic resonance imaging)
Potter	2015	252	Cohort Study (Prospective or Retrospective)	Low-dose Suboxone® (buprenorphine $< 16$ mg/day + naloxone)	BPI	Not described
Rosenblum	2003	390	Cross-sectional	High-dose Methadone ( $\geq 60$ mg/day)	BPI	To operationally define a subpopulation of patients with chronic pain that was relatively likely to be clinically significant, an index of “chronic severe pain” was defined as a score of 5 or higher on the BPI item “worst pain in the past week” or of 5 or higher on the BPI pain interference scale, and pain

						duration for at least 6 months.
Trafton	2004	251	Cross-sectional	High-dose Methadone ( $\geq 60$ mg/day), Low-dose Methadone ( $< 60$ mg/day), High-dose Levoacetylmethadol (LAAM) ( $\geq 85$ mg/day), Low Dose Levomethadyl Acetate Hydrochloride (LAAM) ( $< 85$ mg/day)	SF-36V Quality of Life Index	Reported pain levels were taken from answers to the SF-36V question “How much body pain have you experienced in the last 4 weeks?” Patients answered either “none” (n = 45), “very mild” (n = 28), “mild” (n = 48), “moderate” (n = 60), “severe” (n = 56) or “very severe” (n = 13). For analyses patients were split into those reporting none to mild pain (no-pain group, n = 121) and those reporting moderate to very severe pain (pain group, n = 129).

**Table 6.5.3.1 Summary of Findings for Illicit Opioid Use Outcomes**

Author Last Name	Was illicit opioid abuse an outcome of this study?	Was illicit opioid use behaviour the primary outcome of the study?	How was illicit opioid abuse measured in this study?	How was illicit opioid use defined in this study?	What were the findings for each measurement (reported per chronic pain status)	What statistical analysis was used?	Proportion of Opioid Use Outcomes Showing Pain to Impact illicit Opioid Use Behaviour	Study Findings: Did patients characterized as having pain also have significantly higher rates of illicit opioid use?
Peles	Yes	No	Urine toxicology screening	Participants were categorized as using opioids if $\geq 1$ urine test in the month preceding the survey was positive.	Chronic Pain 15 (16%) positive, Non-chronic pain 20 (26.3%)	chi-square	0	No
Dhingra	Yes	No	Urine toxicology screening, Self-report	A positive urine toxicology screen or indication by self-report as assessed by the ASI past 30 day drug use history.	In univariate analyses, neither UDS nor self-reported drug use on the ASI was statistically associated with clinically significant pain. (report p-values)	t-test, chi-square	0	No
Barry	Yes	No	Self-report	Participants reported any use in the past week, this was then analyzed as a binary variable.	The pain groups reported comparable levels of psychoactive substance use, illegal drug use and non-medical use of prescription drug in the past week. No specific percentages are reported per group.	ANOVA	0	No
Chakrabarti	Yes	No	Urine toxicology screening	Participants showing a single positive opioid urine screen were found to be a	Opioid-positive urine (%) reported by Degree of pain Week 4 Week 8	chi-square	0	No

				positive for illicit opioid use behaviour, confirmed by urinalysis.	<p>Week 12</p> <p>Extreme Pain Patients: 22.2% (2/9) 12.5% (1/8) 37.5% (3/8)</p> <p>Some Pain Patients: 31.3% (10/32) 26.7% (8/30) 37.9% (11/29)</p> <p>No Pain: 21.4% (3/14) 20% (2/10) 66.7% (6/9)</p>			
Dennis	Yes	Yes	Urine toxicology screening	Continued opioid abuse (COA) was determined by calculating the percentage of positive opioid urine screens provided by participants (number of positive opioid urine screens/total number of opioid urine screens). High COA percentage is indicative of a high number of positive opioid urine screens or, alternatively, a higher rate of illicit opioid consumption.	<p>Mean Percentage of Positive Opioid Urine Screens Among Pain Patients: 23.99 (SD 27.14)</p> <p>Mean Percentage of Positive Opioid Urine Screens Among Non-Pain Patients: 15.82 (SD 20.11)</p>	Univariate analysis using only COA outcome as the predictor of comorbid pain in a logistic regression model.	1/1	Yes
Dreifuss	Yes	Yes	Urine toxicology screening, Self-report, Addiction severity tool score	The Substance Use Report, corroborated by weekly urine drug screens, was administered weekly during treatment and every two weeks during follow-up, and was used as the primary measure to determine “successful	<p>Successful with chronic pain: 79 (44.6%)</p> <p>Failure with Chronic Pain: 70 (38.3%)</p>	chi-square	0	No

Dunn	Yes	Yes	Urine toxicology screening	outcome.” The mean percent of urine samples provided by each participant that tested positive for opioids, cocaine, or benzodiazepines were evaluated.	Chronic Pain: 9, No Chronic Pain: 11	Independent group t-tests were used to compare continuous variables	0	No
Fox	Yes	No	Self-report	Self-reported opioid use was obtained from the substance use survey administered at baseline and follow-up, which inquired as to substance use in the 30 days prior to baseline (heroin, methadone, opioid analgesics, cocaine, alcohol, sedatives, hypnotics, or tranquilizers) and follow-ups. These questions were adapted from the ASI.	Not reported per pain status. However, they report that any opioid use decreased from 89% at baseline to 40% at 1 month, 33% at 3 months, and 26% at 6 months. Similar patterns were observed in those with and without baseline or persistent pain, and showed no significant association between any opioid use and baseline pain (AOR=1.06, 95% CI: 0.27–4.17, p = 0.93) or persistent pain (AOR=1.20, 95% CI: 0.31–4.63, p = 0.79), after adjusting for HIV status, depressive symptoms, history of IDU, history of incarceration, baseline opioid use, and time since initiating buprenorphine treatment.	Determined whether pain was associated with use of any opioids during the 6-month follow-up period using non-linear mixed effects (NLME) models with self-reported use of any opioids as the dependent variable. The NLME approach accounts for non-independence of repeated measures of opioid use within individuals.	0	0
Neumann	Yes	No	Urine	Report the number	Methadone: 2	Fishers exact test	0	No

			toxicology screening	of patients (%) who have an opioid positive urine screen at 24 week follow-up	(15.4%), Buprenorphine: 5 (38.5%) p>0.05  Odds Ratio: 0.280 95% CI: 0.042–1.878, p= 0.371			
Potter	Yes	No	Urine toxicology screening, Addiction severity tool score	Not described well or reported by pain status.	Not reported by pain status	n/a	n/a	n/a
Rosenblum	Yes	No	Self-report	A checklist was used to record drugs, including alcohol, that were used during the patient’s last week of active use.	Drugs used in past 3 months (%) P=0.05  None (reference for MMTP): CP 156 (42.9%) OR:1.00 1 : CP:123 (27.6%) OR: 0.51 95%CI (0.31-0.84) 2: CP : 62 (38.7%) OR: 0.84 (0.46-1.53) ≥3: CP 49 (36.7%) 0.77 (0.40-1.50)	Mantel-Haenszel was used for ordinal variables with 3 or more categories	0	No
Trafton	Yes	Yes	Addiction severity tool score	Number of days of opioid use over last 30, as well as self-reported number of days of opioid use over lifetime.	Opiates GP:1.6 days, 1.9 years; NP: 0.8 days, 0.9 years, P: 2.3 days, 2.9 years 0.03/0.005	The Kruskal–Wallis test was used to determine if variables significantly differed across pain severity ratings, followed by multiple t-tests to determine which levels of reported pain differed from the group reporting “none”.	2/3	Yes

**Table 6.5.8 Summary of Findings for Physical Health Outcome(s)**

<b>Author Last Name</b>	<b>Intervention(s) Evaluated</b>	<b>Physical Health Outcome</b>	<b>Measurement of Physical Health Outcome(s)</b>	<b>Findings</b>
Peles	High-dose Methadone ( $\geq 60$ mg/day)	The study evaluated the clinical characteristics of patients reporting pain.	All chronic illnesses were diagnosed by internal medicine physician and included 12 categories: Heart [Angina with/without MI]; Endocrinology, metabolic; Cancer; Asthma; Neurology; Digestive system; Muscles/movement; Eyes, ears; Urine system; Coagulation; Gynecological; and Immune system. Patients reporting one or more of the aforementioned illnesses were defined as chronically ill.	Participants with chronic pain were more often diagnosed with physical comorbidities relating to muscle movement, digestive, urinary as well as problems with eyes and ear function.
Dhingra	High-dose Methadone ( $\geq 60$ mg/day)	The primary outcome of this study was clinically significant pain, used as the dependent variable in a multi-variable logistic regression model. The study evaluated the physical health symptoms associated with chronic pain.	The study measured physical health using self-report for physical comorbidities and the patients HRQL scores	Clinically significant pain was associated with higher number of comorbid, medical conditions ( $p < 0.001$ ) and poorer physical HRQL scores ( $p < 0.001$ ).
Dennis	High-dose Methadone ( $\geq 60$ mg/day)	The study evaluated the clinical and biological characteristics of MMT patients reporting pain. Using a univariate analysis to guide the variable selection, the authors built a multivariable logistic regression model using comorbid pain as the dependent variable. Physical health predictors included in the model were: Inflammatory markers (IL-6, IL-8, IL-1ra, TNF-alpha, IL-10, IL-1B, and CCL2), and the participants infectious disease status (presence of HIV or hepatitis).	Infectious disease status was measured using self-report, while inflammatory markers were measured using The iMDx™ Prep assays	Infectious disease status (HIV/Hepatitis) was not associated with the presence of chronic pain. Of all inflammatory markers tested, IFN-Gamma was shown to be significantly elevated in participants reporting pain (OR): 2.02; 95% confidence interval [CI]: 1.17, 3.50; $P=0.01$ )
Jaimison	High-dose Methadone ( $\geq 60$ )	Evaluated physical health differences in patients reporting pain.	Self-report	Found significant differences in the major health problems reported

	mg/day), Low-dose Methadone (<60 mg/day)			between patients with pain (34.9%) and without pain (9.4%), $p < 0.001$ . Also found major differences between the participants rating their health care as adequate, whereby 75.5% of patients with pain rate their health care as adequate and 94.8% of patients without pain rate their health care as adequate ( $p < 0.001$ ). Among patients with pain, 36.7% report asthma, 20.4% report angina/chest pain, 11.1% report bleeding problems, 6.6% report a past heart attack, 28.9% report some other unlisted condition, in comparison to the patients without pain who report 16.7%, 7.4%, 3.1%, 1.0%, and 9.4% respectively (all comparisons $p < 0.05$ ).
Neumann	Low-dose Methadone (<60 mg/day), Low-dose Suboxone® (buprenorphine < 16 mg/day + naloxone)	Evaluated physical health using reported side effects and percent-change in pain from baseline	Self-report	The number of patients reporting side effects did not vary significantly between patients on methadone ( $n=9$ ) and buprenorphine ( $n=8$ ); (OR:1.125 95%CI:0.209–6.04, $P=1.000$ ). The percent change of pain from baseline also did not significantly differ between patients on methadone (mean percent change; SD, 88.6; 24.5), and buprenorphine 87.4; 33.4), $p=0.918$ . The percent change of functioning from baseline also did not vary significantly between methadone (113.8; 62.5 SD) and buprenorphine groups (121.9; 63.9), $p=0.787$ .
Rosenblum	High-dose Methadone ( $\geq 60$ mg/day)	The study evaluated the prevalence of comorbid chronic illnesses by pain status, as well as the reported drug cravings.	Self-report	Bivariate analyses were used to compare the prevalence of pain, whereby there was a significant association between reporting chronic illness among patients with chronic severe pain. Among patients with chronic severe pain, 122 (20.5%) report having no concurrent illness (OR: 1.00), whereby 263 (43.7%)

				reporting having a chronic illness (OR 3.02; 95%CI 1.82,4.98). Additionally, there was a higher number of participants (N=123, 43.1%) with chronic severe pain reporting high-levels of drug cravings (OR: 1.67; 95%CI 0.99, 2.83).
Trafton	High-dose Methadone ( $\geq 60$ mg/day), Low-dose Methadone ( $< 60$ mg/day), High-dose Levoacetylmethadol (LAAM) ( $\geq 85$ mg/day), Low Dose Levomethadyl Acetate Hydrochloride (LAAM) ( $< 85$ mg/day)	The study evaluated 1) the number of days of medical problems in the last 30 days, 2) physical functioning as assessed according to SF-36V, and 3) general health.	Self-report according to SF-36V	The study found significant differences across each different physical health outcome evaluated. They report the presence of pain to be associated with an increase in the number of days of reported medical problems (Pain:22.1, No Pain 7.5, $p=0.001$ ), the % of patients with good physical functioning (Pain 55%, No Pain:89%, $p<0.001$ ), and the % with good general physical health (pain: 50%, no pain: 70%, $p<0.001$ ).
Fox	High-dose Buprenorphine ( $\geq 16$ mg/day), Low-dose Buprenorphine ( $< 16$ mg/day)	The study evaluated baseline differences between patients with and without pain starting an office-based buprenorphine treatment program	Self-report	Patients with pain reported higher rates of HIV

**Table 6.5.10 Summary of Findings Across Opioid Substitution Therapies**

<b>Intervention</b>	<b>Outcome</b>	<b>Number of Studies Evaluating Outcome</b>	<b>Number of Studies Reporting a Risk Association with Pain</b>	<b>Number of Studies Reporting a Protective Association with Pain</b>	<b>Final Analysis</b>
Methadone	Abstinence and Illicit Substance Use: Opioids	8 <sup>12,14,16,55,71,75,77</sup>	2 <sup>16,55</sup>	0	Not Enough Evidence to Suggest Chronic Pain Effects Treatment
	Abstinence and Illicit Substance Use: Non-opioids	6 <sup>12,14,55,71,72,75</sup>	2 <sup>55,75</sup>	2 <sup>72,75</sup>	Not Enough Evidence to Suggest Chronic Pain Effects Treatment
	Physical Health	7 <sup>12,16,55,77</sup>	5 <sup>12,16,55</sup>	0	Pain increases risk for poor physical functioning
	Psychiatric Health	5 <sup>12,14,15,55,71</sup>	5 <sup>12,14,15,55,71</sup>	0	Pain increases risk for poor psychiatric functioning
	Personal and Social Functioning	2 <sup>15,55</sup>	2 <sup>15,55</sup>	0	Pain increases risk for poor personal and social functioning outcomes
	Intervention Adherence	3 <sup>12,72,77</sup>	1 <sup>72</sup>	0	No Effect
	Intervention Acceptance	3 <sup>15,72,77</sup>	1 <sup>15</sup>	0	No Effect
	Resource Utilization	1 <sup>55</sup>	1 <sup>55</sup>	0	Pain increases resource utilization among patients on MMT
Buprenorphine/Naloxone	Abstinence and Illicit Substance Use: Opioids	4 <sup>73,74,77,78</sup>	0	0	No Effect
	Abstinence and Illicit Substance Use: Non-opioids	1 <sup>73</sup>	0	0	No Effect
	Physical Health	1 <sup>77</sup>	0	0	No Effect
	Psychiatric Health	0	0	0	Not Evaluated
	Personal and Social Functioning	0	0	0	Not Evaluated
	Intervention Adherence	2 <sup>77,78</sup>	0	0	No Effect
	Intervention Acceptance	1 <sup>77</sup>	0	0	No Effect
	Resource Utilization	0	0	0	Not Evaluated
LAAM	Abstinence and Illicit Substance Use: Opioids	1 <sup>55</sup>	1 <sup>55</sup>	0	Pain increases risk for opioid abuse among patients on LAAM
	Abstinence and Illicit Substance Use: Non-opioids	1 <sup>55</sup>	0	0	No Effect

	Use: Non-opioids				
	Physical Health	0	0	0	Not Evaluated
	Psychiatric Health	1 <sup>55</sup>	1 <sup>55</sup>	0	Pain increases risk for poor psychiatric functioning
	Personal and Social Functioning	1 <sup>55</sup>	1 <sup>55</sup>	0	Pain increases risk for poor personal and social functioning outcomes
	Intervention Adherence	0	0	0	Not Evaluated
	Intervention Acceptance	1 <sup>55</sup>	1 <sup>55</sup>	0	Pain increases risk for poor personal and social functioning outcomes
	Resource Utilization	1 <sup>55</sup>	1 <sup>55</sup>	0	Pain increases resource utilization among patients on LAAM
Buprenorphine	Abstinence and Illicit Substance Use: Opioids	2 <sup>72,76</sup>	0	0	Pain has no effect on opioid use behaviour
	Abstinence and Illicit Substance Use: Non-opioids	1 <sup>72</sup>	n/a	n/a	n/a
	Physical Health	1 <sup>76</sup>	0	0	Not Enough Evidence to Suggest Chronic Pain Impacts Treatment (Evaluated baseline physical health)
	Psychiatric Health	1 <sup>76</sup>	0	0	Not Evaluated (Evaluated baseline psychiatric health)
	Personal and Social Functioning	0	0	0	Not Evaluated
	Intervention Adherence	2 <sup>72,76</sup>	0	0	No Effect
	Intervention Acceptance	1 <sup>72</sup>	0	0	No Effect
	Resource Utilization	0	0	0	Not Evaluated

**Table 6.5.11 Translation of Evidence in the Opioid Maintenance Treatment Guidelines**

Title of Guideline	Intervention Assessed	Does the guideline provide suggestions for managing patients with comorbid pain?	Suggestions	Are these suggestions based on evidence?	Evidence cited	Are any recommendations made for managing pain in the opioid maintenance treatment setting?	Discussion of the risk factors associated with pain for this OST
Clinical Practice Guideline for Management of Substance Use Disorders (SUD) <sup>79</sup>	Methadone, Buprenorphine/Naltrexone	Yes	Evaluate opioid dependent patients for severe acute or chronic physical pain that may require appropriate short-acting opioid agonist medication in addition to the medication needed to prevent opioid withdrawal symptoms	No	/	No graded recommendations made	No
Buprenorphine/Naloxone Treatment for Opioid Dependence Clinical Practice Guidelines <sup>80</sup>	Buprenorphine/Naloxone	Yes	When managing patients with comorbid chronic non-cancer pain, (1) do not treat them with chronic opioid analgesic therapy for pain, non-opioid alternatives should be aggressively optimized, (2) referral to a reputable multidisciplinary chronic pain clinic regarding pharmacologic and non-pharmacologic non-opioid alternatives is recommended for patients with pain, and (3) if the decision to initiate opioid analgesics has been made, the patient should be monitored by or advice should be sought from a physician experienced in addiction medicine.	No	/	No graded recommendations made	No
Methadone Maintenance Treatment Program Standards and Clinical Guidelines <sup>11</sup>	Methadone Maintenance Treatment	Yes	Suggest the management of mild to moderate pain in conditions such as fibromyalgia, low back pain with non-opioid treatments. For patients with severe chronic pain (nociceptive or neuropathic pain condition that usually requires opioid therapy) they suggest 1) non opioid treatments, 2) split methadone dose, 3) codeine or tramadol, and lastly 4) morphine. Suggest strong communication with community physicians managing patients pain, as well as informing non-methadone physicians to also perform routine urine drug screens.	No	/	No graded recommendations made	No
Methadone and Buprenorphine for the Management of Opioid	Methadone and Buprenorphine	No	No suggestions made	/	/	No graded recommendations made	No

Dependence <sup>81</sup>							
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/ Indicates this information is not applicable

## 6.10 REFERENCES

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## CHAPTER 7

### Study 5

#### **Comparative Effectiveness of Opioid Substitution and Antagonist Therapies for Patients with Opioid Addiction: A Multiple Treatments Comparison and Network Meta-analysis**

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Keywords: opioid substitution therapy, opioid dependence, methadone maintenance treatment, effectiveness, opioid relapse, addiction, naltrexone, buprenorphine

### *Publications*

*The protocol for this study was published.*

Dennis BB, Naji L, Bawor M, et al. The effectiveness of opioid substitution treatments for patients with opioid dependence: a systematic review and multiple treatment comparison protocol. *Systematic reviews*. 2014;3(1):105

The published protocol can be found in appendix iv

This study is currently under review with the *Drug and Alcohol Dependence*.

## 7.1 ABSTRACT

**Context:** Without treatment opioid addiction can incur a substantial increase in mortality and risk for serious comorbidities such as HIV and hepatitis. Opioid substitution and antagonist therapies (OSATs) are front-line treatments for opioid addiction. The emergence of multiple OSTs renders traditional meta-analysis of direct evidence from randomized trials inadequate to provide hierarchical estimates of the best available treatment.

**Objective:** Utilizing systematic review methods, we provide the first multiple treatments comparison and network meta-analysis to combine evidence from all trials examining OSAT with the aim of distinguishing the most effective treatments for opioid addiction.

**Data Sources:** We searched Medline, EMBASE, PubMed, PsycINFO, Web of Science, Cochrane Library, Cochrane Clinical Trials Registry, World Health Organization (WHO) International Clinical Trials Registry Platform Search Portal, and the National Institutes for Health (NIH) Clinical Trials Registry from inception to January 1, 2014.

**Study Selection:** We included randomized controlled trials assessing the effectiveness OSAT for patients with opioid addiction.

**Data Extraction and Synthesis:** We examined differences in patients' response to intervention and combined all direct and indirect evidence using network meta-analysis.

We also provide a qualitative summary of the outcomes measured and defined too variably to be pooled using traditional meta-analysis.

**Main Outcome Measure(s):** The primary outcome was treatment retention. Secondary end-points included illicit substance use behavior, physical and psychiatric health, personal and social functioning, as well as medication adherence and acceptance.

**Results:** We identified 60 trials eligible for inclusion and among those, 28 trials testing 16 interventions in a total of 3342 participants were included in the network meta-analysis assessing treatment retention. In comparison to all other OSATs, heroin consistently ranked highest for increasing the odds of remaining in treatment when compared to high-dose buprenorphine (OR: 6.01; 95% CI: 1.18, 29.79), high-dose IV heroin + methadone (8.16; 1.27, 49.96), high-dose methadone (3.53; 1.28, 10.13), high-dose naltrexone (22.33; 1.80, 325.57), low-dose buprenorphine (5.11; 1.22, 21.93), low-dose methadone (4.22; 1.24, 15.04), low-dose naltrexone implant (37.21; 5.62, 267.46), low-dose oral naltrexone (27.06; 2.44, 321.99), low-dose Suboxone® (12.38; 1.73, 93.60) and placebo (38.55; 6.40, 250.21). High-dose methadone significantly increased treatment retention when compared to low-dose naltrexone (10.54; 2.06, 57.67) and placebo (10.92; 2.36, 52.48). Heroin showed significant benefit when directly compared against methadone for reducing illicit substance use and addiction severity, as well as improving personal/social functioning and general physical health outcomes. Higher doses of medication, even when compared within the same intervention showed benefit across most outcome domains (e.g. substance use, personal/social function), however the majority of direct comparisons showed no difference against methadone.

**Conclusion and Relevance:** Among patients treated with OSATs, those randomized to heroin-assisted treatment heroin or high-dose methadone were most likely to remain in therapy. There was insufficient evidence to confidently rank the remaining treatments, although heroin and high-dose methadone were the only treatments significantly more effective than placebo. Findings also suggest heroin and higher doses of opioid treatments are most effective for improving other outcome domains including abstinence and illicit substance use, physical health, and personal and social functioning. The evidence base suffers from high risk of bias and imprecision.

## 7.2 INTRODUCTION

Opioid addiction is characterized as a problematic pattern of opioid use leading to impaired social and physical functioning.<sup>1</sup> The risk for serious comorbidities such as HIV,<sup>2</sup> hepatitis,<sup>2</sup> and infective endocarditis<sup>3,4</sup> is high among patients with opioid addiction. A large cohort study found a 50-fold increase in death for opioid dependent patients.<sup>5</sup> Within the United States (U.S) alone the costs of opioid addiction are estimated at 55.7 billion US dollars and comprise the financial loss related to employment opportunity, health care, and crime.<sup>6</sup> The trends in opioid use have steadily increased between 2001 and 2011, where one report shows a 13% increase in the prevalence of opioid addiction, 138% increase in opioid related substance use admissions, 47% increase in excess cost per patient (adjusted for inflation), and 48% increase in the cost of treatment.<sup>6</sup> In the absence of an effective treatment strategy, the costs and harms associated with opioid addiction are expected to rise.

Opioid substitution and antagonist therapies (OSATs) are the current front-line treatments for patients with opioid addiction. Opioid substitution therapies (OSTs) aim to reduce the harms associated with illicit drug use under the supervision of medically trained addiction specialists. Physicians prescribe longer acting opioids to reduce cravings and prevent withdrawal symptoms associated with detoxification.<sup>7</sup> To date, methadone is the most commonly used OST<sup>8,9</sup> and is shown to be effective for reducing opioid craving and HIV risk behaviours such as IV needle sharing.<sup>10</sup> Other treatments include Suboxone,<sup>®</sup> a sublingually administered tablet that comprises a 4:1 combination of buprenorphine and

naloxone. Suboxone<sup>®</sup>'s target effects are less potent than full opioid agonists such as methadone, promoting less physical dependence.<sup>11</sup> While not under the umbrella of traditional OSTs, naltrexone and naloxone are competitive opioid receptor antagonists that act on the opioid receptors of the brain to inhibit the euphoric effects of opioids.<sup>12,13</sup> Opioid antagonist therapies (OATs) are increasingly employed as treatments for opioid dependence. More controversial treatments such as heroin have also been elected for inclusion in the cadre of OSTs. Recent trials in the UK, Netherlands, and Canada sought to determine the effectiveness of diacetylmorphine or better-known heroin assisted treatment (HAT), which involves the administration of injectable diacetylmorphine to patients with severe opioid addiction (e.g. with previous methadone treatment failure).<sup>14,15</sup> The rising number of OATs raises the question as to which intervention is most effective for managing opioid addiction. Given the complex nature of opioid addiction treatment there is no “gold standard” measure of treatment effectiveness and therefore many trials evaluate the effect of therapy on multiple outcomes. Important outcomes considered when evaluating addiction treatment prognosis include attrition rates, illicit substance use behavior, presence of medical and psychiatric comorbidity, and social function as measured by current housing arrangements, collective neighborhood income, educational achievement, employment, and involvement in criminal activity.<sup>16</sup> Several investigations have sought to determine the best intervention for improving the above-mentioned outcomes,<sup>17-19</sup> however, most studies compare new therapies directly to methadone. Therapies such as Suboxone,<sup>®</sup> naltrexone, and HAT have yet to be evaluated against each other. This lack of head-to-head comparisons limited previous meta-analyses from

providing hierarchal estimates for the multiple outcomes evaluated in the literature,<sup>20-23</sup> highlighting the need for a multiple treatment comparison of pharmacological interventions for opioid addiction.

We aimed to assess how different opioid substitution and antagonist therapies compare in their effectiveness as evaluated across multiple outcomes such as treatment retention, illicit substance-use behaviour, as well as physical and psychiatric symptoms. Our secondary objectives were to 1) provide a qualitative summary of the definitions and measurements for effectiveness outcomes reported in the literature, 2) highlight the interventions showing benefit across direct comparisons with an evaluation of the outcomes used for these comparisons, and 3) summarize the interventions showing no benefit with an assessment of the outcomes used for these comparisons.

## 7.3 METHODS

We provide here a brief summary of our study methods; greater detail can be found in the published protocol.<sup>24</sup> We performed a systematic review to identify all OSAT trials. We performed a network meta-analysis to combine the available evidence, disseminating both direct and indirect comparisons of all therapies (methadone, buprenorphine/naloxone, naltrexone, and heroin assisted treatment) evaluating treatment retention. Using a network meta-analysis, we provide here the first statistical summary and ranking of opioid substitution and antagonist therapies for treatment retention. Our original intention was to use network meta-analysis to provide summary statistics for all patient-important outcomes evaluated in the literature, however the large variability in measurement across other outcomes (e.g. substance use behaviour, psychiatric health, physical comorbidities, quality of life) required the use qualitative methods to summarize direct and indirect comparisons. This study was registered in the PROSPERO database (CRD42013006507) and adheres to the PRISMA guidelines.<sup>25</sup>

### 7.3.1 Systematic Review Design

We searched the Medline, EMBASE, PubMed, PsycINFO, Web of Science, Cochrane Library, Cochrane Clinical Trials Registry, World Health Organization (WHO) International Clinical Trials Registry Platform Search Portal, and National Institutes for Health (NIH) Clinical Trials Registry in duplicate using the electronic search strategy described elsewhere.<sup>24</sup> We searched the reference lists of completed Cochrane reviews

and included studies examining the effect of different OSTs. We also contacted all primary investigators listed on the NIH Clinical Trial Registry from eligible studies identified during the title screening to inform them of this review and inquire for information regarding any publications resulting from their trials. This review placed no constraints on language or date of publication. Animal studies and incomplete studies (pilot, preliminary reports) were excluded. Studies without comparison groups were also excluded (i.e. case-report or case-series). Methodological quality assessment was conducted using the Cochrane Risk of Bias Tool for RCTs.<sup>24</sup>

The primary outcome of the network meta-analysis is treatment retention, a binary outcome measuring patients' continued use of intervention and attendance of clinically mandated visits through out the trial follow-up. Patient's achieving successful retention will be considered to have had an "event," whereby successful retention is defined as remaining in treatment, retrieving allocated medication, and attending scheduled appointments for the duration of trial follow-up. Treatment retention is fundamental to the provision of the intervention and the many adjunct therapies such as counseling, pain management, and cognitive behavioral therapy that are reported to substantially increase treatment effectiveness. Reducing treatment attrition in OSAT is critical for improving patient important outcomes,<sup>26,27</sup> with great importance placed on the first year attrition. Less than 15% of patients treated with methadone for example end their treatment as planned, suggesting a majority of patients drop out of treatment prematurely, leaving patients vulnerable to the risks associated with HIV, relapse of OUD, and death.<sup>28,29</sup> Our secondary endpoints include: substance use behavior, physical and psychiatric health,

personal and social functioning, as well as medication adherence and acceptance. Data extraction forms were constructed and pilot tested for use in this review. We abstracted the sample size, mean age, eligibility criteria, intervention description, dose, approaches to missing data, outcome definition, outcome measurement, covariates included in regression models if adjusted analyses were performed, and the statistical association reported (e.g. Odds Ratio[OR], Relative Risk [RR]).

### **7.3.2 Statistical and Descriptive Analysis**

The results are summarized narratively and statistically using network meta-analysis. The detailed description of our statistical methods is published in the review protocol.<sup>24</sup> Many OSATs are not directly compared head-to-head in a trial. The use of indirect treatment comparison methods such as network meta-analysis allows us to remedy such issues by combining all the available evidence, disseminating both direct and indirect comparisons. The relative treatment effects for all possible comparisons are presented in table format to determine if there are differences in effectiveness across interventions. We organized interventions in a comparison network and the comparisons are summarized in a network plot.

### **7.3.3 Network Meta-analysis Methodology**

To be included in the network meta-analysis direct comparisons (e.g. methadone vs. buprenorphine) required a minimum of two studies assessing the comparison. Indirect comparisons within the network meta-analysis are already sensitive to the evidence informing each network, thus we elected to set forward strict criteria for inclusion into the quantitative summary. To prevent the breach of randomization we included all

intervention arms, even those that did not meet the minimum criteria requiring a minimum of two studies evaluating this comparison.

We fit a consistency model with generalized linear model framework<sup>24</sup> with binomial likelihood and logit link function, using a Bayesian estimation framework. Anticipating the presence of relative treatment effect heterogeneity among studies, we adopted a random effects model assumption with a common (single) heterogeneity parameter. Default *non-informative* prior distributions were adopted for all parameters in the model. Statistical inference using the Bayesian approach relies on a computer-intensive Markov chain Monte Carlo (MCMC) simulation strategy to generate posterior samples to form the posterior distributions and get estimates. For the MCMC simulation, after specifying an adaption phase of 20000 samples, we allowed a burn-in of 100000 samples before generating another 100000 samples; after using a thinning interval of 10, we therefore used 10000 samples for inference. We verified that the posterior samples converged by using four chains and the Gelman-Rubin-Brooks plot and diagnostic test.<sup>24,30</sup> We calculated mean residual deviance and the deviance information criterion goodness of fit statistics to assess model fit. Finally, we performed an assessment of heterogeneity throughout the network, where applicable, using pairwise I-squared statistics and an assessment of the assumption of consistency throughout the network, where applicable, using node-splitting.<sup>31</sup> *We assessed the model goodness-of-fit using the mean residual deviance and DIC statistics.*

Using the posterior samples generated from the Bayesian estimation process, we can obtain rank probabilities for the treatments. Our results present probability statements of

treatment effects, allowing us to disseminate as an estimated probability, the highest ranking treatment for increasing retention.<sup>32</sup> These probabilities are displayed in both table and graphical formats. The graphical approach includes a surface under the cumulative ranking (SUCRA) line for each treatments probability rank.<sup>32</sup>

We used R version 3.1.1 (2014-07-10), with R package *gemtc* version 0.6 to specify the model and interface with the *Just Another Gibbs Sampler (JAGS)* MCMC sampling software to run the network meta-analysis model.<sup>33</sup>

#### **7.3.4 Qualitative Summary**

Large variability in definition and measurement prevented the use of network meta-analysis for the majority of outcomes, compelling us to qualitatively summarize secondary endpoint results of all direct comparisons. We organized outcomes into broader categories according to the domains proposed by commonly used measurement scales evaluating addiction severity (i.e., the Addiction Severity Index [ASI]<sup>34</sup> and Maudsley Addiction Profile [MAP]).<sup>35</sup> These tools evaluate treatment response using the broader domains of substance use behavior, physical and mental health, and social functioning.<sup>34,35</sup> Both tools are practical and provide a global assessment of patients' physical and social functioning. Our outcome domains included physical health, psychiatric health and symptoms, abstinence and substance use behavior, and personal and social functioning. Some studies used additional outcomes that did not conform to these domains; thus, we included global quality of life and addiction severity assessments (including global addiction severity measure scores), intervention adherence, acceptance of intervention, and resource utilization (e.g. hospital admission) as additional domains.

While craving can be categorized by both psychiatric and physical symptoms<sup>36,37</sup>, the physical effects of craving (e.g. insomnia, restlessness, tremors/shakes) are implicated in poor treatment prognosis for patients with substance use disorders.<sup>37</sup> Thus, we elected to include craving in the physical health domain. This categorization of outcomes provides researchers and clinicians with an overview of the current outcomes used to assess patients' response to OSAT.

For this qualitative overview, we only considered direct comparisons (intervention A vs B on outcome domain Z) that had a combined sample size of 200 or more participants, regardless of the number of trials involved in that comparison or the number of patients involved in each of those trials. We considered intervention A superior to intervention B for outcome Z if >50% of the trials comparing these interventions showed benefit A over B. For an individual trial to show superiority of A over B in a given outcome domain, it had to show statistically significant ( $p \leq 0.05$ ) benefit across  $\geq 50\%$  of the outcomes/measures pertinent to that domain. For instance, if a study examined the impact of high-dose buprenorphine on illicit opioid consumption compared to placebo and defined illicit opioid use in various ways (e.g. the percentage of positive opioid urine screens, number of days of opioid use, and the number of days till opioid relapse) and used several types of measurements (e.g. self-report and urine toxicology screening), the study was required to demonstrate a statistically significant ( $p \leq 0.05$ ) treatment effect across  $\geq 50\%$  of outcomes taking into account different definitions and measurements.

### **7.3.5 Methodological Assessment**

We assessed trials' risk of bias using the Cochrane Risk of Bias Tool for RCTs.<sup>24</sup> We evaluated the results from the quantitative summary of retention data using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework.<sup>38</sup>

GRADE suggests all direct, indirect, and network estimates (the combined estimate from direct and indirect evidence) be reported for each comparison, and that each estimate be subject to individual quality assessment using the traditional GRADE framework.

## 7.4 RESULTS

### 7.4.1 Overview: Study Selection and Characteristics

An annotated flow diagram of the study selection process is presented in [Figure 7.4.1](#).

We searched databases since inception to January 1, 2014 and identified 6077 articles.

Agreement among independent raters for the title, abstract, and full-text screening was good (Kappa for titles, 0.71 [Standard Error [SE] 0.02]; abstracts, 0.85 (0.03); full texts, 0.73 (0.06)). We identified 60 trials with a combined participant sample of 13341

patients eligible for full text-extraction, of which 28 trials provided sufficient data for the combined statistical summary of treatment retention (summarized in [Table 7.4.1](#)). The network meta-analysis was performed in a sample of 3342 patients.

### 7.4.2 Methodological Quality Assessment

The mean Cochrane risk of bias score was 15.15 (SD: 2.51), with a minimum score of 10 and maximum of 18. Please refer to the supplementary appendix v ([eTable 1](#)) for a summary of the individual risk of bias assessment for included studies. In accordance with the GRADE framework, all estimates (direct, indirect, and network) are provided in supplementary appendix v ([eTable 2](#)). The most common problems contributing to the low ranking of evidence included the high risk of bias from individual studies (can be seen with the Cochrane risk of bias scores) and the limited coherence and precision across estimates.

### 7.4.3 Impact on Patient Retention: Network Meta-analysis Findings

#### 7.4.3.1 Opioid Substitution Treatment Networks

Table 7.4.3.1 provides an outline of the different OSATs evaluated, the number of studies investigating the intervention, and the combined number of participants randomized to each intervention. The dose cutoffs for each intervention were selected in accordance with the literature, whereby the effect changes beyond these cut points.<sup>39-43</sup> The antagonist properties of naloxone enhance the pharmacological effectiveness of the combination buprenorphine naloxone intervention by reducing illicit opioid consumption.<sup>13</sup> Although some studies demonstrate the potential for abuse with combination buprenorphine naloxone therapy<sup>44,45</sup>, it is likely these studies were underpowered with considerably small samples ( $n < 10$ ). Even the most recently published Cochrane review evaluating buprenorphine maintenance treatment for opioid addiction provided minimal rationale for pooling the combination buprenorphine/naloxone therapy with the single formula.<sup>39</sup> Mattick et. al (2014) acknowledged the usefulness of evaluating the combination therapy separately, however decided to pool based on their a priori analysis plan by dose.<sup>42</sup> Due to the strong evidence suggesting the pharmacological properties of naloxone will alter the effectiveness of combination buprenorphine naloxone,<sup>13,46,47</sup> we have chosen to evaluate combination buprenorphine/naloxone separately from single formula buprenorphine.

Of the 28 studies providing results for treatment retention, 16 different interventions were evaluated. The interventions include: heroin, high-dose methadone ( $\geq 60$  mg/day), low-dose methadone ( $< 60$  mg/day), IV heroin + methadone (methadone  $\geq 60$  mg/day), high-dose buprenorphine ( $\geq 16$  mg/day), low-dose buprenorphine ( $< 16$  mg/day), high-dose Suboxone<sup>®</sup> (buprenorphine  $\geq 16$  mg/day + naloxone), low-dose Suboxone<sup>®</sup>

(buprenorphine <16 mg/day + naloxone), high-dose injectable naltrexone (384 mg/day), low-dose injectable naltrexone (192 mg), high-dose oral naltrexone ( $\geq 50$  mg/day), low-dose naltrexone implant (<50 mg/day), low-dose levacetylmethadol (LAAM) (<160 mg/dose), low-dose oral naltrexone, naltrexone implant (200 mg/day) + oral naltrexone placebo, and placebo. We provide the network plot of all interventions ([Figure 7.4.3.1](#)); black lines connect treatment options that have been compared within a trial directly. The numbers along the black lines represent how many trials compared the corresponding pair of treatments. The size of the treatment nodes in the graph reflects the number of studies that involve the corresponding treatment (e.g. the majority of participants [n=2128] and studies [k=16] are represented in the high-dose methadone network).

#### *7.4.3.2 Results from Network Meta-Analysis: The Most Effective Therapy for Treatment Retention*

[Table 7.4.3.2](#) provides a summary of all estimates obtained from the network meta-analysis. Heroin increases the odds of remaining in treatment more than any other intervention, evident by the large and significant treatment effects. Heroin significantly increased the odds of retention in treatment compared to high-dose buprenorphine (OR: 6.01; 95% CI: 1.18, 29.79), high-dose IV heroin + methadone (OR: 8.16; 95% CI: 1.27, 49.96), high-dose methadone (OR: 3.53; 95% CI: 1.28, 10.13), high-dose naltrexone (OR: 22.33; 1.80, 325.57), low-dose buprenorphine (OR: 5.11; 95% CI: 1.22, 21.93), low-dose methadone (OR: 4.22; 95% CI: 1.24, 15.04), low-dose naltrexone implant (OR: 37.21; 95% CI: 5.62, 267.46), low-dose oral naltrexone (OR: 27.06; 95% CI: 2.44, 321.99), low-dose Suboxone<sup>®</sup> (OR: 12.38; 95% CI: 1.73, 93.60) and placebo (OR: 38.55; 95% CI: 6.40,

250.21). The multiple interventions heroin did not demonstrate significant improvement over are summarized in Table 7.4.3.2.

High-dose methadone improved retention compared to low-dose naltrexone (OR: 10.54; 95% CI: 2.06, 57.67) and placebo (OR: 10.92; 95% CI: 2.36, 52.48); it did not demonstrate significant benefit when compared to other interventions (Table 7.4.3.2).

While many of the treatments failed to show a significant difference in effectiveness for retention when compared to each other, some interventions (heroin, high-dose methadone, high-dose Suboxone<sup>®</sup>, low-dose buprenorphine, low-dose injectable naltrexone, low-dose LAAM, low-dose methadone, and the naltrexone implant with oral placebo) managed to demonstrate a significant effectiveness for improving retention when compared to placebo.

We present the estimated rank probabilities for all 16 treatments in a plot known as a rankogram (Figure 7.3.2a), which graphically highlights the comparative ranks among the treatments. Based on these estimated ranks, we estimate that heroin has a 71% chance of being the best modality for increasing treatment retention among the competing interventions in this study. In contrast, low-dose naltrexone and placebo follow closely in their probability of ranking last, approximate probabilities of 16.7 and 15.8% respectively. We also display (Figure 7.3.2b) cumulative rank probability plots with SUCRA values to summarize the comparative effectiveness of each treatment. Based on these estimates, heroin is the overall highest ranked treatment for patient retention with a SUCRA value of 96.9%.

#### *7.4.3.3 Assessment of Model Fit and Assumptions*

*Goodness-of-fit assessment showed a mean residual deviance of 348.69 and a DIC of 410.11. This reflects the fit of a complex model to a relatively small number of studies. Of the 11 pairwise comparisons with at least two trials contributing direct evidence, I-squared values ranged from 34.3% to 93.0%, representing a large degree of heterogeneity present within the network. Of the **seven** pairwise comparisons, none had a statistically significant inconsistency between direct-only and indirect-only estimates emerging from the node-splitting procedure.*

#### **7.4.4 Qualitative Summary of Direct OST Comparisons for all Effectiveness Outcomes Reported in the Literature**

Results from each reported outcome for all direct comparisons are summarized in supplementary appendix v ([eTable 3](#)). As noted by the scale of [eTable 3](#) in supplementary appendix v, a substantial number of outcomes as well as variations in outcome definitions and measurements were reported across 57 trials. In order to manageably compare all interventions (direct and indirect) we grouped outcomes with similar definitions and measurements into more broader “outcome domains.” [Table 7.4.4a](#) summarizes the broad domains, outcome domains, and specific outcome definitions and measurements reported across trials. We appraised the evidence presented in supplementary appendix v ([eTable 3](#)) using the categorizations displayed in [Table 7.4.4a](#) in addition to the evidence algorithm described in our methods.

Comparisons were made across 77 outcomes, including different measurements and definitions ([Table 7.4.4a](#)). Within the 8 broadest domains (abstinence and substance use behavior, physical health, psychiatric health and symptoms, personal and social

functioning, resource utilization, intervention adherence, intervention acceptance, and global quality of life and addiction severity scoring), there are 21 more specific outcome domains (e.g. illicit opioid use, illicit non-opioid substance use), and across these outcomes there exist 53 separate definitions. Among the 177 comparisons made across outcome domains (eTable 4 located in supplementary appendix v), only 59 comparisons (across 45 trials) met the criteria set in our evidence algorithm. Results are summarized in Table 7.4.4b, where 28 comparisons showed no difference between interventions and 5 were inconclusive, meaning we did not see enough evidence to conclude there was an effect (<50% of trials reporting a difference).

Low-dose oral naltrexone (outcome domains: general physical health, intervention preference, intervention compliance) and naltrexone implant (outcome domain: intervention compliance) failed to show benefit when compared against placebo. High-dose Suboxone, low-dose buprenorphine, and dihydrocodeine showed no difference when compared against methadone across the abstinence/substance use behaviour, physical health, global quality of life/addiction severity, and personal/social functioning domains. High dose-interim methadone (domains: abstinence/substance use, global quality of life/addiction severity), and no intervention waitlist (domain: abstinence/substance use behaviour) failed to show benefit over methadone. Dose-response relationships were observed in this summary, where higher doses of more potent opioids resulted in greater patient improvement across domains. Similar to the results of the network meta-analysis, heroin showed significant benefit over high-dose methadone in the abstinence and substance use, global quality of life/addiction severity scoring, personal and social

functioning, as well as physical health domains. Comparisons were inconclusive regarding the effectiveness of high-dose methadone compared to low-dose buprenorphine for reducing illicit opioid use and drug craving, or low-dose methadone as compared to low-dose buprenorphine for restraining non-opioid substance use.

## 7.5 DISCUSSION

Results from this systematic review and network meta-analysis of randomized trials suggest that, among patients treated OSATs, those treated with heroin and high-dose methadone are more likely to remain in therapy. Heroin and high-dose methadone were the only interventions significantly more effective than placebo, however we maintain there was insufficient evidence to confidently rank the remaining treatments. Heroin demonstrated effectiveness over methadone and all other interventions for maximizing retention in treatment. Heroin also showed significant benefit when directly compared against methadone for multiple outcomes including substance use, personal and social functioning, physical health, and addiction severity. For the majority of direct comparisons (buprenorphine, Suboxone, and dihydrocodeine), many interventions were found to be no different than methadone.

The evidence base in this area suffers from important limitations. Trials evaluating OSATs suffer from poor methodological quality, which is reflected in the Cochrane Risk of Bias scores and GRADE assessment. A combination of small sample size, poor design, highly stringent eligibility criteria, effect estimates with tremendous imprecision, short-follow up time, missing data, and a major lack of consensus over patient-important outcomes has led to an accumulation of a large yet very weak body of evidence. In fact, many interventions failed to show significant benefit over placebo across different physical health, behavioral, and social outcomes. Should we trust that these interventions are as good as nothing at all? Whether it be illicit opioid use or risky behavior, the large

number of definitions and measurements used to assess the same attribute suggest the need for more consensus in the field and understanding of what treatment outcomes are most important to addiction patients. Our findings were consistent with previous evidence summaries;<sup>20,22,48-56</sup> however, none to date have used network meta-analysis to obtain summary statistics to evaluate retention or provided the results for all direct comparisons into a single source.

The global impact of opioid use is apparent. There were 15.6 million (0.3 % global population) people engaging in illicit opioid use in 2007.<sup>57</sup> Countries such as Afghanistan and Russia carry one of the largest burdens of opioid use.<sup>58</sup> With over three million reported heroin users, 30,000 deaths per year and a rising HIV epidemic, Russia feels one of the largest impacts of opioid addiction.<sup>59</sup> Afghanistan follows closely behind with the reported number of heroin dependent patients reaching 120,000, of which 15-20% use substances intravenously.<sup>60</sup>

Strategies targeted to reduce opioid addiction have led us to what is considered one of the most controversial solutions. The use of heroin as a treatment for opioid dependence is a novel and difficult concept for both governments and policy makers to approve. Trials in Canada<sup>14</sup> and the Netherlands<sup>61</sup> highlight the effectiveness heroin as a treatment option in opioid addiction. However, the provision of such treatments for opioid addiction is fraught with controversies. Recently, Canadian researchers have been fighting against health ministers decisions to cease all post-trial access to diacetylmorphine, whereby researchers are citing the government for breach of ethical standards as according to the Declaration of Helsinki, which requires “host country governments should make

provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial.”<sup>62</sup> This setback is influenced by the governing paradigms of nations, of which Canada is not alone; the US and Russia follow closely behind. Recent the takeover of Crimea by the Russian army has forced hundreds of patients with opioid addiction on methadone to face the painful effects of immediate withdrawal from methadone due to Russia’s policies on drug dependence treatment.<sup>63</sup> Notwithstanding the ethical and legal dilemmas of heroin use as a treatment option for opioid addiction and the need for trials, it is important to address this problem by carefully weighing the evidence for and against continuing research on heroin and promoting of opioid substitution treatment for medicinal use, emphasizing the need for important rigorous summary of evidence.

The results of this review suggest heroin to be the most effective option for helping patients with opioid addiction to stay in treatment. These findings, in addition to the findings of most trials studying heroin effectiveness, are biased by their outcome assessment. Heroin trials consistently use outcomes that are inherently flawed. For example, the Oviedo-Joekes (2009)<sup>14</sup> trial assessed the effectiveness of heroin in comparison to high-dose methadone using retention in treatment and reduction in crime and illicit substance use as their main outcomes.<sup>14</sup> People addicted to heroin will commit crimes and fail to comply with methadone treatment as a result of the behavior associated with heroin dependence, thus, providing this substance free for enrolled participants will undoubtedly reduce crime, heroin use, and increase retention. The selection of outcomes in these trials were guaranteed to show improvement and calls into question the real

effectiveness of heroin treatment, or possibly the appropriateness of the outcomes we are using. These methodological shortcomings highlight the need for new assessment strategies for opioid addiction treatment options, where future efforts should target the objective assessment of treatment effectiveness employing long-term follow-up using administrative data-linkage for trial participants to evaluate hard long-term outcomes such as incidence of hepatitis, HIV, cardiovascular abnormalities, and mortality. Among the trials included in this review, three evaluated the impact of interventions on mortality<sup>64,65</sup> or cardiac function.<sup>66</sup>

Another important issue is the administration of heroin as a therapy. Heroin is a challenging and complex treatment to provide to patients with opioid addiction. In one trial, for example, patients were required to attend the clinic multiple times per day for supervised consumption.<sup>14</sup> This is due to heroin's short half-life, which requires patients to use the substance several times per day to avoid withdrawal symptoms.<sup>14</sup> This intense treatment regime would prove burdensome to the healthcare system. Consider if we were to conduct studies of strategies for managing heart failure in hospital and the outcome was time in hospital. Technically, we keep people from dying when in hospital, much like you can prevent overdose or infection in an addiction patient if they keep coming to your facility to inject. Of course people want more out of life than to stay in hospital or be controlled by an intensive treatment regime. The goal of treatment is to be able to fulfill your other needs. While some may argue that heroin treatment is a way of tapering down opioid use with the ultimate aim of reaching abstinence, others may see the faults in the administration of this treatment and suggest it keeps patients chained to the addiction

center and prevents them from living normal lives. Although, is employment and access to a more “normal” life more important? We have yet to perform any type of study evaluating patients’ values and preferences with respect to long-term goals, or social/physical trade-offs.

While previous evidence summaries may suggest no further trials are needed,<sup>39</sup> the overwhelming variation in the selection of “patient important outcomes,” as well as the marked range of definitions and measurements of specific outcomes question the validity of this statement. The field of addiction medicine still requires larger trials and a consensus as to the important outcomes for patients suffering from addiction. It may serve future research to 1) evaluate outcomes patients define as important, 2) design adequately powered trials to test effectiveness, 3) test interventions in representative samples (e.g. include participants with psychiatric comorbidity, comorbid substance use problems), and 4) evaluate the long-term effectiveness of interventions in this chronic disorder.

### **7.5.1 Limitations**

The reliability of our results rests on the assumption that the trial design features are similar across studies. Any difference that influences the observed treatment effect will weaken this assumption and our ability to reach firm conclusions from this review.<sup>67</sup>

While the majority of studies included in the quantitative summary were eligible for inclusion based on their similar definition and measurement of retention, heterogeneity was present across studies. Differences in the duration of follow-up and eligibility criteria applied to study populations contributed most to the observed heterogeneity. We acknowledge there is large variability in the duration of follow-up across trials included

in the quantitative summary, which ranges from 2-52 weeks. However, the majority of trials (k=20) evaluate retention over a 6-month period, which is important since treatment attrition for opioid addiction patients is highest within the first 26 weeks<sup>68</sup>.

Our highly sensitive inclusion criteria were employed in efforts to obtain as many studies as possible evaluating the effectiveness of OSATs. We aimed to provide an adequate assessment generalizable to much of the opioid addiction population. However, such high inclusivity can jeopardize the findings since the differences observed may actually be due to differences in study populations or outcome measures. The eligibility criteria reported across trials differed substantially, with some requiring patients to have failed previous treatments of methadone, suggesting the inclusion of a population more vulnerable to treatment failure. Other studies excluded populations with comorbid psychiatric disorders or alcohol and substance use problems, which may suggest the study included participants who would have fared better than the average opioid dependent patient. Such criteria not only question the generalizability of the evidence, it also calls to question the impact of heterogeneity on the quantitative summary.

For instance, the interpretation of the evidence generated from trials evaluating HAT requires additional caution. The strict eligibility criteria used in trials evaluating HAT selects a more marginalized cohort of patients who failed previous methadone treatments, which calls to question the validity of effectiveness comparisons made between HAT and other OSATs. It remains that HAT is shown to be more effective with heroin users that did not respond to other treatment, and may be more effective than methadone within this subgroup. Thus, findings suggesting HAT is most effective is unlikely generalizable to

patients whose addiction is related to non-parenterally delivered prescription opioids.

While selected in accordance with previous literature, we recognize the dose categorizations are higher than what some may consider a clinically “low” dose.

However, the dose categorization were selected in accordance with the evidence, whereby the observed treatment effect is statistically significantly different beyond this cut point.<sup>39-</sup>

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Findings from this review discern the comparative effectiveness of OSATs for considerable number of outcomes. However, notably absent are the results for safety outcomes such as adverse events. We acknowledge that safety outcomes including side effects and adverse events are important, however we established a priori<sup>24</sup> that the aims of this review were to evaluate the impact of OSATs for retaining patients and managing illicit substance use behavior. We did not directly evaluate a category of “safety outcomes”, however many of the adverse events (e.g. overdose, withdrawal, prolonged QTc interval) experienced as a result of medication were qualitatively summarized within the physical health domain.

Adjunct psychosocial therapies can enhance the effectiveness of an OSAT<sup>69</sup>. Addiction counselling, peer support networks (e.g. narcotics anonymous), cognitive behavioral therapy, and motivational interviewing are all examples of the cadre of interventions implemented to address the social problems associated with addiction and ultimately supplement the OSAT. We acknowledge the impact adjunct therapies may have on treatment prognosis, however due to the overwhelming differences in the collection,

description, and delivery of psychosocial therapies we were unable to make a standardized assessment or provide any conclusions as to their overall impact on the review findings. In addition, many of the comparisons evaluated in our qualitative evidence summary did not meet our minimum standard for inclusion (Table 7.4.4b), which excluded over 50% of the evidence for direct comparisons across secondary end-points. While we are uncomfortable with the exclusion of such a large portion of the evidence, we felt it necessary for protecting the integrity of our analysis and interpretation. We are confident the summary evidence penalization methods will reduce the chance of making strong conclusions based on low-powered comparisons with potential for selective reporting and multiple comparisons.

## 7.6 CONCLUSION

Findings from this multiple treatments comparison and network meta-analysis of OSAT suggest heroin assisted therapy is most effective for retaining patients in treatment.

Findings also suggest heroin, as well as higher doses of opioid treatments are most effective for improving other outcome domains including abstinence and illicit substance use, physical health, and personal and social functioning. The effects estimates reported for studies evaluating heroin are likely inflated due to the more marginalized addiction populations HAT is assessed in. Any results suggesting heroin as a superior therapy for managing opioid use disorder should be interpreted with caution. Many treatments showed no difference compared to methadone, and in some cases were no better than placebo. Larger trials with long-term follow-up are needed for many of the interventions evaluated in this review. Identification and use of patient important outcomes represent a vital next step in addiction research.

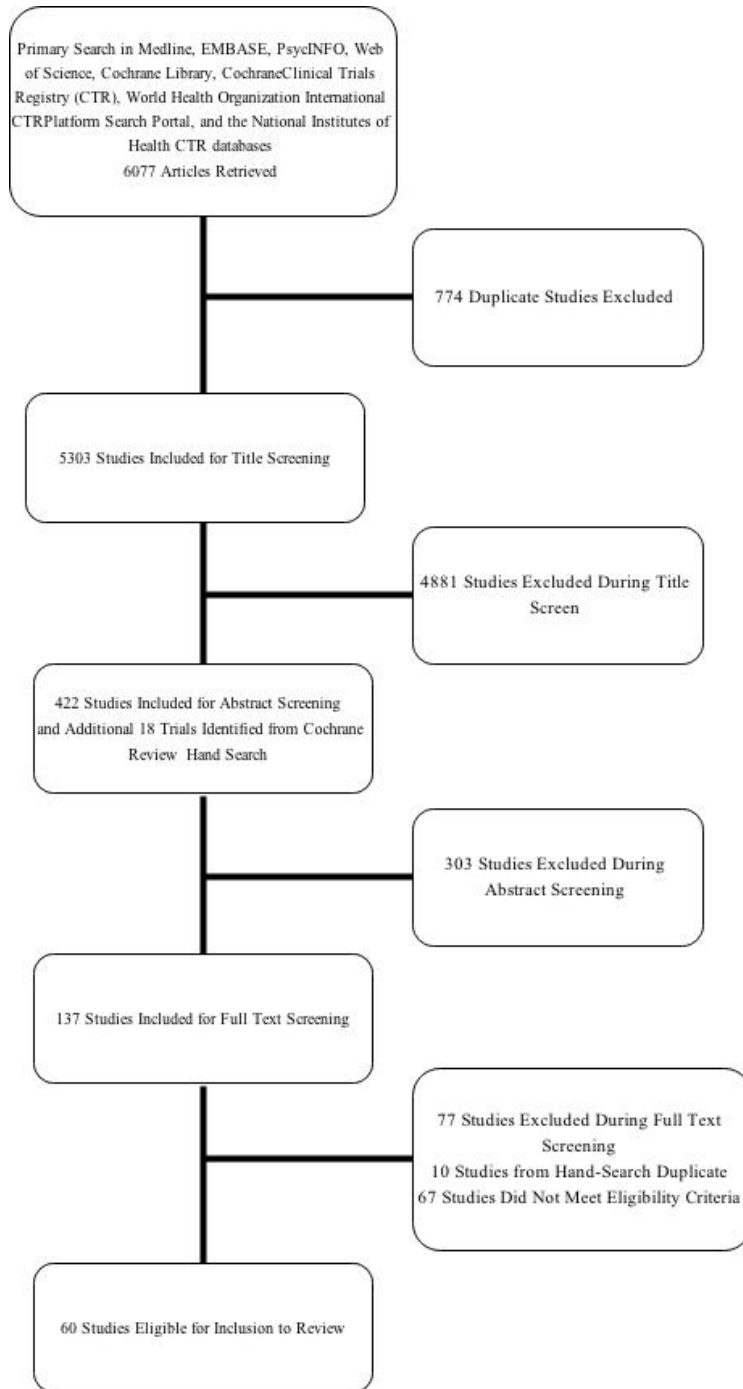
## **7.7 ACKNOWLEDGEMENTS, FUNDING, AUTHOR CONTRIBUTIONS**

We report no competing interests for this investigation. This work was supported by the Peter Boris Centre for Addictions Research and the CIHR Drug Safety and Effectiveness Network (DSEN) grant (grant number: 126639). The funders had no role in study design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript. Dr. Zainab Samaan, Brittany B. Dennis and Lehana Thabane led the development of the project. All authors contributed to the development of the research protocol, which is published in the journal *Systematic Reviews*. Brittany B. Dennis and Ashley Bonner were responsible for all statistical analyses performed in this investigation. All authors contributed to interpreting the data and writing the manuscript. Zainab Samaan had full access to data from this investigation and she is accountable for the reliability of the data and the accuracy of all analyses performed.

We would like to sincerely thank everyone who contributed to the completion of this project. We would like to specially thank Anuja Bhalerao, Arnav Agarwal, and Joshua Kong for their initial help with the screening and data abstraction of studies. This project would not have been possible without the great collaboration cemented between GENOA and the CATC.

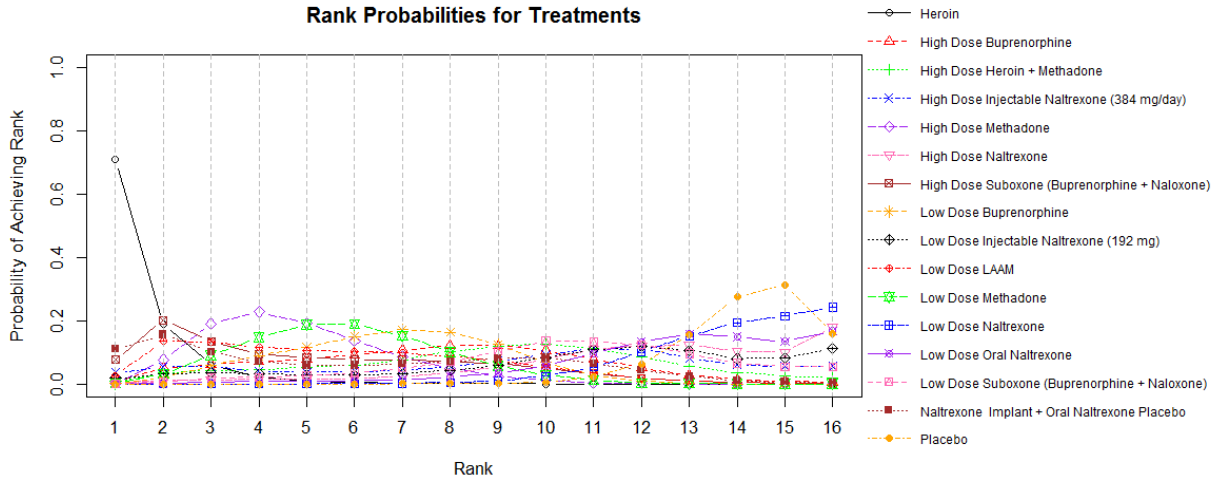
## 7.8 FIGURES AND TABLES

**Figure 7.4.1** Flow diagram of the study selection process

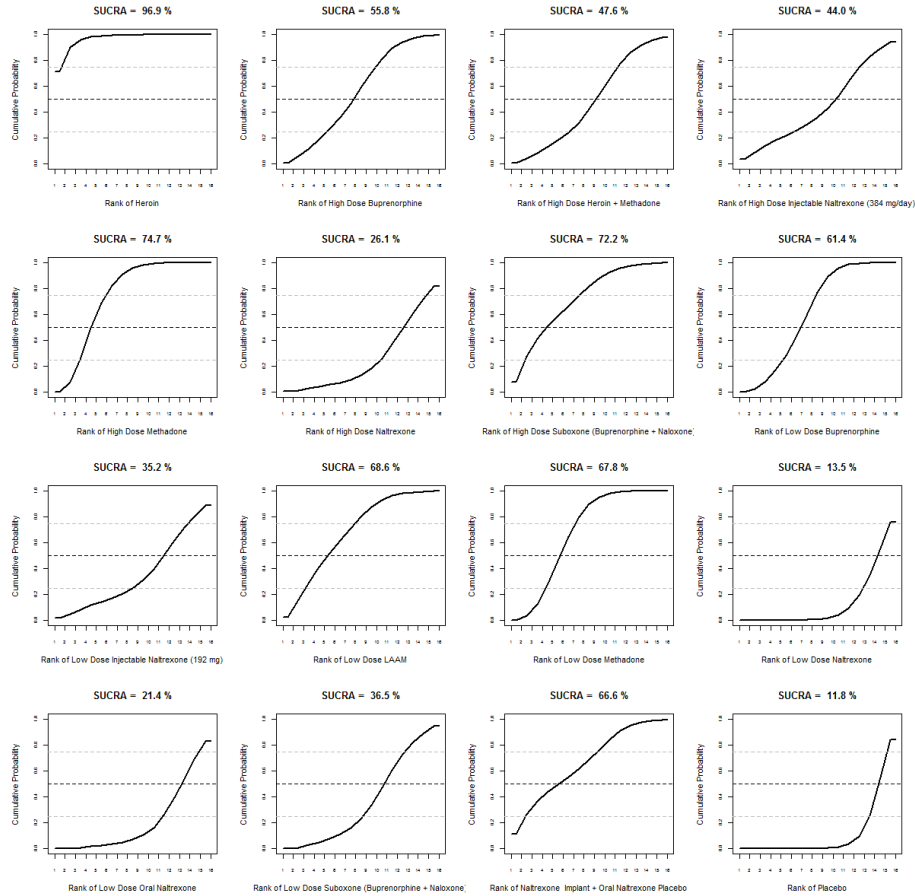




**Figure 7.3.2a Rank Probabilities for Opioid Substitution and Antagonist Therapies**



**Figure 7.3.2b Cumulative Rank Probability Plots For Opioid Substitution and Antagonist Therapies using SUCRA Values**



**Table 7.4.1 Characteristics of Opioid Substitution Treatment Randomized Controlled Trials Included in Network Meta-analysis for Treatment Retention**

Author Last Name, Year	Number of Participants	Duration Followed	Intervention(s)	Definition of Retention in Treatment	Cochrane Risk of Bias Score
Ahmadi, 2009	204	12 Weeks	Low-dose Buprenorphine, Low-dose Methadone, Low-dose Naltrexone	Remaining in treatment, retrieving allocated medication, and attending scheduled appoints for 12-weeks	11
Comer, 2006	60	8 Weeks	High-dose Injectable Naltrexone (384 mg/day), Low-dose Injectable Naltrexone (192 mg), and Placebo	Attendance of maintenance visits and retrieval of allocated medication for eight-weeks	15
Haasen, 2007	1015	52 Weeks	Heroin and High-dose Methadone	Completion of one-year treatment regime of the intervention the participant was randomized to, including attendance at therapy, education, or psychosocial sessions.	15
Hartnoll, 1980	96	52 Weeks	Heroin and High-dose Methadone	Remaining in one-year treatment regime, attendance of clinic appointments, and maintenance on the therapy randomized to.	17
Johnson, 1992	162	25 Weeks	High-dose Methadone, Low-dose Methadone, Low-dose Buprenorphine	Completion of treatment randomized for, maintenance on treatment for 25 week period.	17
Johnson, 1995	150	2 Weeks	Low-dose Buprenorphine and Placebo	Percent of patients in each group who remained on the dose to which they were originally randomized for each day of the 14-day study.	12
Kakko, 2003	40	52 Weeks	Low-dose Buprenorphine and Placebo	Number of participants remaining in treatment for full 350 days.	17
Kamien, 2008	268	17 Weeks	High and Low-dose Methadone, Low-dose Suboxone® (Buprenorphine + Naloxone High-dose Suboxone®)	Completion of 17-week treatment regime, attendance of clinic visits and retrieval of the treatment originally allocated.	18
Krupitsky, 2006	280	26 Weeks	Low-dose Naltrexone and Placebo	Completion of treatment regime over six-month period.	18
Krupitsky, 2012	306	26 Weeks	Low-dose Oral Naltrexone, Naltrexone Implant + Oral Naltrexone Placebo, and Placebo	Completion of treatment regime, attendance of clinic appointments, and maintenance of clean urine screens for the trial duration.	18
Ling, 1976	142	40 Weeks	High-dose Methadone, Low-dose Methadone, Low-dose LAAM	Attendance of 26-week treatment regime allocated to participant.	13
Ling, 1996	225	26 Weeks	High-dose Methadone, Low-dose Buprenorphine, Low-dose Methadone	Completion of 26-week treatment regime on the intervention the participant was randomized to.	15

March, 2006	62	36 Weeks	High-dose Methadone, High-dose Heroin + Methadone	Participants were considered to have retained in the intervention arm if remained within the arm through the duration of the study.	13
Mattick, 2003	405	Not Available	High-dose Buprenorphine and High-dose Methadone	Completion of trial on the medication randomized to the participant for the duration of one year.	17
Neri, 2005	62	52 Weeks	High-dose Buprenorphine and High-dose Methadone	Completion of one-year trial while also receiving the intervention allotted to the participant.	16
Oviedo-Joekes, 2009	226	52 Weeks	Heroin and High-dose Methadone	Remaining in the one year treatment regime.	14
San, 1991	50	26 Weeks	Low-dose Naltrexone and Placebo	Remaining in six-month treatment regime.	15
Saxon, 2013	1269	32 weeks	High-dose Buprenorphine and High-dose Methadone	Remaining on the 32-week therapy randomized to the participant.	15
Schottenfeld, 2008	126	24 Weeks	High-dose Naltrexone, Low-dose Buprenorphine, and Placebo	Remaining abstinent and in treatment for the duration of the 168 day trial and attendance of clinics.	18
Schuffman, 1994	32	12 Weeks	Low-dose Oral Naltrexone and Placebo	Completion of 12-week trial and continuance of medication through out course of the trial.	16
Soyka, 2008	140	26 Weeks	Low-dose Buprenorphine and Low-dose Methadone	Compliance with the treatment regime through out the course of the 26 week trial, this included the daily ingestion of the randomized intervention.	10
Strain, 1994	164	16 Weeks	Low-dose Buprenorphine and Low-dose Methadone	Remaining on 16-week treatment intervention at the end of the study period.	14
Strain, 1999	192	30 Weeks	High-dose Methadone and Low-dose Methadone	Completion of the 30-week intervention on the medication the participant was randomized to.	17
Strang, 2010	127	26 Weeks	Heroin, High-dose Methadone, Low-dose Methadone	Remaining on the 26-week treatment regime, this was completed through attendance of clinic appointments and daily ingestion of the medication the participant was randomized to.	18
Van Den Brink, 2003	549	52 Weeks	High-dose Heroin + Methadone and High-dose Methadone	Completion of the 1-year trial, while also maintaining adherence to daily medication requirements of the intervention the participant was randomized to.	18
Wolstein, 2009	84	24 Weeks	High-dose Methadone and Low-dose LAAM	Remaining in the 24-week trial and continuing the medication during the course of the trial.	12

Woody, 2008	152	12 Weeks	High-dose Suboxone® (Buprenorphine + Naloxone) and Low-dose Suboxone® (Buprenorphine + Naloxone)	Completion of the 12-week trial and daily consumption of the medication the participant was randomized to.	14
Zaks, 1972	20	26 Weeks	High-dose Methadone and Low-dose LAAM	Completion of the six-month trial.	10

**Table 7.4.3.1 Details of the Opioid Substitution Treatments Investigated Across Trials Included in Network Meta-analysis for Treatment Retention**

Treatment Name	Number of Studies Examining Intervention	Number of Events (Participants Completing Intervention)	Number of Participants
Heroin	4	522	715
High-dose Buprenorphine	3	386	971
High-dose Heroin + Methadone	2	158	278
High-dose Injectable Naltrexone (384 mg/day)	1	15	22
High-dose Methadone	16	1248	2128
High-dose Naltrexone	1	4	43
High-dose Suboxone® (Buprenorphine + Naloxone)	2	66	132
Low-dose Buprenorphine	8	261	500
Low-dose Injectable Naltrexone (192 mg)	1	12	20
Low-dose LAAM	3	86	194
Low-dose Methadone	9	343	690
Low-dose Naltrexone Implant	3	45	161
Low-dose Oral Naltrexone	2	25	118
Low-dose Suboxone® (Buprenorphine + Naloxone)	2	32	160
Naltrexone Implant + Oral Naltrexone	1	54	102
Placebo	8	85	347

\*Dose: high-dose methadone ( $\geq 60$  mg/day), low-dose methadone ( $<60$  mg/day), IV heroin + methadone (methadone  $\geq 60$  mg/day), high-dose buprenorphine ( $\geq 16$  mg/day), low-dose buprenorphine ( $<16$  mg/day), high-dose Suboxone® (buprenorphine  $\geq 16$  mg/day + naloxone), low-dose Suboxone® (buprenorphine  $<16$  mg/day + naloxone), high-dose injectable naltrexone (384 mg/day), low-dose injectable naltrexone (192 mg), high-dose naltrexone ( $\geq 50$  mg/day), low-dose naltrexone ( $<50$  mg/day), low-dose LAAM ( $<85$  mg/day), low-dose oral naltrexone, naltrexone implant approx. 200 mg/day + oral naltrexone placeb

**Table 7.4.3.2 Network Meta-analysis Results Summary for Treatment Retention Effectiveness (refer to attached excel file for full image)**

	Heroin	High-dose Buprenorphine	High-dose Heroin + Methadone	High-dose Injectable Naltrexone (384 mg/day)	High-dose Methadone	High-dose Naltrexone	High-dose Suboxone® (Buprenorphine + Naloxone)	Low-dose Buprenorphine	Low-dose Injectable Naltrexone (192 mg)
<b>Heroin</b>	-----	0.17 (0.03, 0.84)	0.12 (0.02, 0.79)	0.09 (0.00, 1.84)	0.28 (0.10, 0.78)	0.04 (0.00, 0.56)	0.29 (0.04, 2.10)	0.20 (0.05, 0.82)	0.06 (0.00, 1.25)
<b>High-dose Buprenorphine</b>	6.01 (1.18, 29.79)	-----	0.73 (0.11, 5.21)	0.56 (0.02, 11.97)	1.70 (0.47, 5.84)	0.27 (0.02, 3.89)	1.74 (0.20, 14.27)	1.18 (0.22, 6.02)	0.38 (0.02, 8.33)
<b>High-dose Heroin + Methadone</b>	8.16 (1.27, 49.96)	1.37 (0.19, 9.34)	-----	0.75 (0.03, 18.24)	2.31 (0.49, 10.22)	0.36 (0.02, 6.04)	2.37 (0.23, 22.29)	1.60 (0.24, 10.07)	0.52 (0.02, 12.57)
<b>High-dose Injectable Naltrexone (384 mg/day)</b>	10.81 (0.54, 222.05)	1.80 (0.08, 41.88)	1.32 (0.05, 35.23)	-----	3.07 (0.18, 54.06)	0.47 (0.02, 12.75)	3.13 (0.13, 81.12)	2.11 (0.15, 30.60)	0.69 (0.07, 6.99)
<b>High-dose Methadone</b>	3.53 (1.28, 10.13)	0.59 (0.17, 2.12)	0.43 (0.10, 2.04)	0.33 (0.02, 5.53)	-----	0.16 (0.01, 1.66)	1.03 (0.18, 5.71)	0.69 (0.24, 2.05)	0.23 (0.01, 3.83)
<b>High-dose Naltrexone</b>	22.33 (1.80, 325.57)	3.72 (0.26, 59.36)	2.78 (0.17, 52.01)	2.11 (0.08, 55.46)	6.32 (0.60, 75.14)	-----	6.52 (0.38, 124.58)	4.39 (0.53, 41.82)	1.44 (0.06, 37.78)
<b>High-dose Suboxone® (Buprenorphine + Naloxone)</b>	3.44 (0.48, 26.34)	0.57 (0.07, 5.07)	0.42 (0.04, 4.43)	0.32 (0.01, 7.84)	0.97 (0.18, 5.52)	0.15 (0.01, 2.62)	-----	0.67 (0.10, 4.61)	0.22 (0.01, 5.50)
<b>Low-dose Buprenorphine</b>	5.11 (1.22, 21.93)	0.85 (0.17, 4.49)	0.63 (0.10, 4.19)	0.47 (0.03, 6.65)	1.45 (0.49, 4.20)	0.23 (0.02, 1.89)	1.48 (0.22, 9.77)	-----	0.33 (0.02, 4.50)
<b>Low-dose Injectable Naltrexone (192 mg)</b>	15.63 (0.80, 323.51)	2.61 (0.12, 61.09)	1.93 (0.08, 50.54)	1.44 (0.14, 14.95)	4.41 (0.26, 77.43)	0.70 (0.03, 18.02)	4.53 (0.18, 115.38)	3.07 (0.22, 44.70)	-----
<b>Low-dose LAAM</b>	4.00 (0.76, 19.70)	0.67 (0.11, 3.88)	0.49 (0.07, 3.62)	0.37 (0.02, 7.49)	1.13 (0.30, 3.95)	0.18 (0.01, 2.41)	1.16 (0.13, 9.21)	0.78 (0.16, 3.72)	0.26 (0.01, 5.17)
<b>Low-dose Methadone</b>	4.22 (1.24, 15.04)	0.71 (0.16, 3.20)	0.52 (0.09, 3.05)	0.40 (0.02, 6.11)	1.20 (0.54, 2.73)	0.19 (0.02, 1.89)	1.24 (0.22, 6.78)	0.83 (0.34, 2.05)	0.27 (0.02, 4.30)
<b>Low-dose Naltrexone Implant</b>	37.21 (5.62, 267.46)	6.19 (0.82, 53.40)	4.57 (0.50, 46.85)	3.49 (0.23, 53.24)	10.54 (2.06, 57.67)	1.67 (0.14, 18.67)	10.93 (1.16, 106.55)	7.30 (1.85, 30.62)	2.38 (0.16, 36.62)
<b>Low-dose Oral Naltrexone</b>	27.06 (2.44, 321.99)	4.49 (0.36, 63.20)	3.33 (0.23, 53.25)	2.53 (0.15, 44.20)	7.66 (0.83, 76.08)	1.22 (0.07, 18.77)	7.80 (0.55, 128.37)	5.31 (0.74, 40.75)	1.74 (0.10, 30.64)
<b>Low-dose Suboxone® (Buprenorphine + Naloxone)</b>	12.38 (1.73, 93.60)	2.06 (0.26, 18.49)	1.52 (0.16, 15.65)	1.15 (0.05, 28.74)	3.48 (0.63, 19.63)	0.55 (0.03, 9.37)	3.59 (0.80, 16.10)	2.42 (0.37, 16.55)	0.79 (0.03, 20.46)
<b>Naltrexone Implant + Oral Naltrexone Placebo</b>	4.19 (0.29, 65.14)	0.70 (0.04, 12.42)	0.51 (0.03, 10.26)	0.39 (0.02, 8.56)	1.18 (0.10, 14.97)	0.19 (0.01, 3.74)	1.21 (0.07, 24.30)	0.81 (0.08, 8.42)	0.27 (0.01, 5.77)
<b>Placebo</b>	38.55 (6.40, 250.21)	6.41 (0.92, 49.53)	4.73 (0.56, 44.48)	3.60 (0.33, 39.20)	10.92 (2.36, 52.48)	1.73 (0.18, 15.88)	11.19 (1.30, 103.18)	7.56 (2.37, 25.53)	2.48 (0.23, 27.04)

**Table 7.4.4a Categorization of Outcomes Reported Across OSAT Trials**

<b>Domains</b>	<b>Outcome Domains</b>	<b>Definition of Outcome</b>	<b>Measurement of Outcome</b>
<b>Abstinence and Substance Use Behaviour</b>	<i>Illicit Opioid Use</i>	Frequency of Illicit Opioid Use (Mean number of negative opioid urine screens or percentage of positive opioid screens, days of illicit use, assessed per treatment arm)	Urine toxicology screening
			A composite score from the Addiction Severity Index (European version)
			Self-report
			Hair sample toxicology screening
			Scores from Addiction Severity Index (American interview) domain assessing number of days of opiate use in last month
			Visual Analog Scale (daily heavy drug abuse was recorded as 10 and ‘drug free’ was recorded as 0)
		Weekly Activity Summary (WAS)	
		‘Dirty rate’ measured using the number of opiate-positive urine screenings divided by the number of weeks of study participation	Urine toxicology screening
		Time to relapse measured using the number of days between baseline and occurrence of the first opiate-positive urine screening	Urine toxicology screening
		Failure to maintain abstinence	Urine toxicology screening
Heroin use in preceding month at three,	Self-reported frequency of use measured using the		

		six, and twelve month interviews	Opiate Treatment Index
		Response to treatment measured as a reduction of regular use of street heroin, which was defined as 50% or more of negative specimens on urinalysis during weeks	Urine toxicology screening
		Percentage of patients in a drug free period, defined as time elapsed between the first day of Naltrexone administration and the first evidence of opiate abuse (day on which positive urine test for opiate was obtained, or alternatively, the day on which the patient reported on opiate abuse)	Urine toxicology screening
		Abstinence from street heroin (zero use) in the past 30 days	Self-reported abstinence obtained by independent researchers in face-to-face interviews
		Assessment of near (<2 opioid positive urine screens) and full abstinence (0 opioid positive urine screens)	Urine toxicology screening
		Percentage of participants per treatment arm who maintained 12 consecutive opioid-free urine screens	Urine toxicology screening
		Slip defined as occasional heroin use, less than three consecutive positive urine screens, and no symptoms of withdrawal	Self-report and urine toxicology screening
		Days to heroin relapse (3 consecutive opiate-positive urine screens)	Urine toxicology screening
		Number of days a patient could remain abstinent measured by the longest duration of opiate negative urine screen	Urine toxicology screening
		Drug use history and routes of substance abuse	Risk Behaviour Survey
		The global severity of all aspects of their current drug problem	Self-report on a scale of 0 (no problem) to 100 (very severe)
		Opioid relapse defined as everyday heroin use, three consecutive positive urine tests, or reported symptoms of	Self-report and urine toxicology screening

		withdrawal		
		Degree of opioid substance abuse	Global rating scale: rating of 2 marked an improvement in rehabilitation and substance use	
<i>Non-opioid Substance Use</i>	Frequency of poly-substance use (eg. Percentage/mean number of positive stimulants/benzodiazepines urine screens per treatment arm cocaine, benzodiazepines, illicit methadone)		Self-report	
			Reported by family members or friends watching the participant	
			Weekly Activity Summary (WAS)	
			Visual Analog Scale (daily heavy drug abuse was recorded as 10 and 'drug free' was recorded as 0)	
			Weekly Drug Use Questionnaire	
			Urine toxicology screening	
			Days of alcohol use per treatment arm	Self-report
			Severity of nicotine dependence	The Fagerström Test for Nicotine Dependence
			Alcohol consumption	Breathalyser test
			The global severity of all aspects of their current drug problem	Measured on a scale of 0 (no problem) to 100 (very severe)
	Drug use history and routes of substance abuse	Risk Behaviour Survey		
<i>Health Risk Behaviour Related to Substance Use</i>	Injecting drug-use behaviour		Self-report	
			AIDS risk inventory	
			Opiate Treatment Index	
			Risk Assessment Battery (RAB) scores	
		Maudsley Addiction Profile		
<i>Money Spent or Gained on Illicit Opioid Consumption</i>	Amount of money spent on illicit opioid consumption per month		Addiction Severity Index	
		Amount of money gained from illicit opioid consumption per month	Addiction Severity Index	

<b>Physical Health</b>	<i>Drug Cravings</i>	Craving for Opioid Substances	Subjective Opiate Withdrawal Scale German Version
			Visual Analog Scale for Heroin Craving
			Craving visual analogue scale (CVAS) (administered every week): a 10 cm line - with an end corresponding to 0 and the other to 100 - was used to record the extent of subjective cravings for heroin, cocaine and alcohol in the preceding week
			Tiffany Heroin Craving Questionnaire
	<i>Overdose</i>	Overdose of illicit or prescribed opioid and non-opioid substances requiring medical attention	Self-report
			Medical chart review
	<i>Withdrawal Symptoms</i>	Opioid physical withdrawal symptoms	The Withdrawal Symptoms Checklist
			Self-reported euphoric feelings
			The Addiction Severity Index
			Subjective Opiate Withdrawal Scale (German version: SOES)
			Self-report
			The Wang Scale
			Addiction Research Centre Inventory
	<i>General Physical Health</i>	General physical health and well-being, an assessment of current physical symptoms, physical functioning, physical role limitations, bodily pain, physical comorbidity as well as medical history	Opioid Treatment Index
			Quality of Life scale (SF-12)
Self reported health measured assessing symptoms, overdoses, and mortality			
Maudsley Addiction Profile			
Short Form 36-item Health Survey			
Physicians perception of disease severity and overall improvement compared to baseline		Clinical Global Impressions Scale German Version	
Immune system functioning	Plasma concentrations of TNF-alpha, IL-2 beta, IL-1beta and CD14 lymphocyte		

		Cardiac Function assessed with corrected QT interval measurements	Electrocardiographic analysis
		Evaluation of patients meeting the categorical QTc prolongation thresholds across treatment groups (e.g. more than 470 milliseconds for males and more than 490 milliseconds for females)	Electrocardiographic analysis
<b>Psychiatric Health and Symptoms</b>	<i>Psychiatric symptoms</i>	Psychiatric Assessment for Depression, Anxiety, and other psychiatric symptoms	Mental health symptoms measured using the SF-12
			Symptom checklist-90 (SCL-90)
			Short Form 36-item
			Self-rating depression (SRD) questionnaire
			Minnesota Multifactorial Personality Inventory (MMPI)
			Symptom checklist (SCL-5)
			The Beck Depression Inventory
			State Trait Anxiety Inventory (STAI)
			Sensation Seeking Scale (SSS)
			Addiction Severity Index
			Maudsley Addiction Profile
	Scale of Anhedonia Syndrome		
		Self-reported assessments (somatization, depression, hostility, anxiety, paranoid ideation, interpersonal sensitivity)	
<i>Psychological Adjustment</i>	Psychological and social adjustment	Addiction Severity Index (family and social relations scores)	
		Opiate Treatment Index (social functioning scores)	
		Clinical Global Impression as assessed by the	

			Brief Psychiatric Rating Scale
<b>Global Quality of Life and Addiction Severity Assessments (outcomes of combined domains)</b>	<i>Composite Addiction Severity Scores</i>	Composite scores from addiction severity assessments that encompass patients physical, psychological, and social functioning, as well as their substance use behaviour	Composite International Diagnostic Interview
			European Addiction Severity Index
			Addiction Severity Index
	<i>Global Quality of Life</i>	Quality of life assessment encompasses the evaluations of physical, Social, physical, and psychological well-being	SCL-90-R subscales
			SCL-90-R global scores
			General Symptomatic Index
			Positive Symptom Total
			Positive Symptom Distress Index
			Lancashire Quality of Life Profile
			Visual Analog Scale (10 = very bad, 0 = very well) and with the temporal satisfaction with life scale (TSLS)
<b>Personal and Social Functioning</b>	<i>Criminal Behaviour</i>	Involvement in illegal activity	Self-reported days involved in illegal activities
			Self-reported time spent with: people still abusing substances, selling drugs, engaging in illegal activity
			Lifestyle Changes Questionnaire (patients indicated whether they had engaged in any of 9 activities to stop, reduce, or avoid cocaine/heroin use during the past week and whether they had committed crimes)
			Weekly Activity Summary (WAS 42)

	<i>Employment and Social Involvement</i>	Social stability assessed using current employment, volunteer, or social activities	Self-reported changes in vocational and social rehabilitation
			Self-reported consumption of meals, type of accommodation, and current employment activities
			Weekly Activity Summary (WAS 42)
			Behavioural observation where the research assistant recorded (yes/no) if patients had initiated new activities or increased the amount of time spent in any of three activity categories: (1) employment; (2) family/social; and (3) personal (spiritual, counselling or psychotherapy, physical fitness)
			Participation in non-study related addiction treatment programs (Narcotics Anonymous, e.c.t)
	<i>Relationships</i>	Evaluation of relationships and personal conflict with others	Personal and social functioning domain of the Maudsley Addiction Profile
			Social functioning measured using SF-36 health survey
			Personal and social function measured by self-reported time spent with people still abusing substances, selling drugs, engaging in illegal activity
	<i>Personal Stability</i>	Evaluation of personal stability through assessment of housing and food consumption	Self-reported consumption of meals and type of accommodation
<b>Resource Utilization</b>	<i>Service utilization</i>	Evaluation of how patients utilize available treatment and social services	Days Patients were seen by counsellors
			Total clinic attendance
<b>Intervention Adherence</b>	<i>Retention in Treatment</i>	Number of patients remaining on the allocated intervention at the end of follow-up	Adjudicated by the trial research staff
		Number of patients remaining on the	Adjudicated by the trial research staff

		allocated intervention, and maintained a standard of opioid-free urine set by the study coordinators at the end of follow-up		
		Time until patient withdraws from treatment		
	<i>Intervention Compliance</i>	Days patients attended clinic as an assessment of how well patient adheres to the treatment regime	Adjudicated by the trial research staff	Adjudicated by the trial research staff
			Treatment attendance, the number of days medicated divided by days in treatment	
			Involvement of a significant other in treatment who was asked to supervise and report on compliance at each study visit, either in person or by telephone	
		Assessment of medication adherence (evaluation of whether patient takes the medication prescribed)	Visual inspection of urine, inclusion of riboflavin 50 mg in the active and placebo naltrexone capsules with visual inspection for its presence using ultraviolet light at the long wave setting (444 nm) in a room with low ambient light	
			Count of remaining capsules at each appointment	
		Involvement in services provided by treatment centres	Study patients were required to respond to a random medication recall once each 4 weeks to monitor and deter potential misuse of methadone	Assessment of the counselling visits, which were based on the length (minutes) and number of contacts the patient had with either individual or

			group treatments
	<i>Successful Medication Induction</i>	At least one dose of medication by the 6th day of the study	Assessed by clinical research staff
<b>Intervention Acceptance</b>	<i>Intervention Preference</i>	Assessment of final drug of choice (at end of cross-over trial participants could chose which therapy to remain on)	Self-report
		Medication preferences (includes a proxy assessment of dosing adequacy)	The Helping Alliance Questionnaire II (HAQ-II; patient version), which is a 19-question self-administered instrument that measures the quality of therapeutic alliance between patients and therapists from the point of view of the patients
			The Client Satisfaction Questionnaire (CSQ), a self-administered questionnaire that assesses overall satisfaction with treatment
			Measured using a visual analogue questionnaire of drug properties which required them to “rate each drug on six different factors: is the drug holding (suppressing withdrawal); how much buzz do you get from the drug; do you experience side effects, do the side effects bother you; do you like the drug, and do you feel more normal?”

**Table 7.4.4b Results from Evidence Based Comparison of Opioid Substitution Treatments**

Intervention A	Intervention B	Number of Trials Evaluating Comparison	Number of Patients in Comparison	Domain: Outcome Domain	Number of Trials for Showing Benefit for Intervention A	Number of Trials showing Benefit for Intervention B	Final Evaluation
High-dose Methadone	Injectable High-dose Heroin + High-dose Methadone	2 <sup>61,70</sup>	236	Global Quality of Life and Addiction Severity Assessment: Composite Addiction Severity Scores	0	2 <sup>61,70</sup>	Intervention B Superior <sup>61,70</sup>
High-dose Levoacetylmethadol (LAAM)	High-dose Methadone	4 <sup>19,71-73</sup>	481	Abstinence and Substance Use Behaviour: Illicit Opioid Use	2 <sup>19,73</sup>	0	Intervention A Superior <sup>19,73</sup>
High-dose Methadone	Low-dose Buprenorphine	8 <sup>74-81</sup>	780	Abstinence and Substance Use Behaviour: Illicit Opioid Use	3 <sup>77,78,81</sup>	2 <sup>75,76</sup>	Inconclusive <sup>75-78,81</sup>
High-dose Methadone	Low-dose Buprenorphine	3 <sup>80-82</sup>	306	Abstinence and Substance Use Behaviour: Non-Opioid Substance Use	2 <sup>77,81</sup>	0	Intervention A Superior <sup>77,81</sup>
High-dose Methadone	Low-dose Buprenorphine	3 <sup>78-80</sup>	280	Physical Health: Drug Craving	1 <sup>78</sup>	0	Inconclusive <sup>78</sup>
High-dose Suboxone	Placebo	1 <sup>83</sup>	218	Abstinence and Substance Use Behaviour: Illicit Opioid Use	1 <sup>83</sup>	0	Intervention A Superior <sup>83</sup>
High-dose Suboxone	Placebo	1 <sup>83</sup>	218	Physical Health: Drug Craving	1 <sup>83</sup>	0	Intervention A Superior <sup>83</sup>

High-dose Buprenorphine	Placebo	2 <sup>83,84</sup>	324	Abstinence and Substance Use Behaviour: Illicit Opioid Use	2 <sup>83,84</sup>	0	Intervention A Superior <sup>83,84</sup>
High-dose Buprenorphine	Placebo	1 <sup>83</sup>	218	Physical Health: Drug Craving	1 <sup>83</sup>	0	Intervention A Superior <sup>83</sup>
Low-dose Buprenorphine	Low-dose Methadone	8 <sup>17,74,76-78,85-87</sup>	961	Abstinence and Substance Use Behaviour: Illicit Opioid Use	2 <sup>74,76</sup>	1 <sup>77</sup>	Inconclusive <sup>74,76,77</sup>
Low-dose Buprenorphine	Low-dose Methadone	2 <sup>17,86</sup>	226	Global Quality of Life and Addiction Severity Assessment: Composite Addiction Severity Scores	0	0	No Difference <sup>17,86</sup>
Low-dose Buprenorphine	Low-dose Methadone	2 <sup>78,86</sup>	236	Physical Health: Drug Craving	0	0	No Difference <sup>78,86</sup>
Low-dose Buprenorphine	Low-dose Methadone	4 <sup>17,82,85,86</sup>	478	Abstinence and Substance Use Behaviour: Illicit Non-Opioid Substance Use	0	0	Inconclusive <sup>17,82,85,86</sup>
High-dose Heroin	High-dose Methadone	3 <sup>14,15,88</sup>	1368	Abstinence and Substance Use Behaviour: Illicit Opioid Use	3 <sup>14,15,88</sup>	0	Intervention A Superior <sup>14,15,88</sup>
High-dose Heroin	High-dose Methadone	2 <sup>14,64</sup>	322	Abstinence and Substance Use Behaviour: Illicit Non-Opioid Substance Use	1 <sup>14,64</sup>	0	Intervention A Superior <sup>14,64</sup>
High-dose Heroin	High-dose Methadone	2 <sup>14,64</sup>	322	Personal and Social Functioning: Employment and Social Involvement	1 <sup>14</sup>	0	Intervention A Superior
High-dose Heroin	High-dose Methadone	1 <sup>14</sup>	226	Psychiatric Health and Symptoms: Psychiatric Symptoms	1 <sup>14</sup>	0	Intervention A Superior <sup>14</sup>
High-dose Heroin	High-dose Methadone	1 <sup>15</sup>	1015	Physical Health: General Physical Health	0	0	No Difference <sup>15</sup>
Low-dose Methadone	High-dose Methadone	6 <sup>40,43,65,76,78,89</sup>	771	Abstinence and Substance Use Behaviour: Illicit Opioid Use	0	5 <sup>40,43,65,76,78,89</sup>	Intervention B Superior <sup>40,43,65,76,78,89</sup>
Low-dose Methadone	High-dose Methadone	2 <sup>78,89</sup>	209	Physical Health: Drug Craving	0	2 <sup>78,89</sup>	Intervention B Superior

							78,89
Low-dose Methadone	High-dose Methadone	3 <sup>40,43,89</sup>	379	Abstinence and Substance Use Behaviour: Illicit Non-Opioid Substance Use	0	0	No Difference <sup>4</sup> 0,43,89
Low-dose Oral Naltrexone	Placebo	6 <sup>41,90,94</sup>	812	Abstinence and Substance Use Behaviour: Illicit Opioid Use	2 <sup>41,90</sup>	0	Inconclusive <sup>41,90</sup>
Low-dose Oral Naltrexone	Placebo	3 <sup>41,91,94</sup>	396	Physical Health: General Physical Health	0	0	No Difference <sup>4</sup> 1,91
Low-dose Oral Naltrexone	Placebo	2 <sup>90,94</sup>	84	Physical Health: Drug Craving	1	0	Intervention A Superior
Low-dose Oral Naltrexone	Placebo	1 <sup>90</sup>	302	Intervention Acceptance: Intervention Preference	0	0	No Difference <sup>9</sup> 0
Low-dose Oral Naltrexone	Placebo	3 <sup>41,91,94</sup>	396	Intervention Adherence: Intervention Compliance	0	0	No Difference <sup>4</sup> 1,91
Naltrexone Implant	Placebo	1 <sup>41</sup>	204	Abstinence and Substance Use Behaviour: Illicit Opioid Use	1 <sup>41</sup>	0	Intervention A Superior <sup>41</sup>
Naltrexone Implant	Placebo	1 <sup>41</sup>	204	Intervention Adherence: Intervention Compliance <sup>41</sup>	0	0	No Difference <sup>4</sup> 1
Naltrexone Implant	Oral Naltrexone	1 <sup>41</sup>	204	Abstinence and Substance Use Behaviour: Illicit Opioid Use	1 <sup>41</sup>	0	Intervention A Superior <sup>41</sup>
Naltrexone Implant	Oral Naltrexone	1 <sup>41</sup>	204	Intervention Adherence: Intervention Compliance	0	0	No Difference <sup>4</sup> 1
Low-dose Buprenorphine	Placebo	2 <sup>93,95</sup>	233	Abstinence and Substance Use Behaviour: Illicit Opioid Use	1 <sup>93</sup>	0	Intervention A Superior <sup>93</sup>
High-dose Methadone	Waitlist	1 <sup>96</sup>	301	Abstinence and Substance Use Behaviour: Illicit Opioid Use	1 <sup>96</sup>	0	Intervention A Superior <sup>96</sup>
High-dose Methadone	Waitlist	1 <sup>96</sup>	301	Abstinence and Substance Use Behaviour: Illicit Non-Opioid Substance Use	0	0	No Difference <sup>9</sup> 6
High-dose	High-dose Methadone	2 <sup>4343</sup>	1303	Abstinence and Substance Use	0	0	No

Suboxone				Behaviour: Illicit Opioid Use			Difference <sup>4</sup> 343
High-dose Suboxone	High-dose Methadone	2 <sup>43,97</sup>	1303	Abstinence and Substance Use Behaviour: Illicit Non-Opioid Substance Use	0	0	No difference <sup>43</sup> 43
High-dose Suboxone	High-dose Methadone	1 <sup>98</sup>	1269	Physical Health: General Physical Health	0	0	No Difference <sup>4</sup> 343
High-dose Suboxone	High-dose Methadone	2 <sup>43,97</sup>	1303	Psychiatric Health and Symptoms: Psychiatric Symptoms	0	0	No difference <sup>97</sup>
High-dose Suboxone	High-dose Methadone	2 <sup>43,97</sup>	1303	Global Quality of Life and Addiction Severity Assessment: Global Quality of Life	0	0	No Difference <sup>9</sup> 7
Dihydrocodeine (30 or 60 per day)	Methadone (no specified dosing)	1 <sup>99</sup>	218	Abstinence and Substance Use Behaviour: Illicit Opioid Use	0	0	No Difference <sup>9</sup> 9
Dihydrocodeine (30 or 60 per day)	Methadone (no specified dosing)	1 <sup>99</sup>	218	Abstinence and Substance Use Behaviour: Health Risk Behaviour (related to substance use)	0	0	No Difference <sup>9</sup> 9
Dihydrocodeine (30 or 60 per day)	Methadone (no specified dosing)	1 <sup>99</sup>	218	Personal and Social Functioning Relationships	0	0	No Difference <sup>9</sup> 9
Dihydrocodeine (30 or 60 per day)	Methadone (no specified dosing)	1 <sup>99</sup>	218	Personal and Social Functioning: Criminal Behaviour	0	0	No Difference <sup>9</sup> 9
Dihydrocodeine (30 or 60 per day)	Methadone (no specified dosing)	1 <sup>99</sup>	218	Personal and Social Functioning: Employment and Social Involvement	0	0	No Difference <sup>9</sup> 9
Dihydrocodeine (30 or 60 per day)	Methadone (no specified dosing)	1 <sup>99</sup>	218	Physical Health: General Physical Health	0	0	No Difference <sup>9</sup> 9
Dihydrocodeine (30 or 60 per day)	Methadone (no specified dosing)	1 <sup>99</sup>	218	Physical Health: Overdose	0	0	No Difference <sup>9</sup> 9
High-dose Buprenorphine	Low-dose Buprenorphine	1 <sup>100</sup>	736	Abstinence and Substance Use Behaviour: Illicit Opioid Use	1 <sup>100</sup>	0	Intervention A Superior <sup>100</sup>
High-dose Buprenorphine	Low-dose Buprenorphine	1 <sup>100</sup>	736	Physical Health: Drug Craving	1 <sup>100</sup>	0	Intervention A Superior

ne							100
High-dose Buprenorphine	High-dose Methadone	2 <sup>101,102</sup>	456	Abstinence and Substance Use Behaviour: Illicit Opioid Use	1 <sup>101</sup>	0	Intervention A Superior <sup>101</sup>
High-dose Buprenorphine	High-dose Methadone	1 <sup>102</sup>	394	Abstinence and Substance Use Behaviour: Health Risk Behaviour (related to substance use)	0	0	No Difference <sup>102</sup>
High-dose Methadone	High-dose Interim Methadone	1 <sup>103</sup>	203	Global Quality of Life and Addiction Severity Assessment: Composite Addiction Severity Scores	0	0	No difference
High-dose Methadone	High-dose Interim Methadone	1 <sup>103</sup>	203	Abstinence and Substance Use Behaviour: Illicit Opioid Use	0	0	No difference
High-dose Methadone	High-dose Interim Methadone	1 <sup>103</sup>	203	Abstinence and Substance Use Behaviour: Illicit Non-Opioid Use	0	0	No difference
High-dose Methadone	High-dose Interim Methadone	1 <sup>103</sup>	203	Abstinence and Substance Use Behaviour: Money Spent on Illicit Substance Consumption	0	1 <sup>103</sup>	Intervention B Superior <sup>103</sup>
High-dose Methadone	High-dose Interim Methadone	1 <sup>103</sup>	203	Personal and Social Functioning: Criminal Behavior	0	1 <sup>103</sup>	Intervention B Superior <sup>103</sup>
High-dose Interim Methadone	Waitlist	1 <sup>104</sup>	319	Global Quality of Life and Addiction Severity Assessment: Composite Addiction Severity Scores	0	0	No Difference
High-dose Interim Methadone	Waitlist	1 <sup>104</sup>	319	Abstinence and Substance Use Behaviour: Illicit Opioid Use	1 <sup>104</sup>	0	Intervention A Superior <sup>104</sup>
High-dose Interim Methadone	Waitlist	1 <sup>104</sup>	319	Abstinence and Substance Use Behaviour: Illicit Non-Opioid Use	0	0	No Difference
High-dose Interim Methadone	Waitlist	1 <sup>104</sup>	319	Abstinence and Substance Use Behavior: Money Spent on Illicit Substance Consumption	1 <sup>104</sup>	0	Intervention A Superior <sup>104</sup>

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## **CHAPTER 8**

### **THESIS CONCLUSION**

#### **8.1 Overview**

The work presented in this thesis highlights challenges many clinicians face when determining the optimal treatment for patients with opioid addiction. Acknowledging these disorders are multifaceted and may require adjunct psychosocial therapies, this work provides evidence to suggest patients with chronic pain respond poorly to methadone and no other OST demonstrates advantage for managing this subgroup of patients. This work identifies a major source of heterogeneity in the previous literature and provides an important consensus on the prognostic value of the BPI—a commonly employed pain measurement. Using data from the first network meta-analysis in the field we discuss 1) the most optimal therapies for opioid addiction patients, 2) major problems in outcome selection, 3) feasibility issues associated with OST administration, and 4) a summary of the limitations of this evidence base. This work tackles major questions in the field of opioid addiction and shines light on future directions research can help improve the current management of disease.

#### **8.2 The Role of Pain In Opioid Addiction Patients**

Findings from our initial review of the evidence (Study 1) suggest a lack of consensus as to the real effect of chronic pain on illicit opioid use behaviour. Upon screening 826

articles, we identified five studies evaluating the impact of pain on substance use behavior among MMT patients. Only three studies showed a significant relationship between the presence of pain and an increase in substance abuse, albeit the studies varied largely in the definitions and measurement of both pain and “opioid use behavior.” Whether it be the lack of a single “gold standard” measurement of response, or a lack of consistent measurement of pain, it is difficult to summarize and compare the results of these relatively small investigations. Findings from this review confirmed a need for future research to assess the effect of chronic pain on the treatment prognosis of MMT patients and explore the sources of heterogeneity in previous studies. We further assessed these questions using data from the GENOA research collaborative. Findings from Study 2 and Study 3 demonstrate chronic pain to be important predictor of continued opioid abuse among addiction patients receiving MMT. In a sample of 235 MMT patients, we found patients reporting comorbid pain were also found to have an increase in positive opioid urine screens (OR: 1.02 95% CI 1.00, 1.03;  $p=0.01$ ), indicating an increase in illicit opioid use. We also identified an important inflammatory biomarker (IFN- $\gamma$ ) to distinguish pain in the MMT setting. Analysis of inflammatory profile showed IFN- $\gamma$  to be significantly elevated among patients reporting comorbid pain.

While results from Study 2 appear promising, they were not without their own limitations. Effect estimates were small, whereby chronic pain was only slightly associated with an increase in positive opioid urine screens (OR: 1.02 95% CI 1.00, 1.03;  $p=0.01$ ). This study also presents data from the GENOA cross-sectional pilot study, inhibiting us from making any inference of causality between pain and opioid abuse. Additionally, we did

not use on any, “validated” assessment tools to ascertain chronic pain, we relied solely on an invalidated self-reported measure. However, these limitations are corrected for in Study 3 using data collected from the GENOA prospective cohort investigation. In Study 3 illicit opioid use behavior was determined using prospectively collected urine data, reflecting opioid consumption patterns for the three months following pain assessment. Thus, the association between pain and opioid consumption in Study 3 can be interpreted as an effect, or “risk” association between pain and continued opioid abuse. Study 3 also uses multiple pain measures to evaluate the prognostic value of different pain classification including the BPI (a validated assessment) in a sample of patients with opioid addiction.

Findings from Study 3 show that while the BPI may be more sensitive in capturing pain among patient with opioid addiction, this tool is of less value for predicting the impact of pain on illicit opioid use. The BPI was highly sensitive, classifying a large number of GENOA participants with pain (n=281 of the 297 classified with pain by both tools, 94.6% of total pain cases) in comparison to the simple self-reported measure as determined with the GENOA CRF (n=154 of 297 classified with pain according to both measures, 51.8% of total pain cases). Participants classified as having pain according to both measures were found to have an estimated 7.79% increase in positive opioid urine screens and a four times greater odds of engaging in a “high risk” level of illicit opioids use. The prognostic relevance of pain classification was not maintained for the additional participants classified by the BPI (n=143 discordant), whereby pain classification was not predictive of positive opioid urine screens or a “high-risk” level of opioid consumption.

Findings from Study 3 provide consensus as to the real effect of pain on opioid consumption in MMT patients. Among the previous studies evaluating this question (identified in Study 1), those measuring pain using the BPI report no effect of pain on illicit opioid consumption. To the contrary, the studies reporting a significant effect of pain on opioid abuse behaviour did not classify pain using the BPI. We acknowledge the BPI may indeed appropriately identify participants with comorbid pain, however its classification casts a net so wide it loses prognostic value. We contend the previous findings suggesting pain is not an important predictor for treatment prognosis, whereby results from this well-conducted methodological study suggest 1) pain is an important predictor that should be screened for by OST clinicians and 2) directly inquiring into patients' history of pain using question such as, "are you currently experiencing or have been diagnosed with chronic pain?" will distinguish patients at high-risk for dangerous opioid consumption behaviour.

The latter papers (Study 4 and Study 5) of this thesis aim to evaluate optimal treatments for opioid addiction patients using systematic review evidence. Both review protocols were previously published.

Study 4 sought to determine the optimal therapy for opioid addiction patients with comorbid pain. We performed a multiple treatments comparison, evaluating the mediating effects of pain across all OSATs. Upon screening 3540 unique articles with moderate agreement, 14 articles with a combined sample of 3128 patients fulfilled our inclusion criteria. While results from the meta-analysis suggest pain has no effect on illicit opioid consumption, these findings summarize the effect of pain on "any time use," as their

outcome of interest. As expected the studies evaluating illicit opioid consumption using other definitions of opioid use behavior (e.g. number of days of opioid use, % of positive opioid urine screens) did report an effect suggesting that pain increases risk for opioid abuse for patients maintained on OST. Participants with pain were also found to report higher rates of physical health impairment, treatment attrition, and psychiatric comorbidity (pOR: 2.18; 95%CI 1.6, 2.9,  $I^2:0.0\%$ ). Our review of the current Canadian, American, and British treatment guidelines for OSTs suggests neither guidelines discuss the important impact of pain on treatment prognosis nor provide any formal recommendations for treatment management in this subpopulation.

Findings from Study 4 further highlight substantive problems in the field. We did not find any evidence to suggest a specific OST is superior for managing comorbid pain and addiction. We caution the interpretation of evidence from the meta-analyses since these results preclude a substantial portion of the evidence. Major findings from Study 4 suggest 1) clinicians should be aware of the adverse impact of chronic pain among OST patients, 2) important outcomes are unstudied in the literature, and 3) major efforts are needed to improve the translation from evidence to practice.

The final paper (Study 5) assesses the optimal therapy for all opioid addiction patients. Utilizing systematic review methods, I provide the first multiple treatments comparison and network meta-analysis to combine evidence from all trials examining OSAT with the aim of distinguishing the most effective treatments for opioid addiction. Among 60 trials fulfilling the review inclusion criteria, we evaluated 28 trials testing 16 interventions in a

total of 3342 participants. In comparison to all other OSATs, heroin consistently ranked highest for increasing the odds of remaining in treatment when compared to high-dose buprenorphine, high-dose IV heroin + methadone, high-dose methadone, high-dose naltrexone, low-dose buprenorphine, low-dose methadone, low-dose naltrexone implant, low-dose oral naltrexone, low-dose Suboxone<sup>®</sup> and placebo. Heroin also showed significant benefit when directly compared against methadone for reducing illicit substance use and addiction severity, as well as improving personal/social functioning and general physical health outcomes. The qualitative summary in Study 5 revealed higher doses of any opioid medication (e.g. methadone, buprenorphine), even when compared within the same intervention (e.g. high vs. low dose methadone) showed benefit across most outcome domains (e.g. substance use, personal/social function).

These findings are not without limitation, particularly the problems with outcome selection for the majority of studies evaluating heroin as a treatment for addiction. Outcomes selected for these trials were guaranteed to show improvement and calls into question the real effectiveness of heroin treatment, or possibly the appropriateness of the outcomes we are using. These methodological shortcomings highlight the need for new assessment strategies for opioid addiction treatment. Future efforts should target more objective assessments for treatment effectiveness. Evaluating long-term follow-up using administrative data-linkage for trial participants is both novel and feasible for assessing large samples of addiction patients. Hard long-term outcomes such as incidence of hepatitis, HIV, cardiovascular abnormalities, and mortality require further attention.

Notwithstanding the problems associated with selecting outcomes for heroin specific

studies, the sheer volume of outcomes ( $k=77$ ) assessed across the 60 trials highlighted the lack of consensus as to what outcomes matter for determining success in addiction patients. Moving forward, Study 4 and Study 5 highlight the important limitations in the evidence as well as provide insight into the future directions needed to improve the field.

### **8.3 Future Directions**

Providing clinicians with information on the distinguishing risk factors for high-risk opioid consumption is imperative for enhancing the management of addictive disorders. Before designing a proper trial to evaluate optimal therapies for patients with comorbid pain, it will be useful to determine patient important outcomes in the field of addiction medicine. What best captures successful treatment outcomes for patients with addiction? Is it opioid use behavior? Employment? Family conflict? These questions can be feasibly evaluated in a large cohort of addiction patients.

Secondly, we need to determine how to best manage OST patients with chronic pain. Recognizing opioid addiction is a multifaceted disorder, future research may wish to explore targeting psychosocial interventions as adjunct therapies for OST patients with comorbid pain. After demonstrating the serious risks associated with managing pain among OST patients, treatment approaches such as anti-inflammatory medications may aid as safe alternatives for MMT patients with comorbid pain.

Thirdly, it is important we identify measures that are no longer useful for evaluating the impact of pain on substance use behaviour. As demonstrated in [Study 3](#), the BPI provide a pain classification that is prognostically irrelevant for distinguishing high-risk opioid

use. Future research may wish to develop and properly validate a new pain measure specific for opioid addiction patients.

#### **8.4 Concluding Remarks**

Chronic pain is highly prevalent among patients with opioid addiction. This may be directly related to the unprecedented rise in prescription opioid use in North America. Even more important than the notable presence of pain in the addiction setting are the effects of pain in patients receiving OST. Pain is demonstrated to negatively impact treatment effectiveness, posing a serious risk for adverse events among patients receiving OST. While no specific OST is demonstrated superior for managing patients with comorbid pain and addiction, more work evaluating patients' response to different OSTs is required before we can reach such firm conclusions. Notably absent from the literature are studies evaluating pain among patients with opioid addiction receiving Naltrexone. From a lack of consensus on patient important outcomes to concerns about the prognostic value of different pain measurements, we have yet to determine the most appropriate therapy for patients with comorbid pain. However, what we have established is 1) patients with chronic pain respond different to therapy and have elevated inflammatory markers, 3) choice of pain measurement can seriously impact on study findings and should be considered when evaluating the evidence, 4) directly inquiring into patients experience of pain using a simple self reported question distinguishes patients at risk for dangerous opioid use behavior, 5) overall the presence of pain negatively impact patients response to OST across multiple domains including psychiatric, physical health, and substance use behavior , 6) heroin therapy improves treatment retention in the general population of

patients with addiction receiving OSAT, and 7) investment into future research concerning patient important outcomes will help untangle some of the major issues in the field of addiction medicine.

The complex nature of addictive disorders prevents us from developing a one-stop solution for opioid dependence. It is important to recognize the literature is building and findings from this work only pave the way for future research. First establishing what outcomes we should judge treatments effectiveness by is required before we can firmly evaluate the effects of pain. Findings from this study require we probe into patients' physical pain history and monitor those reporting pain more closely. While we have not demonstrated effectiveness for any adjunct therapies for patients with comorbid pain and addiction, this may be a useful area of future research. Additional counseling, intense urine drug screen monitoring, or even the use of anti-inflammatory medications are all possible alternatives for patients with opioid addictions and pain receiving OST.

# Evaluation of clinical and inflammatory profile in opioid addiction patients with comorbid pain: results from a multicenter investigation

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**Background:** Chronic pain is the most commonly reported comorbidity among patients with opioid addiction receiving methadone maintenance treatment (MMT), with an estimated prevalence ranging between 30% and 55%. Evidence suggests that patients with comorbid pain are at high risk for poor treatment response, including continued illicit substance use. Due to the important relationship between the presence of pain and illicit substance abuse within the MMT setting, it is imperative that we target our efforts toward understanding the characteristics of this patient population.

**Methods:** The primary objective of this study was to explore the clinical and inflammatory profile of MMT patients reporting comorbid pain. This multicenter study enrolled patients (n=235) on MMT for the treatment of opioid dependence. Clinical history and blood and urine data were collected. Blood samples were obtained for estimating the serum levels of inflammatory markers (tumor necrosis factor [TNF]- $\alpha$ , interleukin-1 receptor antagonist [IL-1ra], IL-6, IL-8, IL-10, interferon [IFN]- $\gamma$  and chemokine (C-C motif) ligand 2 [CCL2]). The study objectives were addressed using a descriptive statistical summary and a multivariable logistic regression model constructed in STATA version 12.

**Results:** Among the participants eligible for inclusion (n=235), serum IFN- $\gamma$  level and substance abuse behavior proved to be important delineating characteristics for the detection of comorbid pain. Analysis of inflammatory profile showed IFN- $\gamma$  to be significantly elevated among patients reporting comorbid pain (odds ratio [OR]: 2.02; 95% confidence interval [CI]: 1.17, 3.50;  $P=0.01$ ). Patients reporting comorbid pain were also found to have an increase in positive opioid urine screens (OR: 1.02; 95% CI: 1.00, 1.03;  $P=0.01$ ), indicating an increase in illicit opioid consumption.

**Conclusion:** MMT patients with comorbid pain were shown to have elevated IFN- $\gamma$  and higher rates of continued opioid abuse. The ability to objectively distinguish between patients with comorbid pain may help to both improve the prediction of poor responders to MMT as well as identify treatment approaches such as anti-inflammatory medications as safe alternatives for MMT patients with comorbid pain.

**Keywords:** methadone maintenance treatment, inflammatory markers, TNF- $\alpha$ , IFN- $\gamma$ , interleukins, CCL2, Brief Pain Inventory, opioid dependence

## Introduction

Attention toward improving treatments for opioid dependence is increasing in conjunction with efforts to control the abuse of opioids. These efforts are seriously challenged by the increase in opioid prescriptions worldwide, and the global population of opioid users is now estimated to be 21.9 million people.<sup>1</sup> Methadone – a synthetic opioid – is the most common treatment for opioid dependence.<sup>2</sup> It is given to alleviate



the symptoms of withdrawal and prevent relapse.<sup>2</sup> Studies examining patients on methadone maintenance treatment (MMT) report chronic pain as a common comorbid disorder, with prevalence ranging from as low as 37% in some studies<sup>3</sup> to as high as 55.3% in others.<sup>4</sup> Chronic pain is both prevalent and concerning for patients with opioid addiction. Patients with comorbid chronic pain report a higher incidence of continued opioid abuse (COA).<sup>3,5,6</sup> Concomitant use of illicit opioids in combination with MMT poses a serious risk of abnormal cardiac conductivity,<sup>7,8</sup> overdose,<sup>9,10</sup> and death.<sup>9</sup> MMT patients with comorbid chronic pain are thought to be in the highest risk category for such adverse events due to the larger amount of illicit opioid consumption that chronic pain patients report.<sup>3,5,6</sup> Such reported outcomes, in combination with the high reported prevalence of pain, dictate the need for further investigation into the characteristics and treatment effects of pain in patients with opioid use disorder. Determining the important delineating features of pain among MMT patients will help clinicians to develop a stronger understanding of the clinical profile and risks associated with comorbid pain.

Inflammatory profile is a recent development in the search for objective measures of pain and serves as a possible source of discrimination between patients with and without chronic pain. Both cytokines and chemokines operate as neuromodulators, regulating neuroinflammation and neurodevelopment.<sup>11</sup> The deregulation of cytokines and chemokines is associated with both neuroinflammation and neurodegeneration,<sup>12,13</sup> and any increase in neuroinflammation can result in neuropathic pain as well as inflammation.<sup>14–16</sup> Proinflammatory cytokines and chemokines have been noted to also provoke hyperalgesia.<sup>17,18</sup> One such study demonstrated a dose–response relationship between elevated cytokine levels (interleukin [IL]-1 $\beta$ , IL-2, IL-6, interferon [IFN]- $\gamma$ , and tumor necrosis factor [TNF]- $\alpha$ ) and chronic pain severity.<sup>18</sup> However, this study was restricted by a small sample size (94 patients with pain and six healthy controls), wherein most cytokines failed to reach significance after adjusting for multiple testing.<sup>18</sup>

Due to the important relationship between the presence of pain and illicit substance abuse, as well as the overwhelming presence of pain within the methadone setting, it is imperative that we target our efforts toward understanding the characteristics of this patient population. Understanding pain is not only important in preventing adverse health outcomes for patients, it is vital for reducing social expenditure on treatments that may stand ineffective for specific subpopulations. The studies examining the characteristics of chronic pain are

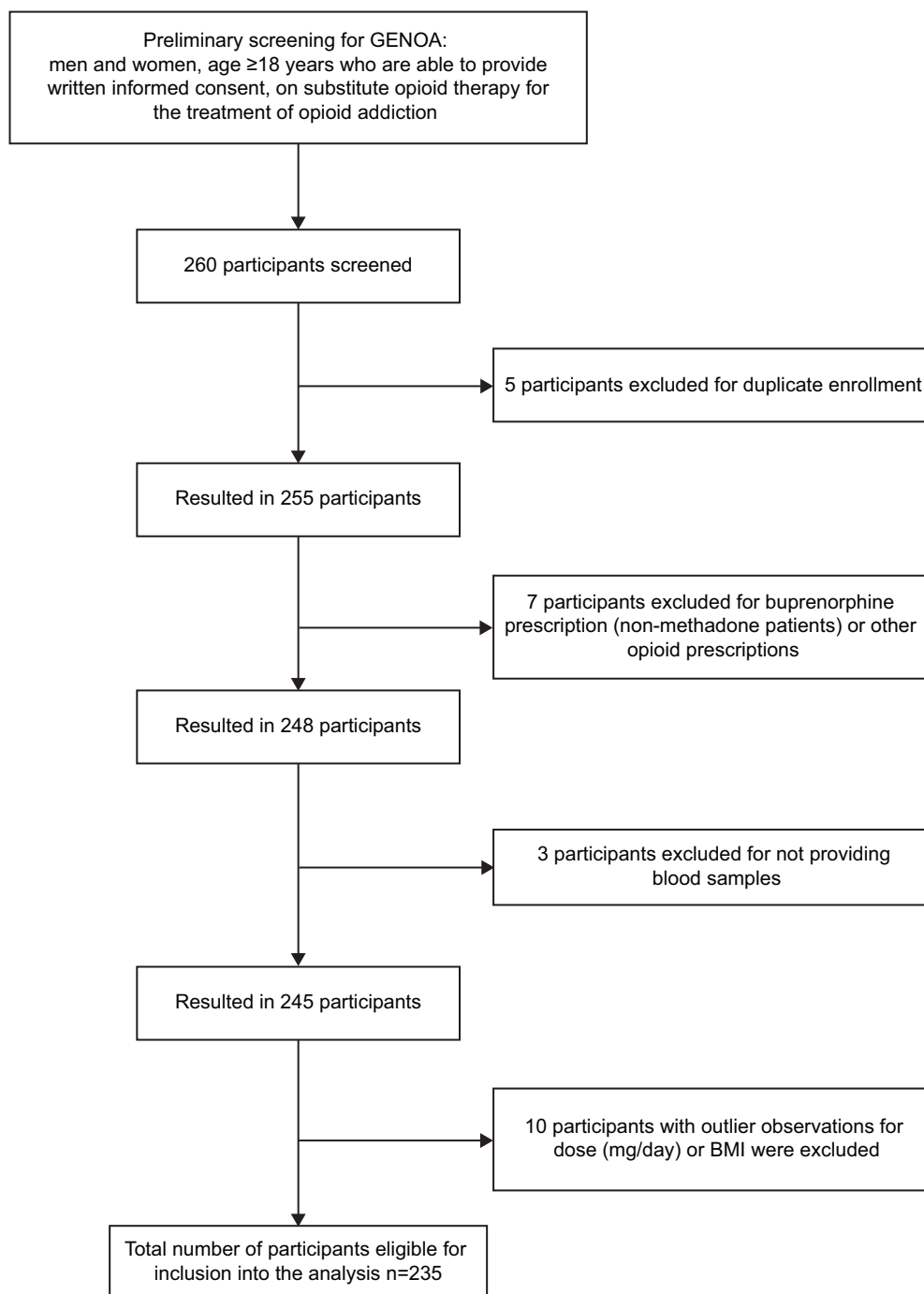
small in number and marked by inconsistent findings. There are an equal number of studies reporting a positive association between chronic pain and COA<sup>3,5</sup> as those reporting no significant findings.<sup>19,20</sup> Moreover, we have yet to properly identify the mechanisms of pain among MMT patients. These shortcomings prompted us to commence a sizable investigation of MMT patients to address our primary research objective, namely, to explore the clinical and inflammatory profile of MMT patients reporting comorbid pain. We addressed our objective using data collected for the GENetics of Opioid Addiction (GENOA) research collaborative.<sup>21</sup> GENOA is a multicenter cross-sectional investigation, accomplished through the partnership between McMaster University and the Ontario Addiction Treatment Centres (OATC).<sup>21</sup>

## Methods

### Overview of GENOA

Data have been collected for this study from the GENOA research collaborative between the OATC – the largest MMT network of opioid dependence treatment centers in North America – and the Population Genomics Program in the Faculty of Health Sciences at McMaster University. The detailed methodology of the GENOA investigation has been described previously.<sup>21</sup> The GENOA study is a multicenter cross-sectional analysis, which includes clinical data from four sites (methadone clinics) in southern Ontario. Participants were enrolled in the study between June and December 2011. The Hamilton Integrated Research Ethics Board approved this study.

The study inclusion criteria were as follows: men and women, age  $\geq 18$  years, ability to provide informed consent and willingness to provide a blood sample and receiving methadone for opioid-dependence treatment. All study participants were diagnosed with opioid dependence according to *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition criteria, based on clinical interviews at the time of entry into treatment with methadone. This study will focus on the data collected from 235 MMT patients (Figure 1), investigating the relationship between self-reported comorbidities and methadone response. Information on participants' physical comorbidities was gathered from face-to-face clinical interviews performed by trained OATC nurses. The presence of chronic and/or comorbid pain was determined by asking patients to respond to the following question: "Are you currently experiencing or have been diagnosed with chronic pain?" The use of this question to define chronic pain cases has been validated against the Brief Pain Inventory (BPI) in a previous study (Dennis et al, unpublished data, 2014).



**Figure 1** Flow diagram for eligibility screening and participant selection.

**Abbreviations:** GENOA, GENetics of Opioid Addiction; BMI, body mass index.

Results from the validation suggest that simply asking patients whether they have pain shows an 88.8% specificity, 84.4% positive predictive value, and C-statistic of 0.69. COA was determined through the assessment of weekly urinalysis for illicit opioid testing. Pain was also examined in relationship to the following inflammatory markers: TNF- $\alpha$ , IL-1 receptor antagonist (IL-1ra), IL-6, IL-8, IL-10, IFN- $\gamma$ , and chemokine

(C-C motif) ligand 2 (CCL2) in serum. Evidence shows that different anticoagulants (such as ethylene diamine tetraacetic acid, present in blood collection tubes) influence absolute cytokine levels in various manners<sup>22-24</sup> because serum samples were used in preference to plasma.

Interviewers obtained weight and height measurements from all participants. Information on social demographic

factors, medical history, methadone dose, methadone treatment duration, family history of drug use, and psychiatric disorders were obtained during the interview process. All participants received the Mini International Neuropsychiatric Interview drug and alcohol modules. Blood samples were taken for estimation of serum levels of inflammatory markers. Participant blood specimens were processed within 2 hours and stored on site in  $-20^{\circ}\text{C}$  freezers, then shipped monthly to the Hamilton research laboratory, and stored in liquid nitrogen until the time of analysis.

## Laboratory analyses

Laboratory measures included urine toxicology screens to measure illicit opioid abuse and Bio-Plex™ (Bio-Rad Laboratories, Hercules, CA, USA) cytokine assay<sup>25</sup> to measure serum inflammatory markers.

## Urine analysis

Qualitative and semiquantitative urinalysis was conducted using iMDx™ Prep assay.<sup>26</sup> The iMDx™ Prep assays are intended for the measurement of drugs of abuse, as well as the identification of adulteration in human urine samples, on the iMDx™ Analyzer and are used in drug rehabilitation clinics and physician offices by trained users. OATC clinics require patients to provide weekly urine samples as part of routine clinical care. While participants are also tested for cocaine, tetrahydrocannabinol, and benzodiazepines, we are primarily interested in the patients' use of opioids. Using the iMDx™ Prep assays, we are able to differentiate between specific types of opioids, such as naturally occurring opioids (heroin), prescribed synthetic opioids, and methadone.<sup>26</sup> In this investigation, opioid use is an indicator for methadone response. Because methadone is not used for the treatment of benzodiazepine or cocaine addiction, a patient's continued use of these substances does not indicate a methadone treatment failure. Urine toxicology screening was used to determine whether opioids (natural and synthetic) were present in the participants' urine.

Participants provided urine samples at supervised facilities; there were no missing urine samples from study participants. COA was determined by calculating the percentage of positive opioid urine screens provided by participants (number of positive opioid urine screens/total number of opioid urine screens). High COA percentage is indicative of a high number of positive opioid urine screens or, alternatively, a higher rate of illicit opioid consumption. We chose to include a measure of continued opioid abuse that adjusts for the entire duration of methadone treatment. Opioid dependence

is a remitting, relapsing disorder, and as such, restricting the measurement of response to such a short time frame of the patient's overall treatment course is of limited use.

## Serum levels of inflammatory markers: Bio-Plex assay

Serum samples were collected from participants using BD Vacutainer tubes and allowed to clot for 30 minutes. Samples were centrifuged at  $1,500\times g$  for 15 minutes at room temperature and the serum was frozen in liquid nitrogen until further analysis.

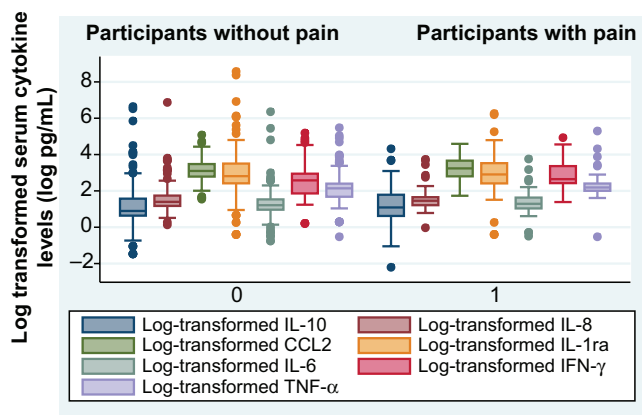
Samples were thawed only once and 50  $\mu\text{L}$  aliquots were transferred to 96-well plates. Serum cytokine levels were determined using the Bio-Plex assay (Bio-Rad Laboratories); levels of IL-6, IL-8, IL-1ra, TNF- $\alpha$ , IFN- $\gamma$ , IL-10, IL-1 $\beta$ , and CCL2 were measured, and standard curves were generated as per manufacturer's instructions. The Bio-Plex Manager 6.0 software was used for data analysis. Cytokine measurements were expressed as picograms per milliliter.

While IL-1B was originally tested for in all participants, more than 50% of the samples were inconclusive. With such a high proportion of data missing, we chose not to include IL-1B in any analyses.

## Statistical analysis

STATA version 12 was used to complete all analyses. All study data have been quality checked and entered into the Research Electronic Data Capture database at the Population Genomics Program, McMaster University.

Multiple imputation using chained equations was employed to adjust for missing data. Age, sex, COA, chronic pain, and methadone dose (milligrams per day) were the variables selected to aid in the multiple imputation prediction of missing values. When running analyses of inflammatory biomarkers, if the value was below detectable range, the lowest value before detection cutoff was imputed. All data were tested for normal distribution, where log transformations were made when necessary. All outlier data were removed before performing the primary analyses. To adjust for outlier variables, box plots were constructed for all predictors included in each model using STATA version 12, these being methadone dose, duration on MMT, age, body mass index, and all inflammatory biomarkers. The box plots resulted in the identification of ten outlier observations across predictors ( $n_{\text{participants}}=10$ ). The inflammatory biomarkers proved to have an overwhelming number of outlier observations due to their wide distribution, limiting our ability to adequately remove them from the sample (Figure 2). However, we



**Figure 2** Distribution of inflammatory biomarkers.

**Notes:** Cytokine data provided in this figure were originally measured in picograms per milliliter using participants' serum samples; the distribution here is provided using log-transformed values.

**Abbreviations:** IL, interleukin; IL-1ra, interleukin 1 receptor antagonist; TNF, tumor necrosis factor; CCL2, chemokine (C–C motif) ligand 2; IFN, interferon.

acknowledge how sensitive inflammatory profiles are and that currently no normal range has been established in the MMT patient population.

We determined the appropriateness of our sample size ( $n=235$ ) to address our primary analysis, the multivariable logistic regression of chronic pain. With response to treatment (COA) as our primary independent variable, in addition to eleven other a priori defined covariates, we determined that our model could withstand the addition of 20 covariates under the assumption that model stability is maintained with ten to 12 observations per covariate. Within this model, we have added 12 covariates, allowing for 20 observations per covariate in our sample of 235.<sup>27</sup> Reporting of this study follows the Strengthening of Reporting of Observational Studies in Epidemiology (STROBE) guidelines.<sup>28</sup>

## Primary analysis

All demographic characteristics are summarized using descriptive statistics, reporting means and standard deviations (SDs) for continuous values and percentages for dichotomous values. All demographic characteristic data are presented by pain status. A multivariable logistic regression model was constructed to address our primary objective, determining the clinical and inflammatory profile of patients reporting comorbid pain, where self-reported pain was the binary dependent variable. This model included multiple covariates identified as or trending toward significance during the univariate analysis (age, IFN- $\gamma$ , and response to treatment [COA]). The model also adjusted for important confounding variables, such as age, presence of inflammatory medications,

sex, presence of infectious disease, and methadone dose (milligrams per day).

## Results

### Demographic characteristics of GENOA participants

The recruitment process led to a completed sample of 249 participants eligible for this study. Any participants reporting prescribed opioids in their current medication list were removed from any analyses, leaving us with a sample of 235 MMT patients. A flow diagram of participant screening and selection is presented in Figure 1.

Among the participants eligible for inclusion into the analyses ( $n=235$ ), 40.42% were female, with mean age of 36.82 (SD: 10.36) years and mean body mass index of 26.59 (SD: 5.46) kg/m<sup>2</sup>. Participants self-reported the following comorbidities: 0.43% human immunodeficiency virus infection, 22.98% hepatitis, 5.11% liver disease, 24.68% chronic pain, 2.13% epilepsy, and 23.40% other, with a total of 58.40% of participants reporting at least one of the aforementioned comorbidities. When asked to indicate any “other” physical comorbidities, participants' responses included the following: diabetes ( $n=8$ ), cardiac functioning abnormalities and stroke history ( $n=7$ ), hypertension ( $n=3$ ), high cholesterol ( $n=1$ ), neurological deficit ( $n=2$ ), Crohn's disease ( $n=4$ ), asthma ( $n=8$ ), renal functioning problems ( $n=2$ ), gall stones ( $n=3$ ), fibromyalgia ( $n=1$ ), thyroid abnormalities ( $n=3$ ), arthritis ( $n=5$ ), respiratory problems ( $n=2$ ), allergies ( $n=3$ ), hernia ( $n=1$ ), gout ( $n=1$ ), spondylitis ( $n=1$ ), and endometriosis ( $n=1$ ). Reporting of these “other” comorbidities did not vary between patients with and without pain. All participants' demographic information presented by pain status is summarized in Table 1.

### Clinical and inflammatory profile of MMT patients with comorbid pain

The demographic characteristics summarized in Table 1 suggest that participants reporting pain are similar in demographic and clinical profiles to participants without pain. We find age, methadone dose (milligrams per day), sex, treatment duration (months), and onset age of opioid abuse to be relatively the same across patient groups (Table 1). A distinct aspect of the clinical profile for patients with pain is noted in the significantly different treatment response rates across groups. Another distinction between patients with and without pain is their inflammatory profile, whereby we found participants with pain to have elevated IFN- $\gamma$ , trending toward significance.

**Table 1** Participant demographic characteristics (divided by pain status) (n=235)

	Comorbid pain (n=58)	No comorbid pain (n=177)	P-value (univariate analysis)
Demographic characteristics			
Female (%)	41.38	40.11	0.90
Mean age (years)	39.45 (±10.29)	35.95 (±10.26)	0.02
Mean BMI (kg/m <sup>2</sup> )	27.46 (±5.08)	26.31 (±5.56)	0.15
Mean methadone dose (mg/d)	84.64 (±51.51)	85.74 (±50.14)	0.76
Mean response to MMT (mean % opioid-positive urine screens)	23.99 (±27.14)	15.82 (±20.11)	0.02
Duration on MMT (months)	41.31 (±38.99)	38.25 (±42.79)	0.61
Mean onset age of opioid abuse	23.21 (±11.28)	23.16 (±8.61)	0.98
Patients with HIV (%)	0.00	0.56	Unable to determine
Patients with hepatitis (%)	29.31	20.90	0.22
Inflammatory profile			
IL-10	1.15 (±1.14)	1.16 (±1.28)	0.86
IL-8	1.55 (±0.67)	1.56 (±0.76)	0.97
CCL2	3.25 (±0.60)	3.14 (±0.57)	0.26
IL-1ra	2.96 (±1.30)	2.96 (±1.33)	0.92
IL-6	1.35 (±0.72)	1.30 (±0.85)	0.62
IFN- $\gamma$	2.78 (±0.89)	2.55 (±0.89)	0.08
TNF- $\alpha$	2.25 (±0.77)	2.20 (±0.80)	0.69

**Notes:** All inflammatory biomarker concentrations have been log-transformed for this table (originally measured as picograms per milliliter). These are the results for the 235 participants eligible for study inclusion; outliers identified for BMI and methadone dose were removed for regression models (n=10). Data are presented as mean (± standard deviation).

**Abbreviations:** MMT, methadone maintenance treatment; IL, interleukin; IL-1ra, interleukin 1 receptor antagonist; BMI, body mass index; TNF, tumor necrosis factor; CCL2, chemokine (C–C motif) ligand 2; HIV, human immunodeficiency virus; IFN, interferon.

We chose to construct a multivariable logistic regression model to further assess these associations using patient-reported pain as our outcome of interest. Regression models allow the assessment of association between factors while also adjusting for other important confounders. Using results from the univariate analysis to guide our selection of covariates, we included COA (treatment response) and IFN- $\gamma$  as our primary independent variables. We adjusted this model

for presence of inflammatory medications, sex, presence of infectious disease, and methadone dose (milligrams per day). The results from the multivariable regression model are summarized in Table 2. Results suggested IFN- $\gamma$  to be significantly elevated among patients reporting chronic pain, while adjusting for important covariates (odds ratio [OR]: 2.02; 95% confidence interval [CI]: 1.17, 3.50;  $P=0.01$ ). The results also suggest that patients reporting comorbid pain

**Table 2** Clinical and inflammatory characteristics of comorbid pain: a multivariable logistic regression model (n=235)

Covariates	Odds ratio	95% Confidence interval	P-value
Age (years)	1.03	0.99, 1.06	0.08
Sex	1.08	0.56, 2.07	0.82
Response to MMT (% positive opioid urine tests)	1.02	1.00, 1.03	0.01
Infectious disease status	1.40	0.65, 3.00	0.38
Methadone dose (mg/d)	1.00	0.99, 1.01	0.94
Presence of inflammatory medications	1.26	0.41, 3.92	0.69
TNF- $\alpha$	0.69	0.37, 1.30	0.25
IFN- $\gamma$	2.02	1.17, 3.50	0.01
IL-6	1.18	0.60, 2.32	0.63
IL-1ra	0.84	0.51, 1.37	0.49
CCL2	1.60	0.88, 2.88	0.12
IL-8	0.73	0.43, 1.21	0.22
IL-10	1.01	0.69, 1.48	0.97

**Notes:** Sex is interpreted as female, in reference to males. Infectious disease status was a binary measure of the presence of HIV and/or hepatitis. All cytokine measurements have been log-transformed, and the original measurements were in picograms per milliliter.

**Abbreviations:** MMT, methadone maintenance treatment; IL, interleukin; IL-1ra, interleukin 1 receptor antagonist; TNF, tumor necrosis factor; CCL2, chemokine (C–C motif) ligand 2; HIV, human immunodeficiency virus; IFN, interferon.

have an increase in positive opioid urine screens (OR: 1.02; 95% CI: 1.00, 1.03;  $P=0.01$ ), indicating an increase in illicit opioid consumption.

## Discussion

### Summary of findings

Considerations of pain in the clinical setting for patients on MMT for opioid dependence are complicated by the inconsistent findings reported across studies. While some studies appear to be reporting a strong association between chronic pain and substance abuse among MMT patients,<sup>3,5</sup> other studies report no association.<sup>19,20</sup> There is also limited research on the inflammatory characteristics of pain patients within the MMT setting. Results from this investigation provide a thorough evaluation of the clinical and inflammatory characteristics of opioid-dependent patients with pain, wherein we show that 1) response to MMT is significantly influenced by the presence of pain and 2) MMT patients reporting chronic pain show elevated levels of IFN- $\gamma$ .

### Context of comorbid pain and opioid abuse in the current literature

MMT patients with severe pain are known to have increased methadone dose<sup>4</sup> and an increased rate of illicit substance use.<sup>4</sup> Findings from this study are consistent with some of those in literature,<sup>3,5</sup> where response to treatment was highly associated with chronic pain status. When determining the source of contention across studies examining pain and opioid abuse, we took a closer look at the differences in measurement and definition of response to MMT. While in this study we chose to use the percentage of opioid-positive urine screens as an objective proxy outcome measure for response to methadone treatment, other studies report response to treatment as the number of days of illicit heroin or opioid abuse in the previous month<sup>5,20</sup> or the percentage of patients who report using illicit opioids in the month.<sup>3,6,19</sup> In addition, a number of studies rely on different measurements for response such as self-report,<sup>3,6,19</sup> and some studies go so far as using validated tools to assess the severity of substance abuse behavior.<sup>5,20</sup>

In comparison to our investigation, the majority of clinical studies assess response to treatment over a very short time frame (7 days to 3 months).<sup>3,20,29</sup> It is known that opioid dependence is a chronic, remitting, relapsing disorder, with the average methadone treatment duration being 2 years. As such, capturing “response” over a short time frame of a patient’s overall treatment course appears of limited use. Determining response to MMT by reviewing patients for the

entire duration of MMT appeals as a more adequate approach for characterizing the course of and patient response to methadone. In this study, we looked at the number of positive opioid urine screens as a percentage of the total number of screens in an effort to adjust for these duration effects, which may explain why our results may differ from studies basing treatment response on a shorter time frame (ie, 7–9 days).<sup>20</sup>

Similar to the measurement of response, the measurement of chronic pain also varies across studies. This variation may also be a source of discrepancy in the reported findings in the current literature. The measurement of pain varies from validated pain measures in some studies<sup>3,20</sup> to the use of self-reported pain in others.<sup>6,19</sup> Even results from studies selecting “validated” pain measures such as the BPI<sup>3</sup> should be interpreted with caution, for no pain measurement tool has undergone specific psychometric testing or predictive/criterion validation within the MMT patient population.

### Inflammatory profile and comorbid pain

Our results have shown IFN- $\gamma$  to be elevated among MMT patients reporting comorbid pain. The role of IFN- $\gamma$  in pain can be inferred from animal studies in which IFN- $\gamma$  is noted to induce pain.<sup>30</sup> Tsuda et al<sup>30</sup> found that the IFN- $\gamma$  receptor mediates spinal microglia activation, ultimately leading to neuropathic pain.<sup>30</sup> When the spinal microglia is activated, it increases pain processing inside the dorsal horn to a significant level that triggers neuropathic pain.<sup>31–34</sup> This is one of the mechanisms by which inflammation causes and propagates pain.

Our findings are consistent with other studies, where IFN- $\gamma$  is elevated during periods of pain.<sup>18,35</sup> In one investigation, 21 patients with lumbar degenerative disc disease were compared against three controls, for inflammatory profile differences, where the authors identified immunoreactivity of IFN- $\gamma$  in patients with axial back pain.<sup>35</sup> Another study, examining 94 chronic pain patients and six healthy volunteers, found that proinflammatory cytokines such as IL-1 $\beta$ , IL-2, IL-6, IFN- $\gamma$ , and TNF- $\alpha$  correlated with increasing pain intensity.<sup>18</sup> In addition, proinflammatory cytokines have been demonstrated to directly oppose opioid actions, and one study has demonstrated that an increase in morphine and methadone administration is directly linked to an increase in spinal glial activation as well as elevated cytokine level.<sup>36</sup>

To date, no study has explored the association between comorbid pain and inflammatory profile within the MMT patient population. This investigation showed the significant association between elevated IFN- $\gamma$  level and the presence of chronic pain. The importance of these results rests on

our understanding of treatment strategies for patients with concurrent opioid dependence and chronic pain. The ability to objectively distinguish between patients with comorbid pain through the identification of IFN- $\gamma$  may be able to help distinguish treatment approaches such as anti-inflammatory medications as a safe alternative to opioid analgesics in this patient population.

## Strengths and limitations

The major limitation of this study is the use of self-reported chronic pain. The true prevalence of pain could have been under- or overestimated. Without the use of a validated pain assessment for opioid-dependent patients receiving MMT, the reported results should be subject to cautious interpretation. However, in a recent study, we have validated the use of patient-reported pain in comparison with the BPI assessment, where results suggest that simply asking patients whether they have pain shows an 88.8% specificity, 84.4% positive predictive value, and C-statistic of 0.69. Such results indicate that the use of patient-reported pain very closely identifies the same population as the BPI assessment. In addition, we should not discount the use of more objective markers for reported pain. This study found elevated levels of inflammatory markers, supporting the case for both the use of objective pain indicators and consideration of anti-inflammatory agents as adjunct therapy for MMT patients.

## Conclusion

While our study shows a significant association between pain and poor response to MMT, it also proves the importance of determining an objective measure of inflammation for MMT patients with comorbid pain. We determined that pain is significantly associated with an increase in positive opioid urine screens, as well as a substantial elevation of IFN- $\gamma$ . In an effort to adequately manage patients at an increased risk for methadone overdose and poor response, future research should determine the therapeutic impact of using anti-inflammatory analgesics to prevent the use of illicit opioids and reduce pain in opioid-dependent patients on MMT.

## Acknowledgments

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## Author contributions

Dr Zainab Samaan, Brittany B Dennis, and Dr Lehana Thabane were responsible for the development of the question and research protocol for this study. Brittany B Dennis was responsible for all statistical analyses performed in this investigation. Dr M Constantine Samaan designed and performed all laboratory analyses for the inflammatory profile. All authors contributed equally during manuscript development. Zainab Samaan had full access to data from this investigation, and she is accountable for the reliability of the data and the accuracy of all analyses performed. All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work.

## Disclosure

The authors report no conflicts of interest in this work.

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PROTOCOL

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# The impact of chronic pain on opioid addiction treatment: a systematic review protocol

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## Abstract

**Background:** The consequences of opioid relapse among patients being treated with opioid substitution treatment (OST) are serious and can result in abnormal cardiovascular function, overdose, and mortality. Chronic pain is a major risk factor for opioid relapse within the addiction treatment setting. There exist a number of opioid maintenance therapies including methadone, buprenorphine, naltrexone, and levomethadyl acetate (LAAM), of which the mediating effects of pain on treatment attrition, substance use behavior, and social functioning may differ across therapies. We aim to 1) evaluate the impact of pain on the treatment outcomes of addiction patients being managed with OST and 2) identify the most recently published opioid maintenance treatment guidelines from the United States, Canada, and the UK to determine how the evidence is being translated into clinical practice.

**Methods/design:** The authors will search Medline, EMBASE, PubMed, PsycINFO, Web of Science, Cochrane Database of Systematic Reviews, ProQuest Dissertations and theses Database, Cochrane Central Register of Controlled Trials (CENTRAL), World Health Organization International Clinical Trials Registry Platform Search Portal, and the National Institutes for Health Clinical Trials Registry. We will search [www.guidelines.gov](http://www.guidelines.gov) and the National Institute for Care and Excellence (NICE) databases to identify the most recently published OST guidelines. All screening and data extraction will be completed in duplicate. Provided the data are suitable, we will perform a multiple treatment comparison using Bayesian meta-analytic methods to produce summary statistics estimating the effect of chronic pain on all OSTs. Our primary outcome is substance use behavior, which includes opioid and non-opioid substance use. We will also evaluate secondary endpoints such as treatment retention, general physical health, intervention adherence, personal and social functioning, as well as psychiatric symptoms.

**Discussion:** This review will capture the experience of treatment outcomes for a sub-population of opioid addiction patients and provide an opportunity to distinguish the best quality guidelines for OST. If chronic pain truly does result in negative consequences for opioid addiction patients, it is important we identify which OSTs are most appropriate for chronic pain patients as well as ensure the treatment guidelines incorporate this information.

**Systematic review registration:** PROSPERO CRD42014014015 [http://www.crd.york.ac.uk/PROSPERO/display\\_record.asp?ID=CRD42014014015#.VS1Qw1wkKGM](http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42014014015#.VS1Qw1wkKGM)

**Keywords:** Chronic pain, Opioid maintenance, Addiction, Opioid substitution therapies, Opioid dependence, Buprenorphine/naloxone, Methadone, Methadone maintenance therapy, Naltrexone, Systematic review, Network meta-analysis

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## Background

Chronic non-cancer pain is a serious comorbidity impacting the lives of over 95 million people, an estimated 30.7% of the US population [1]. Chronic pain is defined as pain lasting longer than 3 months or past the standard time for tissue to heal [2]. Front-line treatments include the prescription of long-acting opioids, although there is minimal evidence to suggest that opioids provide any long-term relief for chronic pain [3]. Trends in current prescribing practice suggest that the rise in prescription opioid use [4] has been paralleled by a concerning increase in opioid-related deaths, addiction, and medication diversion [5-9]. Opioids are highly liable for misuse, which is evident from the reported incidence of addiction, ranging from 3.2% to 27% among the chronic pain population [10].

While methadone is employed in the management of chronic pain, its most common use is in the treatment of opioid addiction [11], known formally as methadone maintenance treatment (MMT). Under the supervision of addiction specialists, methadone (a synthetic opioid) is prescribed to alleviate the symptoms of withdrawal and prevent relapse [11]. Within the addiction population being treated with methadone, chronic non-cancer pain is the most commonly reported comorbidity, with an estimated prevalence ranging from 37% to 55.3% [12-14].

The intersection between pain management, opioid dependence, and addictive behavior inflates the challenges of treating both addiction and chronic pain. In addition to psychiatric disturbance and inadequate social support, chronic pain is known to be one of the greatest risk factors for opioid relapse within the methadone setting [15,16]. These effects are argued to be the result of opioid-induced hyperalgesia, characterized as a status of heightened nociceptive sensitization caused by opioid exposure [17]. This effect has been demonstrated repeatedly, whereby patients with non-cancer chronic pain taking methadone showed increased hyperalgesic response (assessed by cold pressor test but not stimulus) in comparison to their placebo-matched controls [17,18].

The risk for abnormal cardiovascular function [19,20], overdose [21,22], and mortality [21] is highest among patients abusing opioids in combination with MMT. Classifying chronic pain as a risk factor for continued opioid abuse [12,15,16,23] calls to question which addiction treatment is most appropriate for patients with comorbid pain. There exist a number of opioid maintenance therapies including methadone, buprenorphine, naltrexone, and levomethadyl acetate (LAAM), of which the mediating effects of pain on treatment attrition, substance use behavior, and social functioning may differ across therapies.

Is chronic pain an important mediating factor when evaluating patient response to opioid addiction treatment? Which opioid maintenance therapy is best for improving physical, psychiatric, and substance use behavior

outcomes in patients with opioid addiction and chronic pain? We aim to evaluate these questions using evidence gathered from all studies evaluating chronic pain in the opioid addiction patient population. The lack of current summary of evidence evaluating the mediating effects of pain suggests that our current effort to combine the evidence will serve to 1) distinguish the best therapy for opioid addiction patients with comorbid pain and 2) enable clinicians to tailor treatments based on an important and highly prevalent risk factor.

## Objectives

We aim to 1) evaluate the impact of comorbid chronic non-cancer pain on all opioid addiction treatment outcomes reported in the literature including treatment retention, illicit substance-use behavior, as well as physical and psychiatric symptoms, 2) determine how different opioid maintenance treatments compare in their effectiveness for patients with comorbid chronic non-cancer pain, 3) provided the data are suitable, combine the evidence from direct and indirect comparisons using network meta-analysis, and 4) identify the most recently published opioid maintenance treatment guidelines from the United States, Canada, and the UK to determine how the evidence is being translated into clinical practice for addiction management.

## Research questions

- 1.1 Among patients with opioid addiction being treated with (or randomized to) opioid substitution treatment (OST): 1) does chronic non-cancer pain interfere with the effect of OST, and 2) which OST is best for improving treatment response for patients with comorbid chronic non-cancer pain? We will evaluate response across multiple outcome domains including: substance use behavior, physical health, psychiatric symptoms, as well as personal and social functioning.
- 1.2 Do the most recently published United States, Canadian, and United Kingdom OST clinical practice guidelines capture and properly translate the evidence obtained from the studies evaluated in this review?

## Methods/design

### Systematic review methods

#### *Inclusion and exclusion criteria*

To be included in this review, the study must evaluate the impact of chronic pain on patient's response to opioid addiction treatment. The study must have provided a comparison of response to treatment outcomes (for example, continued opioid abuse, general physical health) between patients with and without chronic pain.

We also require the studies to have evaluated patients on an OST for opioid addiction. We will not place any restrictions on the types of OST or measurement of chronic pain. All study designs will be accepted into this review, (that is, randomized controlled trials, observational studies, or qualitative studies). No restrictions were placed on socioeconomic, geographic, or ethnic backgrounds of participants for this review.

To be eligible for inclusion, all studies must be primary (original research in patients with pain, no secondary reporting), completed (no interim analyses will be allowed in this review), and performed in a human population.

### **Outcome measures**

The primary outcome in this review is illicit opioid use, which can be measured in various ways including urine toxicology screening or self-report. We anticipate many definitions and measurements of opioid use. For example, some studies measure opioid use behavior as the number of days of opioid use in the last month, while others report the mean number of positive opioid urine screens or days until opioid relapse. We will accept any definition or measurement of illicit opioid use, provided the study performs an analysis comparing opioid use behavior based on patients' chronic pain status. We will also abstract data on all other efficacy end-points including non-opioid substance abuse, general physical health, psychiatric symptoms, personal and social functioning, intervention adherence (for example, treatment retention, dropout rate), resource utilization (for example, hospital admissions) as well as treatment preference. However, short-term outcomes (initial dosing, initial response in a period of <3 weeks, or early detoxification response) will not be evaluated.

### **Data sources and search strategy**

We will perform an electronic search using the Medline, EMBASE, PubMed, PsycINFO, Web of Science, Cochrane Database of Systematic Reviews, ProQuest Dissertations and theses Database, Cochrane Central Register of Controlled Trials (CENTRAL), World Health Organization International Clinical Trials Registry Platform Search Portal, and the National Institutes for Health Clinical Trials Registry. In addition, the reference lists of all Cochrane reviews addressing this topic will be reviewed. We will use the Cochrane reviews to validate our own searches of databases and ensure that we have captured the relevant articles in our field. This supplementary search will be applied to Cochrane reviews since they are considered the gold standard in systematic reviews.

We will use a comprehensive search strategy tailored for each database. Please refer to Table 1 for an outline of the search strategy. We consulted a McMaster University

Faculty of Health Science librarian as needed throughout the design and investigation phases of the study. The search will be restricted to human studies. Our search will not be restricted to the published literature. We acknowledge that studies in the unpublished literature may not be subject to the same scrutiny as the investigations published in peer-reviewed journals. However, the unpublished literature meeting the inclusion criteria will still be subject to the same rigorous risk of bias assessment as all studies included in this review. To ascertain the gray literature, we will perform a search using the ProQuest Dissertations and theses Database. The title, abstract, and full-text screening will be performed in duplicate by two independent reviewers (Dennis, B and Bawor, M).

### **Selection of studies**

Two independent reviewers will screen titles and abstracts and potentially eligible full-text articles using pre-defined inclusion criteria. Any disagreements or variability between reviewers will be resolved by discussion. If discussion does not lead to a resolution, a third author (Samaan, Z) will be consulted and have the final judgment over the disputed article. We will calculate and report the kappa statistic for each stage (title, abstract, full-text) of screening to display the level of agreement between reviewers.

This review will be reported in accordance with the PRISMA guidelines [24]. The review will include a flow diagram (Figure 1) of the article screening process.

### **Data abstraction**

The two authors (BD and MB) will independently extract data from the studies using a pre-established data extraction form (DEF), which is available upon request. All study information will be recorded onto the DEF and later entered onto an electronic Microsoft Excel sheet. The independent reviewers will extract all eligible studies in duplicate. Similar to the methods for disagreement resolution during the title and abstract screening, the independent reviewers will first discuss the disagreements they have during the data abstraction. When discussion does not lead to a resolution, a third reviewer (Samaan, Z) will provide the final decision over the disagreement.

Information extracted during the data abstraction will include author, date of publication, journal of publication, number of study participants, type of population (clinical, incarcerated, pregnant), eligibility criteria, OST(s), OST dose (by chronic pain status), definition of chronic pain, identification of primary outcome, definition of response outcome(s), measurement of chronic pain, measurement of response outcome(s), percentage/number of participants with chronic pain, statistical analysis performed, study findings, overall statistical findings, factors associated with treatment response (if reported), and author's conclusions.

**Table 1 Electronic search strategy for the identification of relevant studies across multiple databases**

Databases	Search strategies
MEDLINE Search = _____	<ol style="list-style-type: none"> <li>1. substance related disorders.mp. or Substance-Related Disorders/</li> <li>2. opioid related disorders.mp. or Opioid-Related Disorders/</li> <li>3. Opioid-Related Disorders/or Methadone/or Analgesics, Opioid/or Heroin Dependence/</li> <li>4. 1 or 2 or 3</li> <li>5. methadone.mp. or Methadone/</li> <li>6. Opiate Substitution Treatment/or Naloxone/ or Buprenorphine/or Opioid-Related Disorders/ or Narcotic Antagonists/</li> <li>7. buprenorphine.mp. or Buprenorphine/</li> <li>8. naltrexone.mp. or Naltrexone/</li> <li>9. Substance Abuse Treatment Centers/or Heroin/or Heroin Dependence/or Opioid-Related Disorders/or Randomized Controlled Trials as Topic/or Methadone/</li> <li>10. opioid substitution treatment.mp. or Opiate Substitution Treatment/</li> <li>11. Buprenorphine/or Analgesics, Opioid/or Opioid-Related Disorders/or Methadone/or Heroin Dependence/</li> <li>12. 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12</li> <li>13. chronic pain.mp. or Chronic Pain/</li> <li>14. 4 and 13 and 4</li> <li>15. limit 15 to humans</li> </ol>
Web of Science Search = _____	<ol style="list-style-type: none"> <li>1. Topic = ("methadone" OR "methadone maintenance therapy" OR "naltrexone" OR "suboxone" OR "buprenorphine" OR "heroin assisted treatment")</li> <li>2. Topic = ("opioid dependence" or "addiction")</li> <li>1. Topic = ("chronic pain" OR "pain" OR "opioid induced hyperalgesia")</li> <li>2. 1 AND 2 AND 3</li> </ol>
EMBASE = _____	<ol style="list-style-type: none"> <li>1. methadone treatment/or methadone.mp. or methadone/or methadone plus naloxone/</li> <li>2. heroin dependence/or maintenance therapy/or methadone/or opiate addiction/or diamorphine/or methadone treatment/</li> <li>3. buprenorphine/or buprenorphine.mp.</li> <li>4. naltrexone.mp. or morphine sulfate plus naltrexone/or naltrexone/</li> <li>5. opioid substitution treatment.mp. or opiate substitution treatment/</li> <li>6. methadone/ or diamorphine/or heroin dependence/</li> <li>7. levomethadyl acetate.mp. or levacetylmethadol/</li> <li>8. 1 or 2 or 3 or 4 or 5 or 6 or 7</li> <li>9. substance related disorder.mp. or addiction/</li> <li>10. naltrexone/ or buprenorphine/or opioid addiction.mp. or methadone/</li> <li>11. 9 or 10</li> <li>12. chronic pain.mp. or chronic pain/</li> <li>13. 8 and 11 and 12</li> <li>14. limit 13 to human</li> </ol>
PsychINFO Search = _____	<ol style="list-style-type: none"> <li>1. exp Drug Therapy/or exp Methadone Maintenance/or exp Heroin Addiction/</li> <li>2. exp Methadone/or exp Naloxone/or exp Drug Therapy/or exp Drug Dependency/or buprenorphine.mp.</li> <li>3. naltrexone.mp. or exp Naltrexone/</li> <li>4. exp Heroin Addiction/or exp Drug Rehabilitation/or exp Drug Dependency/or exp Clinical Trials/</li> <li>5. exp Drug Therapy/or exp Methadone Maintenance/</li> <li>6. 1 or 2 or 3 or 4 or 5</li> </ol>

**Table 1 Electronic search strategy for the identification of relevant studies across multiple databases (Continued)**

	7. exp Drug Abuse/or substance related disorder.mp. or exp Drug Dependency/
	8. substance abuse.mp. or exp Drug Abuse/
	9. 7 or 8
	10. chronic pain.mp. or exp Chronic Pain/
	11. 6 and 9 and 10
Cochrane Library: Cochrane Review and Cochrane Central Register of Controlled Trials = _____	Search title, abstract, keywords:  1. "methadone" OR "naltrexone" OR "buprenorphine" OR "opioid substitution treatment" OR "levo-methadyl acetate" OR "heroin assisted treatment" OR "heroin substitution treatment"  2. "substance abuse disorder" OR "opioid abuse" OR "substance-related disorder" OR "opioid addiction"  3. "chronic Pain" OR "pain" OR "hyperalgesia" OR "neuropathic pain"
Clinical Trials Registry through National Institutes for Health = _____	"methadone" OR "suboxone" OR "Buprenorphine" OR "substitute opioid therapy" OR "naltrexone" OR "heroin assisted treatment" OR "heroin adjustment therapy" AND "opioid addiction" AND "chronic pain", with additional criteria including: Completed studies, all trials had to be listed as Phase 3, 4
World Health Organization International Clinical Trials Registry Platform Search Portal = _____	"opioid addiction" OR 'opioid substitution treatment' OR 'opioid maintenance treatment' OR 'methadone maintenance treatment' AND "chronic pain"
ProQuest Dissertations and theses Database = _____	"opioid addiction" OR "opioid dependence" AND "pain" OR "Chronic Pain"

**Assessment of methodological quality**

Two independent reviewers will assess the methodological quality of the studies in duplicate using a modified Newcastle Ottawa scale for case-control and cohort studies [25], the NIH National Heart, Lung, and Blood Institute: Quality Assessment Tool for Cross-Sectional Studies [26], and the Cochrane Risk of Bias Tool [27] for randomized controlled trials. As mentioned above, any discrepancies between the independent reviewers will first be resolved by discussion; if discussion does not lead to an adequate solution, a third reviewer (Samaan, Z) will be brought in with the responsibility of resolving the dispute.

All summary estimates obtained from meta-analysis will be subject to evaluation using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) guidelines [28]. Provided the data are appropriate, summary statistics derived for direct and indirect estimates using NMA will also be subject to assessment using the GRADE framework [29].

**Statistical analysis methods**

The results of this systematic review will be reported in a narrative and where possible, a combined statistical manner. Agreement levels between the independent reviewers will be measured using the kappa statistic. Provided there is little heterogeneity between studies, we plan to conduct a meta-analysis to derive a summary statistic representing the combined statistical result of multiple studies across our primary outcome (illicit

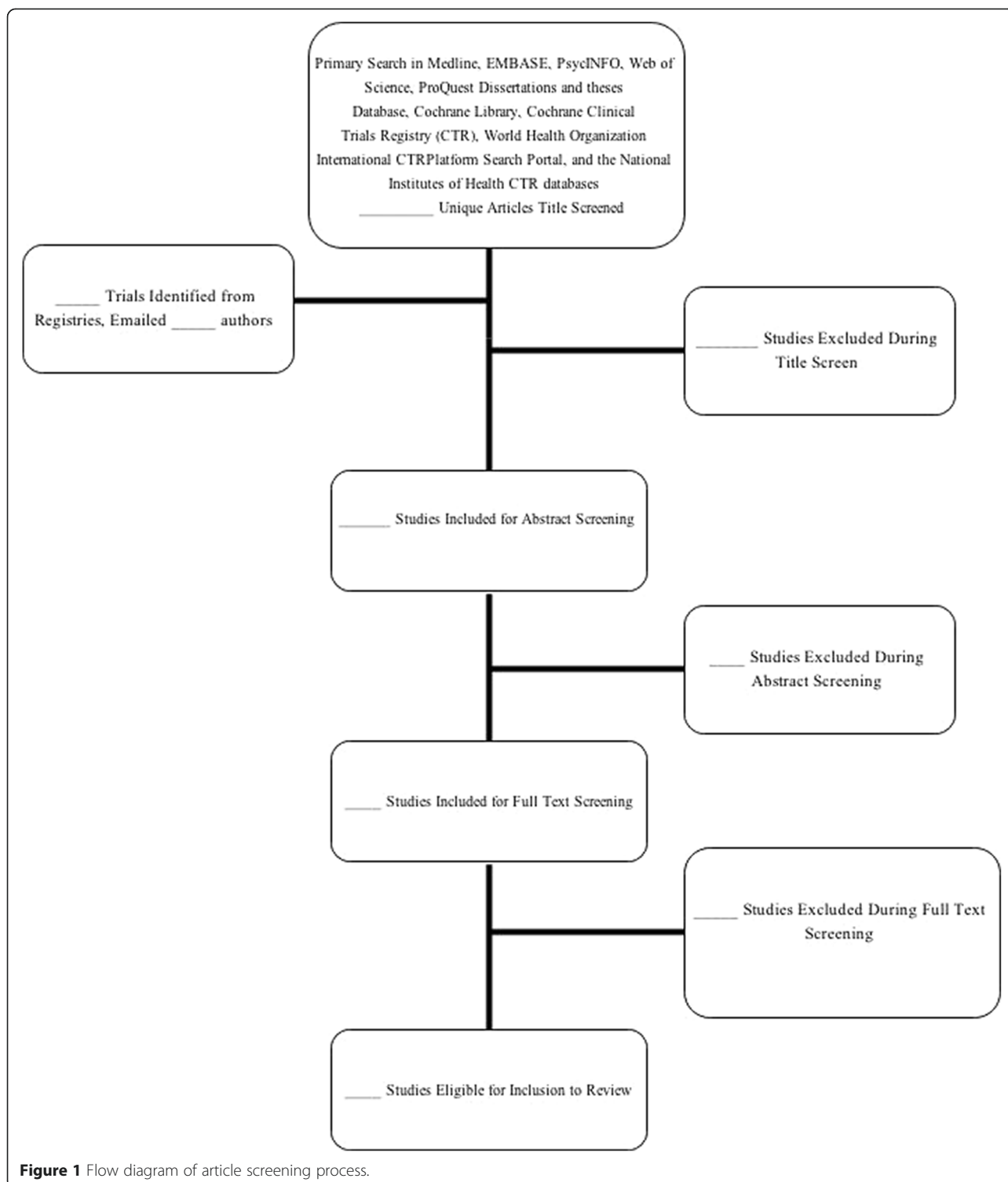
opioid use behavior) and secondary efficacy end-points. As described previously [30], the lack of direct comparisons reported in the literature is a common problem when combining the evidence from studies evaluating OSTs. The majority of studies evaluate new therapies in direct comparison to methadone or placebo, leaving us to question the comparative effectiveness compared to other OSTs. To circumvent this problem, we are proposing using network meta-analysis (NMA) to provide the pooled effect estimates of chronic pain mediating effects on the primary outcome (illicit opioid use behavior) for all OSTs.

Research methodologists highly caution against the pooling of studies with fundamentally different designs, [31,32] largely because of imbalanced susceptibility to selection bias non-randomized studies face [31]. Thus, we will combine the results of randomized and non-randomized studies in separate meta-analyses.

**Direct comparisons**

We will perform a meta-analysis to pool results for our primary outcome as well as all secondary efficacy end-points. Findings abstracted from direct comparisons will be pooled together using a random-effect meta-analysis with Knapp-Hartung (KH) estimator [33]. All analyses will be performed using the metafor and rmeta packages in R [34].

Dichotomous outcome(s) will be combined into a pooled odds ratio, where continuous outcomes (for example, mean number of positive opioid urine screens evaluated by chronic pain status) will be pooled using



the standardized mean difference. All direct comparisons will be weighted using the inverse of the variance.

Results from studies deemed eligible for inclusion into the meta-analysis will be presented in a forest plot, with the associated 95% confidence intervals presented. We will calculate and report the inconsistency index ( $I^2$ )

statistics and  $P$  values as the measure of heterogeneity in the results of the studies and whether the actual observed difference can be attributable to chance alone [35]. We will interpret the  $I^2$  statistic using the thresholds set forth by the Cochrane Collaboration, these include  $I^2$  of 0% to 40% (might not be important), 30% to

60% (moderate heterogeneity), 50% to 90% (substantial heterogeneity), and 75% to 100% (considerable heterogeneity) [31]. The Egger's test will be used to assess for publication bias.

We anticipate a study's scoring on methodological quality assessment as well as differences in measurement selection (for example, urine toxicology screening *versus* self-report) to be important factors accounting for heterogeneity between studies. The methodological quality of individual studies will be captured using the Cochrane Risk of Bias tool, Newcastle Ottawa Scale, and the NIH National Heart, Lung, and Blood Institute: Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies. Subgroup analyses will stratify on the basis of the study's performance on the risk of bias assessment. We will stratify our analyses on the basis of Cochrane risk of bias responses, whereby studies will be characterized as having an overall 'high risk of bias' if at least one domain on the Cochrane risk of bias tool is rated as high risk. Thus, results of any study with  $\geq 1$  'high risk of bias' rating across domains will be considered at risk for confounding. For observational studies, we will need to address risk of bias according to the appropriate assessment tools, thus we will not be able to use Cochrane risk of bias across all studies. For cohort and case-control studies, any study with zero stars in  $\geq 1$  section will be considered high risk of bias based on the Newcastle Ottawa Scale. According to the Newcastle Ottawa Scale, receiving stars indicates a lower risk of bias. The lack of stars in any section indicates the study has not addressed a possible source of confounding. For cross-sectional studies rated with the NIH tool, any study receiving a 'fair' or overall 'poor' quality rating will be classified as high risk of bias and included for subgroup analysis. We anticipate the studies with improper adjustment for important confounding variables to have high susceptibility for confounded treatment effects.

We will also stratify our meta-analyses based on outcome measurement. A clear example of how measurement can influence the study results is noted with the measurement of opioid use, where some studies use urine toxicology screening to determine concomitant opioid abuse and other studies use self-report. Self-report is susceptible to social desirability bias, where some patients may be reluctant to report continued opioid abuse in an effort to maintain a positive standing with physicians and clinical staff. Thus, quality of measurement can contribute to large difference in the study findings.

Acknowledging the impact of publication status as a potential source of bias, we will perform sensitivity analysis to determine whether a study's publication status impacts the observed effect estimates. Studies in the gray literature are not subject to the same level of scrutiny as those in peer-reviewed journals. The peer review process leads to the identification of potential sources of confounding and

allows authors to re-perform their analyses by properly adjusting for newly identified sources of error. Thus, some of the unpublished literature may present different treatment effects simply due to the lack of external evaluation. We will evaluate this potential concern by performing an additional sensitivity analysis, stratifying our meta-analyses by the articles publication status.

#### **Combining direct and indirect evidence: the network meta-analysis**

Provided the data are suitable for NMA, we propose building a Bayesian hierarchical model using maximum likelihood estimation to derive summary statistics for binary outcomes. This model will introduce a random effect representing the variation in effect estimates resulting from the comparison itself. Any variation in the random effect will be considered 'inconsistency' [36]. This method allows for treatment heterogeneity, sampling variability, and inconsistency [36] while also applying maximum likelihood estimation [36].

Due to the fragility of the NMA, we propose selecting the best evidence for inclusion into the model. Thus, only evidence from randomized trials with  $\geq 200$  people in the comparison will be selected for inclusion into the NMA model. We set this sample size requirement to adjust for the high susceptibility of type I error in studies evaluating multiple treatment outcomes.

We will use node splitting to identify inconsistency [37,38], a method that identifies loops with large inconsistency. The inconsistency will be taken into consideration during the interpretation of the results. We will also use the deviance information criterion (DIC) to estimate how parsimonious the data are [37].

Findings from the NMA will be presented using probability statements of treatment effects as well as a ranking of these probabilities, which illustrates each interventions probability of ranking first [39]. We will also graphically display the probability ranks using the surface under the cumulative ranking (SUCRA) line [39].

#### **Methods for evaluating the clinical guidelines**

To identify the most recently published North American guidelines on opioid maintenance treatments, we will search [www.guidelines.gov](http://www.guidelines.gov). We will search using the terms 'opioid dependence, opioid addiction, and opioid substitution treatment.' We will also search the National Institute for Health and Care Excellence (NICE) database to identify the most recently published guidelines used by the National Health Service in the UK. We will use pilot-tested data abstraction forms to extract data on: the recommendations made by each guideline, the strength of the recommendation, the evidence cited by the guideline for each recommendation, whether the guideline developers interpreted any clinical subgroup

effects with caution, and whether the guideline discussed the impact of pain on poor treatment response. We will also quantitatively appraise the quality of the guidelines using the Appraisal of Guidelines for Research & Evaluation II (AGREE) Instrument, a validated tool used for guideline assessment [40,41]. We will use this tool to assess the transparency in the development of guideline recommendations for chronic pain subpopulations. However, the use of the AGREE II will be unjustified if no formal recommendations are made for managing this population.

## Discussion

Understanding the impact of comorbid disorders on addiction treatment outcomes is essential for enhancing evidence-based practices within the field of mental health and addiction. This investigation will focus on determining the role that chronic non-cancer pain has on the patient's experience of opioid addiction treatment. Acknowledging the complexity of comorbid pain management within the addiction treatment setting, we aim to understand the extent to which chronic pain is related to negative health outcomes including functional disability, physical difficulty, and mental health problems such as depression and anxiety in the context of opioid addiction [10]. Determining the influence of chronic pain on response to OST will require a detailed assessment across several different patient important outcomes. This review will capture the experience of treatment for a substantive sub-population of opioid addiction patients. If chronic pain truly does result in negative consequences for opioid addiction patients, it is important that we identify which OST is most appropriate for chronic non-cancer pain patients. We will also identify how current evidence is translated into practice by thoroughly reviewing international guidelines for OST. We aim to address how addiction treatment guidelines propose managing patients with comorbid pain. This objective provides an opportunity to distinguish the best quality guidelines and ultimately identify future areas for improvement.

## Abbreviations

DEF: Data extraction form; EMBASE: Excerpta Medica DataBase; LAAM: Levomethadyl acetate; MMT: Methadone maintenance therapy; NOS: Newcastle-Ottawa Scale; OST: Substitute opioid therapy; PRISMA: Preferred Reporting Items for Systematic reviews and Meta-Analyses; RCT: Randomized controlled trial; WHO: World Health Organization.

## Competing interests

The authors declare that they have no competing interests.

## Authors' contributions

BBD, MB, LT, ZS, JP, CP, MV, JD, DCM, DD, GP, and AW conceived the research question and designed the review protocol. JP provided guidance for the evaluation of pain measures in opioid-dependent populations. BBD and MB performed the literature search, tested, and revised the electronic search strategy, as well as designed and pilot tested the data extraction

forms. BBD and LT designed the statistical analysis plan. BBD, MB, LT, JP, ZS, CP, MV, JD, DCM, DD, GP, and AW contributed equally to writing and revision of the manuscript. All authors read and approved the final manuscript.

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## Appendix iii Supplemental Material for Study 4

**Table S1: Cross-sectional Risk of Bias Assessment using National Institute of Health Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies**

	<b>Peles, 2005</b>	<b>Dhingra, 2013</b>	<b>Barry, 2009</b>	<b>Chakrabarti, 2009</b>	<b>Dennis, 2014</b>	<b>Dreifuss, 2012</b>	<b>Dunn, 2014</b>	<b>Jamison, 2000</b>	<b>Rosenblum, 2003</b>	<b>Trafton, 2004</b>
<b>Was the study population clearly specified and defined?</b>	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
<b>Was the participation rate of eligible persons at least 50%?</b>	Yes	Not Reported	Not Reported	Not Reported	No	Not Reported	Yes	Not Reported	Not Reported	Not Reported
<b>Was the research question or objective in this paper clearly stated?</b>	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes
<b>Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?</b>	Yes	Yes	Yes	No	Yes	Cannot Determine	Yes	Yes	Yes	Yes
<b>Was a sample size justification, power description, or variance and effect estimates provided?</b>	No	No	Not Reported	Yes	Yes	No	Not Reported	Not Reported	Yes	No
<b>For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?</b>	No	Cannot Determine	No	Yes	No	Yes	No	No	No	No
<b>Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?</b>	Yes	Cannot Determine	No	Yes	Yes	Yes	No	No	Yes	No
<b>For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?</b>	Yes	No	Yes	Yes	No	No	No	No	Yes	Yes
<b>Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?</b>	Yes	Yes	Yes	Yes	Yes	Cannot Determine	Yes	No	Yes	Yes
<b>Was the exposure(s) assessed more than once over time?</b>	No	No	No	Yes	No	No	No	No	No	No
<b>Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?</b>	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
<b>Were the outcome assessors blinded to the</b>	Not	Not	Not	Not Reported	Yes	Not	Not	Not	Not	Not

<b>exposure status of participants?</b>	Reported	Reported	Reported			Reported	Reported	Reported	Reported	Reported
<b>Was loss to follow-up after baseline 20% or less?</b>	Not Reported	Not Reported	Not Reported	Not Reported	Yes	Not Reported	Not Reported	Not Reported	Yes	Not Reported
<b>Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?</b>	No	Yes	No	Yes	Yes	No	Yes	No	No	No
<b>How would you rate the quality of this article?</b>	<b>Good</b>	<b>Fair</b>	<b>Fair</b>	<b>Good</b>	<b>Good</b>	<b>Fair</b>	<b>Good</b>	<b>Poor</b>	<b>Good</b>	<b>Fair</b>

**Table S2: Newcastle Ottawa Scale Risk of Bias Assessment for Cohort Studies**

	Bounes, 2013	Fox, 2012	Potter, 2015
Were cohorts drawn from the same population?	3	3	3
Is the source population (sampling frame) representative of the cohort of interest?	3	2	3
Was the outcome analysis of high quality and the methodology of the outcome assessment explicitly detailed?	2	3	2
Did the study use statistical analysis methods to adjust for prognostic variables across participant groups?	3	3	3
Is there little missing data?	1	2	1
Were all outcome assessors blinded to the treatment group (i.e. methadone or buprenorphine) information of the participant?	1	1	1
Was there an objective assessment of the outcome of interest?	3	3	2
Did the study identify and adjust for any possible influence a concurrent therapy or unintended exposure might have on the results of the investigation?	1	2	2
Risk of Bias Score	17	19	17

\*Risk of bias score minimum of 0 and maximum of 24, higher scores indicate lower risk of bias

**Table S3: Risk of Bias Assessment for Randomized Controlled Trials Using the Cochrane Risk of Bias Tool**

<b>Author Last Name, Year</b>	<b>Was the allocation sequence adequately generated?</b>	<b>Was allocation adequately concealed?</b>	<b>Was knowledge of the allocated intervention adequately prevented during the study?</b>	<b>Were incomplete outcome data adequately addressed?</b>	<b>Are reports of the study free of suggestion of selective outcome reporting?</b>	<b>Was the study apparently free of other problems that could put it at a high risk of bias?</b>	<b>Cochrane Score</b>
Neumann, 2013	1	1	1	3	3	2	11

\*Cochrane risk of bias scores are summed from individual ranking among multiple subdomains, giving a total score out of 18. Higher scores indicate increasing risk of bias

!

**Table S4: Summary of Findings for Studies Evaluating Psychiatric Health Outcomes**

Author Last Name	Outcome	Measurement of Psychiatric Symptoms	Findings
Dhingra	Evaluated whether severe depressive symptoms were associated with the presence of chronic pain, using clinically significant pain as the dependent variable in a multi-variable logistic regression model.	Beck Depression Inventory (used to assess depressive symptoms)	Using a dependent variable of presence or absence of clinically significant pain, the model was significant (Wald score 2(8, N = 480) = 85.55, $p < 0.0001$ ) and four variables remained independently associated with pain: current use of prescribed opioid therapy for pain, higher methadone dose, higher level of comorbid medical conditions, and more severe depressive symptoms.
Barry	The study evaluated the association between pain and psychiatric symptoms, using t-tests to assess for differences in psychiatric rating scale scores across pain categories.	Measured psychiatric symptoms using the Brief Symptom Inventory 18 (BSI-18; (14))—the BSI-18 is an 18-item instrument, designed to screen for psychiatric disorders, that contains 3 subscales: depression, somatization and anxiety, and a total global severity index (GSI) score.	Using ANOVA to assess the differences in psychiatric symptoms scores, Barry et. al (2009) found significant differences ( $p < 0.05$ ) across all groups indicating the presence of pain is associated with a higher severity of psychiatric symptoms.
Jaimison	Jamison et. al evaluated whether participants reporting pain have a higher incidence of mental health diagnoses, Jamison et. al found that 67.1% of the participants categorized as having pain reported a mental health diagnosis and 51% of the non-pain group reported a mental health diagnosis ( $\chi^2: 6.38, p < 0.05$ ). Jamison also evaluated the differences in the absence of anxiety (% of participant reporting no anxiety; pain: 5.3%, No pain 9.4%; $\chi^2, 22.41 p < 0.001$ ), no depression (pain 6.0%, no pain 17.7%; $\chi^2, 32.53 p < 0.001$ ), and no irritability (Pain 5.9%, no pain 9.4%; $\chi^2 10.08, p < 0.05$ ), all of which showed patients with pain to have lower rates of reporting no psychiatric symptoms.	Self-report to a mood questionnaire generated for study	Evaluated the differences in proportions using chi-square
Rosenblum	Evaluated the history of psychiatric diagnosis among patients, finding the prevalence of CSP participants reporting yes to be 112 52.7%, while the percentage of non-chronic pain patients reporting a psychiatric medical history to be 247 (28.3%). These results indicate an increased risk of psychiatric comorbidity among patients reporting pain.	Self-report (psychiatric comorbidity), Symptom Checklist-90 (SCL-90) for psychiatric distress	When evaluating the differences in psychiatric in the presence of illness between patients with and without pain, the OR was shown to be 2.82 (95%CI 1.77-4.47), indicating an increased risk for psychiatric comorbidity among patients reporting pain. Rosenblum also showed participants with chronic severe pain to have higher ratings for moderate and high levels of psychiatric distress ( $p < 0.05$ )
Trafton	Evaluated psychiatric functioning over a 30-day period by	Addiction Severity Index: Measures	Trafton (2004) report a significant effect of pain on psychiatric

	evaluating the differences in the percentage of participants reporting depression, anxiety, hallucinations, trouble understanding, serious thoughts of suicide, violent behaviour, attempted suicide, and prescribed psychiatric symptoms.	psychological problems in the last month	symptoms, showing patients with pain to have a statistically significantly higher prevalence of 30-day depression, anxiety, hallucinations, trouble understanding, violent behaviour serious thoughts of suicide ( $p < 0.05$ for all chi-square tests evaluating differences in proportions). However, the reporting of actual suicide attempt was not found to statistically differ between groups (only one participant reported this)
Dennis (unpublished)	Using author requested data, we evaluated the prevalence of self-reported psychiatric diagnoses among patients reporting pain.	Dennis et. al used a self-report tool to determine the presence of psychiatric comorbidity, which was measured as composite outcome for depression, anxiety, schizophrenia, bipolar, and personality disorder	Among the GENOA sample of opioid dependent patients ( $n=250$ ), 64 participants reported having chronic pain, whereby 186 report no pain. Among those reporting chronic pain, 37 report any history of psychiatric illness, where only 85 of the non-chronic pain patients report a history of psychiatric comorbidity. Evaluating the differences in proportions between groups showed a trending effect.

**Table S5 - The Impact of Pain on Substitute Opioid Therapy Treatment Outcomes**

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pain	No Pain	Relative (95% CI)	Absolute (95% CI)		
Illicit Opioid Use (assessed with: self-report measures and urine toxicology screening)												
2	observational studies	serious <u>12345</u>	not serious <u>6</u>	not serious <u>7</u>	serious <u>8</u>	all plausible residual confounding would suggest spurious effect, while no effect was observed <u>9</u>	62/153 (40.5%)	163/252 (64.7%)	<b>OR 0.70</b> (0.41 to 1.17)	85 fewer per 1000 (from 35 more to 218 fewer)	⊕○○○ VERY LOW	IMPORTANT
Illicit Substance Use (cocaine, methamphetamine) (assessed with: self-report, urine toxicology screening, addiction severity index)												
2	observational studies	serious <u>12345</u>	not serious <u>6</u>	not serious <u>7</u>	not serious <u>8</u>	all plausible residual confounding would reduce the demonstrated effect	125/276 (45.3%)	211/341 (61.9%)	<b>OR 0.57</b> (0.41 to 0.79)	138 fewer per 1000 (from 57 fewer to 219 fewer)	⊕⊕○○ LOW	IMPORTANT
Psychiatric Comorbidity: Do Patients With Pain Report Higher Rates of Psychiatric Disorders? (assessed with: Self-report)												
3	observational studies	serious <u>12345</u>	not serious <u>6</u>	not serious <u>7</u>	not serious <u>8</u>	none	198/345 (57.4%)	187/512 (36.5%)	<b>OR 2.16</b> (1.60 to 2.90)	189 more per 1000 (from 114 more to 260 more)	⊕⊕○○ LOW	IMPORTANT

MD - mean difference, OR- odds ratio

1. Lack of demonstration of dose-response with pain severity
2. Chronic pain measurement, BPI not validated in the OST setting
3. No reported sample size calculation (Peeles)
4. Serious reporting issues: follow-up of participants, missing data, and blinding of outcome assessors
5. Exposure of Interest not measured prior to outcome, also no repeated assessment of exposure
6. Results were consistent across studies, low I2 estimates and overlapping confidence intervals
7. All treatments were evaluated in a representative observational sample (minimally restrictive eligibility criteria applied)
8. Wide confidence intervals
9. No explanation was provided

PROTOCOL

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# The effectiveness of opioid substitution treatments for patients with opioid dependence: a systematic review and multiple treatment comparison protocol

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## Abstract

**Background:** Opioids are psychoactive analgesic drugs prescribed for pain relief and palliative care. Due to their addictive potential, effort and vigilance in controlling prescriptions is needed to avoid misuse and dependence. Despite the effort, the prevalence of opioid use disorder continues to rise. Opioid substitution therapies are commonly used to treat opioid dependence; however, there is minimal consensus as to which therapy is most effective. Available treatments include methadone, heroin, buprenorphine, as well as naltrexone. This systematic review aims to assess and compare the effect of all available opioid substitution therapies on the treatment of opioid dependence.

**Methods/Design:** The authors will search Medline, EMBASE, PubMed, PsycINFO, Web of Science, Cochrane Library, Cochrane Clinical Trials Registry, World Health Organization International Clinical Trials Registry Platform Search Portal, and the National Institutes for Health Clinical Trials Registry. The title, abstract, and full-text screening will be completed in duplicate. When appropriate, multiple treatment comparison Bayesian meta-analytic methods will be performed to deduce summary statistics estimating the effectiveness of all opioid substitution therapies in terms of retention and response to treatment (as measured through continued opioid abuse).

**Discussion:** Using evidence gained from this systematic review, we anticipate disseminating an objective review of the current available literature on the effectiveness of all opioid substitution therapies for the treatment of opioid use disorder. The results of this systematic review are imperative to the further enhancement of clinical practice in addiction medicine.

**Systematic review registration:** PROSPERO CRD42013006507.

**Keywords:** Opioid substitution therapies, Opioid dependence, Methadone, Buprenorphine/naloxone, Naltrexone, Heroin, Systematic review, Network meta-analysis

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## Background

Opioids are psychoactive analgesic drugs prescribed for pain relief and palliative care [1]. Due to their addictive nature, effort and vigilance in controlling prescriptions is needed to avoid misuse and dependence. Despite such effort, opioid use disorder is commonly associated with both illicit and prescription opioid use [2]. The DSM-5 characterizes opioid use disorder as a 'problematic pattern of opioid use leading to clinically significant impairment or distress' [3]. Characteristics of opioid use disorder include increased tolerance, continued use despite personal and social problems, as well as withdrawal and tolerance, among other behavioral changes [3]. Opioid use has been on the rise for the past several years, although common and available treatment options have not adjusted to meet the increasing demand for therapy [4].

The rapid rise in opioid prescriptions worldwide in conjunction with the increase in misuse and addiction is concerning [2,5]. Opioid-related deaths in ON, Canada have doubled between 1991 and 2004 [6,7]. In the United States, opioid sales have surged 627% between 1997 and 2007 [8]. Accompanying this dramatic rise in prescription opioid sales, the number of opioid-related overdoses in the United States has increased tenfold since 1990 [9]. Aside from the negative impact of drug use on the patient's lifestyle and psychological state, many physical health issues are associated with opioid abuse. For instance, IV opioid use is found to be associated with serious cardiac abnormalities such as infective endocarditis [10,11]. Furthermore, opioid use has been correlated with increase HIV risk and susceptibility to other opportunistic infections such as hepatitis C and tuberculosis [12].

Today, opioid substitution treatment (OST) is used to treat opioid dependence. This medical intervention employs strategies to control rather than prevent drug use in attempts to limit the incidence of adverse events. This involves prescribing controlled amounts of longer acting but less euphoric opioids to reduce cravings and prevent withdrawal symptoms [13]. Currently, the most commonly used substitute opioid is methadone [14,15]. First introduced for the treatment of opioid use disorder in 1965, methadone maintenance treatment (MMT) has been shown to be effective in ameliorating symptoms of opioid craving and reducing the negative effects that illicit drug use has on individuals, such as increased HIV risk [16]. It has also been shown to alleviate some of the burden that illicit drug use places on society, including criminal acts and the spread of infectious disease to others [15,17-21]. Reported methadone effectiveness varies by studies, with some investigations reporting as low as 20% to as high as 70% [10-12]. These rates are largely accounted for by the numerous definitions of methadone effectiveness reported in the literature.

Interindividual variability in clinical responses to methadone and dose requirements depend on several factors including age, diet, metabolism, protein binding, medications, genetic variants, and other substance use [22-26].

MMT is used by 20%–25% of opioid-dependent individuals in North America, leaving approximately 75% of the opioid-dependent population on another intervention or without any treatment at all [27]. While methadone is claimed to be an effective treatment for patients with opioid use disorder, it is important to note that alternative therapies are on the rise. Suboxone® is a relatively new drug approved in Canada since 2007, comprised of a combination of buprenorphine and naloxone in a 4:1 ratio [28]. When taken sublingually, only buprenorphine exerts its partial agonistic effects because naloxone is not adequately absorbed. However, in case of parenteral abuse, the administration naloxone exerts a withdrawal effect in opioid-dependent patients [29,30]. Therefore, the role of this combination is to ultimately alleviate withdrawal symptoms while also deterring intravenous use of the medication. Suboxone's effects are less prominent than full opioid agonists, as such it induces less physical dependence than other full opioid agonists such as heroin, morphine, and methadone [31]. It is also associated with less dysphoric effects than methadone, encouraging a greater portion of patients to continue in treatment. As well, it has a ceiling effect, such that its effectiveness remains constant beyond a certain dose, thus helping to control use and limit abuse [32].

According to one study, buprenorphine/naloxone patients reported significantly improved social life, educational level, and response to treatment (measured through urine toxicology screens), as compared to patients on MMT [33]. However, further studies including a 17-week randomized single-center trial reported no significant difference in the proportion of opioid-negative urine samples between patients on buprenorphine relative to methadone [31].

Naltrexone, another alternative opioid substitution therapy, is a competitive opioid receptor antagonist that blocks the euphoric effects of opioids by acting on receptors in the brain [34]. The oral form has been available since 1980s but due to the lack of patients' adherence to the therapy, it has been deemed ineffective until the recent introduction of long-acting injections and implants of naltrexone [34]. Long-lasting injectable naltrexone therapy was approved by the FDA in 2010 after a 6-month placebo-controlled trial showed that over 50% of patients remained on treatment and refrained from using illicit drugs for the entire study period [34,35]. A double-blinded randomized controlled trial (RCT) ( $n = 60$ ) investigating the efficacy of injectable naltrexone against placebo demonstrated a significantly reduced 'need' for heroin, as per patient reporting, after treatment (192 or 384 mg) in

comparison to placebo [36]. Naltrexone is easy to administer, does not induce tolerance over time, and it is not addictive [37].

However, naltrexone removes tolerance to opioids and thus increases the risk of overdose should patients choose to abstain from therapy and return to illicit opioid use. According to a search of the National Coronal Information System (2000–2003), deaths associated with oral naltrexone use are three to seven times higher than those of methadone [38].

Heroin-assisted therapy (HAT) is a novel and controversial treatment for opioid dependence which involves the administration of injectable diacetylmorphine, the active ingredient of heroin. HAT is more effective than oral methadone in terms of both reduction of illicit drug use (67.0% and 47.7%) and increase in retention in treatment (87.8% vs 54.1%). A study by Oviedo-Joekes et al. has shown that HAT is slightly more effective than methadone for increasing quality of life years gained (7.46 vs 7.92) [39]. As well, the study shows that HAT is more cost effective in terms of long-term incurred societal costs compared to methadone, primarily due to the fact that patients adhere to treatment longer and are less likely to relapse, resulting in less criminal activity [40].

Due to the aforementioned concerns and inconsistent findings related to the effectiveness of OSTs currently available, it is important to determine the most effective OST for increasing patient retention and restraining illicit opioid use. This systematic review will investigate the effectiveness of methadone, buprenorphine/naloxone, naltrexone, heroin-assisted therapy (HAT) and any other OST in terms of the continued opioid use (response to treatment) retention in treatment, physical and psychological well-being, social implication (criminal activity), as well as incidence of adverse events or toxic effects from the opioid intervention.

### Objectives

This systematic review aims to assess and compare the effectiveness of all available OSTs in the treatment of opioid use disorder, including but not limited to methadone, buprenorphine/naloxone (Suboxone®), naltrexone, and heroin (diacetylmorphine)-assisted therapy. Specifically, the objectives of this investigation include:

- 1) Assessing the effectiveness of the aforementioned therapies based on retention in treatment and continued opioid use (response to treatment).
- 2) Conduct direct comparisons using random effects meta-analytic models and when appropriate, conduct a network meta-analysis to synthesize a mean difference, relative risk, or odds ratio that encompasses results from multiple studies.

- 3) Critically evaluate current literature and identify important areas of addiction medicine that future research should address.
- 4) Offer unbiased report of the effectiveness of different treatments in relation to one another to enhance current clinical treatment of opioid use disorders.

### Research question

Among patients being treated for opioid use disorder, which OST (methadone, buprenorphine/naloxone, naltrexone, HAT, and/or other) is most effective for increasing retention in treatment and restraining continued opioid use?

### Methods/Design

#### Data sources and search strategy

In order to conduct a comprehensive search of the available literature, we will use a set of predetermined and separate key terms to search the following online databases: Medline, EMBASE, PubMed, PsycINFO, Web of Science, Cochrane Library, Cochrane Clinical Trials Registry, World Health Organization (WHO) International Clinical Trials Registry Platform Search Portal, and the National Institutes for Health (NIH) Clinical Trials Registry. Searches will be performed independently by two authors (LN and BD). The authors will perform additional manual searches of all completed Cochrane reviews examining the effect of different OSTs. The manual search will be used to identify any RCT or observational study on OSTs that have been combined statistically and narratively in a Cochrane review, as Cochrane is the leader and gold standard in systematic reviews. We will also contact each primary investigator listed on the NIHs Clinical Trial Registry from studies deemed eligible during the title screening, where we will inform the investigators of our review and ask for information regarding any publications resulting from their trial. We will also contact a librarian from the McMaster Faculty of Health Sciences Library with expertise in systematic reviews throughout the process of devising the search strategy and conducting the literature search. The two authors (LN and BD) will then independently refer to the bibliographies of articles that pass the initial abstract screening. No constraints will be set on language or date of publication in order to allow for a more thorough search of the literature. However, only human studies will be included. As well, we will eliminate incomplete studies, as they would not provide sufficient data for extraction. We will inform the authors of the eligible articles about the review during the data extraction process to consult them for clarification of their data when needed. Please refer to Table 1 for full search strategy.

**Table 1 Defined search strategy for the extraction of pertinent studies from multiple databases**

CINAHL search strategy search = ____	<ol style="list-style-type: none"><li>1. (MH 'methadone+')</li><li>2. (MH 'suboxone+')</li><li>3. (MH 'heroin assisted treatment+')</li><li>4. (MH 'diacetylmorphine+')</li><li>5. (MH 'heroin adjusted therapy+')</li><li>6. (MH 'buprenorphine+')</li><li>7. (MH 'Revia+')</li><li>8. (MH 'Depade+')</li><li>9. (MH 'Naltrexone+')</li><li>10. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9</li><li>11. (MH 'disorder, substance abuse') or (MH 'substance withdrawal syndrome+') or (MH 'substitute opioid therapy+')</li><li>12. 10 AND 11</li></ol>
Medline search strategy search = ____	<ol style="list-style-type: none"><li>1. methadone/th [Therapy]</li><li>2. limit 1 to humans</li><li>3. opioid substitution treatment/ae mo [adverse effects, mortality]</li><li>4. limit 3 to humans</li><li>5. substance-Related Disorders/de, ep, th [Drug Effects, Epidemiology, Therapy]</li><li>6. Limit 5 to humans</li><li>7. Opiate Substitution Treatment/or Naloxone/or Buprenorphine/or Opioid-Related Disorders/or Heroin Dependence/or Substance Withdrawal Syndrome/or Narcotic Antagonists/</li><li>8. Limit 7 to humans</li><li>9. Naltrexone/ae, ag, ai, tu [Adverse Effects, Agonists, Antagonists &amp; Inhibitors, Therapeutic Use]</li><li>10. Limit 9 to humans</li><li>11. Substance Abuse Treatment Centers/or Substance Abuse, Intravenous/or Heroin/or Heroin Dependence/or Opioid-Related Disorders/or Randomized Controlled Trials as Topic/or Methadone/</li><li>12. Limit 11 to humans</li><li>13. methadone/</li><li>14. limit 13 to humans</li><li>15. 2 OR 4 OR 8 OR 10 OR 12 OR 14</li><li>16. 15 AND 6</li></ol>
Web of science search strategy search = ____	<ol style="list-style-type: none"><li>1. Topic = ('methadone' OR 'methadone maintenance therapy' OR 'naltrexone' OR 'suboxone' OR 'buprenorphine' OR 'heroin assisted treatment')</li><li>2. Topic = ('substitute opioid therapy' OR 'opioid substitution therapy')</li><li>3. 1 AND 2</li></ol>
EMBASE search strategy Search = ____	<ol style="list-style-type: none"><li>1. methadone treatment/or methadone/or methadone plus naloxone/</li><li>2. limit 1 to human</li><li>3. buprenorphine plus naloxone/</li><li>4. limit 3 to human</li><li>5. morphine sulfate plus naltrexone/or naltrexone/</li><li>6. limit 5 to human</li><li>7. opiate addiction/or heroin dependence/or methadone/or diamorphine/</li><li>8. limit 7 to human</li></ol>

**Table 1 Defined search strategy for the extraction of pertinent studies from multiple databases (Continued)**

	9. opiate substitution treatment/ae [Adverse Drug Reaction]
	10. methadone/or buprenorphine/or opiate addiction/or substitute opioid therapy.mp.
	11. 9 or 10
	12. 2 or 4 or 6 or 8
	13. 11 and 12
	14. substance abuse/or addiction/or drug dependence/
	15. 13 and 14
	16. randomized controlled trial/
	17. 15 and 16
PsycINFO search strategy search = _____	1. exp Methadone Maintenance/or exp Methadone/ 2. limit 1 to human 3. exp Treatment Outcomes/or exp Drug Therapy/or exp Methadone Maintenance/or exp Drug Dependency/or exp Maintenance Therapy/or exp Methadone/or exp Heroin/ 4. limit 3 to human 5. exp Drug Addiction/or exp Clinics/or exp Drug Therapy/or exp Drug Dependency/or exp 'Recovery (Disorders)'/or exp Maintenance Therapy/ 6. limit 5 to humans 7. exp naltrexone/ 8. limit 7 to humans 9. exp Maintenance Therapy/or exp Naloxone/or exp Drug Therapy/or exp Drug Dependency/or exp Heroin Addiction/ 10. limit 7 to humans 11. exp Treatment Outcomes/or exp Clinical Trials/or exp Drug Therapy/or exp Heroin Addiction/or exp Methadone Maintenance/ 12. limit 9 to humans 13. 2 and 8 and 10 14. 2 and 10 15. 2 and 12 16. 2 and 6 and 12 17. 13 or 14 or 15 or 16
Cochrane library search strategy search = __	1. search title, abstract, keywords: methadone 2. search title, abstract, keywords: buprenorphine 3. search title, abstract, keywords: naltrexone 4. search title, abstract, keywords: heroin assisted treatment
Clinical Trials Registry through National Institutes for Health search strategy Search = _____	'methadone' OR 'suboxone' OR 'Buprenorphine' OR 'substitute opioid therapy' OR 'naltrexone' OR 'heroin assisted treatment' OR 'heroin adjustment therapy' AND 'opioid addiction', with additional criteria including: Completed studies, exclude unknown status, adult age requirements, and all trials had to be listed as Phase 3, 4
Cochrane Central Register of Controlled Trials search strategy Search = _____	'substitute opioid therapy' OR 'methadone' OR 'naltrexone' OR 'buprenorphine' OR 'heroin assisted treatment' OR 'heroin adjustment therapy' in title abstract keywords and opioid addiction in title abstract keywords in Trials

### Selection of studies

The authors (LN and BD) will independently conduct a primary title search, title screening, abstract screening, and full-text extraction. We will refer to the inclusion and exclusion criteria throughout the screening process.

All data extraction forms will be pilot tested before use. In the case of a disagreement during the search and selection process, we will engage in a discussion to reach a mutual agreement. However, should the conflict persist, we will resort to a third author (ZS) to facilitate the

resolution. Agreement level between reviewers will also be assessed using the kappa statistic [41]. As per guidelines set by the Meta-analysis of Observational Studies in Epidemiology (MOOSE) and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), we will include both a flow diagram displaying screening process (Figure 1) and a detailed table of the studies selected in the systematic review [42,43].

### Inclusion and exclusion criteria

The authors will limit the studies included in this review to RCTs and observational studies evaluating the effectiveness of methadone, buprenorphine/naloxone, naltrexone, HAT, and/or any other unlisted OST for the treatment of opioid dependence. The study will have had to examine the effectiveness of one of the aforementioned treatments with one or more of the outcomes of interest: retention in treatment, response to treatment (as measured through continued opioid use), criminal activity (as measured by self-report), mortality, physical and psychological health, as well as incidence of toxic and adverse events. No age restrictions will be set. In addition, we will also exclude

articles examining specialized populations such as prisoners examined within penitentiaries or other settings as well as pregnant women. All studies must also be primary investigations with comparison groups (separated by a treatment or placebo), we will not allow studies such as case reports or case series to be included in the review, arguably due to their lack of an appropriate comparison group. We have noted that we are primarily interested in patient important long-term outcomes such as illicit substance abuse behavior, retention in treatment, and side effects; we will not be including studies whose primary objective is to determine dosing and detoxification effects or precipitated withdrawal. Our primary concern is the influence of OSTs on retention in treatment and restraining continued opioid use. We are not interested in studies determining the effectiveness of OSTs on other substances such as cocaine or alcohol. We will not include pilot studies or RCTs at phases 0, 1, and 2. We will review any studies indexed within the databases allotted time frame and no restrictions on publication date will be set. All studies selected for inclusion into the manuscript will be required to demonstrate appropriate ethics committee approval in

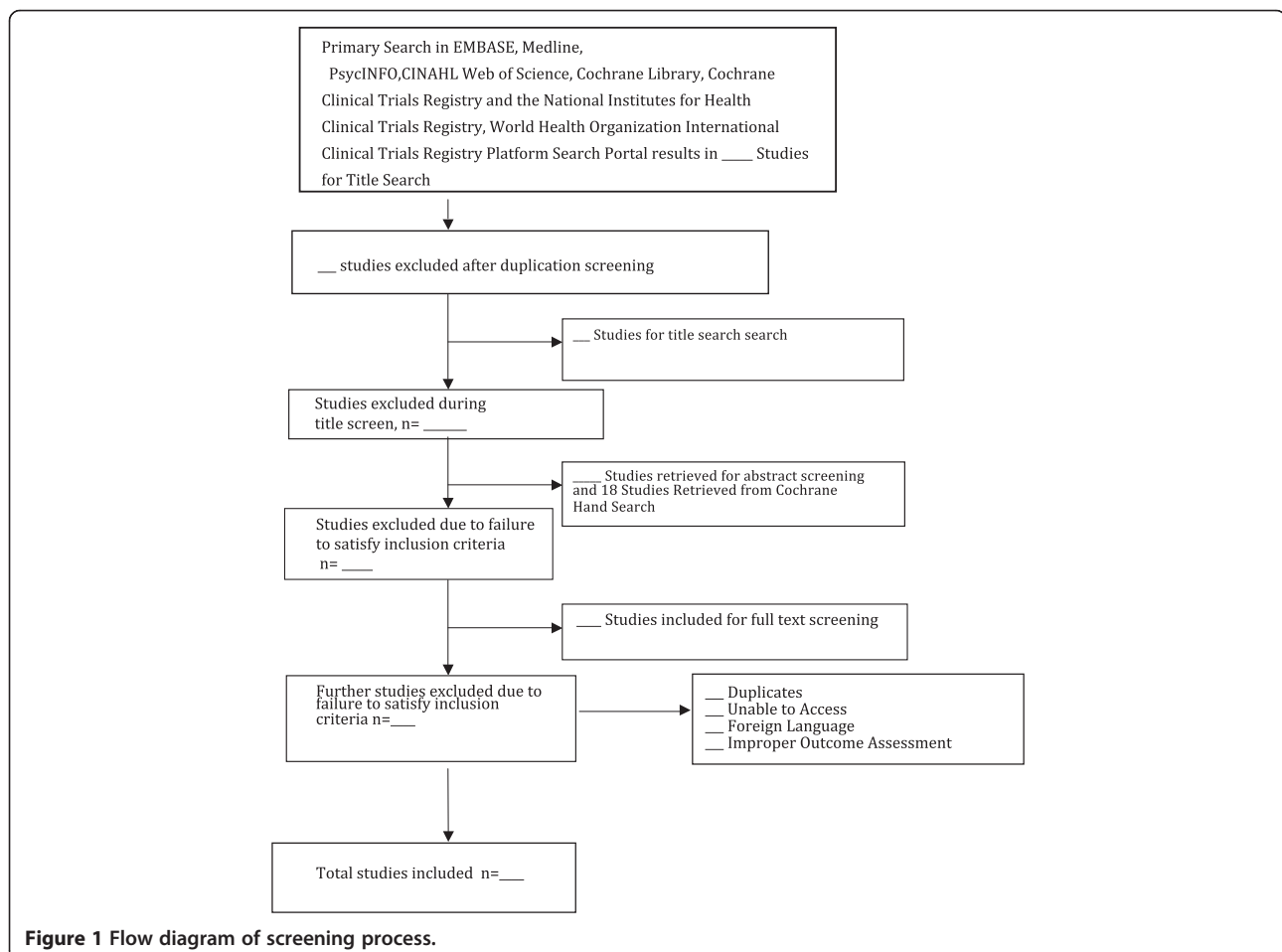


Figure 1 Flow diagram of screening process.

accordance with the objectives stated within the Helsinki Declaration. This investigation will not require direct human experimentation; however, we will still comply with all objectives of the Helsinki Declaration.

#### **Quality assessment of individual studies**

Two authors (LN and BD) will independently conduct a methodological quality assessment of the studies selected for the systematic review. We will use the Newcastle-Ottawa Scale (NOS) for observational studies to assess the risk of bias [44]. We will use the Cochrane risk of bias tool to assess the risk of bias for RCTs [45]. Discussions will be used to resolve any discrepancies that should arise. A third author (ZS) will be contacted to facilitate resolution in the case that a mutual consensus is not reached. When assessing risk of bias using the Cochrane tool for RCTs, scores of 1, 2, or 3 will be assigned for each domain that is ranked as 'low risk', 'unclear', or 'high risk' of bias, respectively. Scores from all the domains addressed by the Cochrane risk of bias tool will be added to give a total score out of 18, with higher scores indicating a higher risk of bias. When assessing risk of bias using the modified Newcastle Ottawa Scale for observational studies, scores of 1, 2, or 3 will be assigned for domains ranked as 'high risk', 'unclear', or 'low risk' of bias. Scores from all the domains will be totaled to a score of 21, with higher scores indicating lower risk of bias.

#### **Outcome measures**

This systematic review will compare methadone, buprenorphine/naloxone, naltrexone, and HAT among other substitute opioid therapies in terms of retention and response to treatment (as measured through continued opioid use). Retention in treatment has multiple definitions and measurements across studies, where some chose to define retention as a continuous value such as the number of days a patient continued in treatment until the last day of receiving an intervention receipt [46]; other studies chose to measure retention as a binary outcome such as the percentage of patients who completed their treatment course [47]; and lastly, some studies chose to report the number of patients who received the treatment for a pre-defined number of treatment days [39]. Due to the numerous ways retention is defined, measured, and reported, we will collect any information the articles offer on patient retention. We will statistically combine results from studies that similarly report, measure, and define retention. We will contact authors of studies who uniquely measure/report patient retention results in an effort to obtain results in the more commonly defined retention method.

Furthermore, we define response to treatment as abstinence from use of illicit opioids as indicated by absence of any opioids not pertaining to the treatment in urine

toxicology screening. We will compare the percentage of opioid-negative urine samples between treatments, calculated by dividing the number of opioid-negative urine screens by the total number of urine samples provided as used in the studies by Mattick et al. (2003) and Samaan et al. (2014) [48,49]. Please refer to Table 2 for detailed information on how these variables are defined and measured in the current literature.

#### **Data abstraction**

For the purpose of this review, we will construct full-text extraction forms. Data will be later transferred from these forms and entered into a Microsoft Excel 2011 document. The data abstraction forms were pilot tested in duplicate to ensure their feasibility in this review. These forms are available upon request. Any contention that arises during the extraction process will be resolved through discussion, and if necessary, a third author (ZS) will be brought in. The data extraction forms will allow us to adequately manage the large amount of information being extracted from individual studies. This information includes: title of the journal, number of study participants, study methodology (i.e. RCT and cohort), participant mean age, outcomes assessed, methods of statistical measurement, covariates measured in regression models, outcome statistical association value, *p*-value, confidence intervals, data quality (i.e. percentage of missing data and how missing data were handled), and methods used to correct for multiple testing.

#### **Statistical analysis plan**

When summarizing the evidence of multiple therapies, we often find that there are a limited number of studies providing direct comparisons. For example, a number of systematic reviews compare new therapies (i.e. Naltrexone and heroin-assisted treatment) only to placebo or the standard of care, this being methadone. Using novel statistical approaches to multiple treatment comparisons (MTC) such as the network meta-analysis (NMA), we will provide the pooled effect estimates of all OSTs for continued opioid abuse and patient retention, disseminating both direct and indirect comparisons of all therapies. The results of this review will be summarized both narratively and statistically where possible. For this review, we will provide summary estimates (pooled odds ratios for binary outcomes and standardized mean differences for continuous outcomes) calculated using direct and indirect sources of evidence, as well as those arising from mixing both direct and indirect evidence, provided the assumption of consistency is reasonable.

Due to the stark differences in methodology, we will not be pooling data retrieved from observational studies with data from RCTs. All direct estimates will be pooled separately based on study design (randomized

**Table 2 Definitions of outcomes in opioid substitution investigations**

Outcome	Definition	Measurement of variable (units)	Statistical estimates and measurement of association of this outcome	Studies
Continued illicit drug abuse	Abstaining from illicit opioid use throughout treatment.	-Urine toxicology screening -Self-reported drug use	OR, rate ratio	[39,46,47,50,51]
Retention in treatment	Proportion of participants completing treatment and days in treatment from beginning of the study until the last day of therapy.	-Number of days patient remains in treatment (days)	Comparing means (SD), HR, adjusted HR using Cox model, rate ratio, Kaplan-Meier estimator	[39,47,52-54]
Adverse events	Reaction to drugs and/or change in health status during course of therapy.	-Interviews -Physical examination -Randomly recorded at visits -Total number of adverse events per day	t-test	[30,39,51,54]

vs non-randomized). While some studies suggest the differences in treatment estimates obtained from well-designed observational research do not differ greatly from RCTs of the same topic [55,56], pooling data from observational studies and RCTs is highly cautioned against [57,58]. This separation stems largely from the inherent differences between RCTs and observational designs, whereby non-randomized designs face high susceptibility to selection bias [57].

#### Direct comparisons

Direct evidence will be pooled using a random-effect meta-analysis with Knapp-Hartung (KH) estimator [59]. All analyses will be performed using the metafor and rmeta packages in R [60].

Pooled results from the direct comparisons will be presented in forest plots. The most commonly used estimator is DerSimonian-Laird (DL) and is most often the default estimator in statistical software packages like Review Manager [61]. The DL estimator is demonstrated to be inadequate in capturing study heterogeneity, producing narrow confidence intervals and over-inflating treatment effects [61,62]. The KH estimator works on assumptions that variances are estimated from small samples, in addition to constructing confidence intervals based on the *t*-distribution (with *k*-1 degrees of freedom) [59,63]. Direct comparisons will weight studies eligible for inclusion using the inverse of the variance. For the direct comparison meta-analyses pooling the results from studies investigating retention in treatment, data will be pooled using risk ratios. The standardized mean difference will be used when pooling the results of studies investigating continued opioid abuse when measured as a continuous variable (mean number of opioid-positive urine screens per treatment arm). Provided we have an appropriate number of studies, we will use an Egger's plot to assess for publication bias.

We anticipate differences in outcome measurement and methodological quality to be important factors for explaining heterogeneity. These differences will be captured in our methodological quality assessment using the modified Newcastle-Ottawa Scale for observational studies and the Cochrane risk of bias tool for RCTs. Scores from these tools are determined from a thorough assessment of study design features such as: sampling strategy, methodological design (e.g. blinding), and outcome measurement (e.g. urine toxicology screening vs self-report). We will conduct subgroup analyses to address the robustness of our results when stratified by methodology quality based on the risk bias assessment scores. Studies will be separated into 'high and low' quality based on their scoring, where studies scoring 5 or lower on the Newcastle Ottawa scale and 6 points or higher on the Cochrane risk of bias tool will be assessed. These are standard methodological scoring cut offs used in previous reviews [64]. Provided the data is suitable, we will perform subgroup analyses based on the scoring procedures described above.

Some studies suggest using an  $I^2$  test statistic cut off of 40% or greater as an indication of heterogeneity among the pooled studies [57]; however, using such thresholds may be 'misleading' since heterogeneity represented in the  $I^2$  statistic is influenced by multiple factors [57]. We will rely on multiple thresholds set forth by the Cochrane Collaboration to aid in our  $I^2$  statistic interpretation, these include  $I^2$  of 0%–40% (might not be important), 30%–60% (moderate heterogeneity), 50%–90% (substantial heterogeneity), and 75%–100% (considerable heterogeneity) [57].

#### Direct and indirect evidence: the network meta-analysis

We propose using a Bayesian hierarchical model for binary outcomes, where we can account for sampling variability, treatment heterogeneity, and inconsistency while also applying maximum likelihood estimation [65].

The statistical model for the MTC we propose to use allows for an additional random effect, representing change in the treatment effect as a result of the comparison being made [65]. Variation in this random effect across comparisons will be interpreted as inconsistency [65]. Assumptions guiding NMA dictate that trials must be equivalent in their study design and population selection or the statistical results may be compromised [66]; thus, we will only be including evidence from RCTs into the NMA model. When trials evaluating a specific treatment are fundamentally distinct from other trials within that collection, the statistical results may be compromised by inconsistency [66]. To identify inconsistency, we will compare direct and indirect evidence using an approach known as node splitting [67,68]. Comparing inconsistency using this approach allows us to identify the loops with large inconsistency and ultimately consider this during interpretation of the results. Within the Bayesian framework, we will also use the deviance information criterion (DIC) to inform how parsimonious the data are, with a lower value being desired [67].

Provided the data is suitable, we will also address inconsistency using meta-regression to adjust for covariates (effect modifiers) across studies. We will perform a regression using study level data such as OST dose (mg/day), publication date, or study design features (blinding) to examine the improve or change in model fit after covariates are included into the model [67].

We will present our results with probability statements of treatment effects, by which ranking these probabilities allows the advantage of clarifying the sometimes over-complex reporting of pairwise *p*-values [69]. Ranking probabilities allows us to disseminate as a chance percentage, which treatment ranks the highest [69]. After displaying these rank probabilities graphically, we will construct the surface under the cumulative ranking (SUCRA) line for each treatment, in an effort to the graphically displayed probability ranks [69].

#### **GRADE framework**

We will assess the summary estimates of this investigation using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) guidelines [70]. Both direct and indirect estimates obtained from the NMA will be subject to thorough review using the GRADE framework. Evidence from indirect comparisons will be subject to additional scrutiny due to our inability to reliably show that the features of trial design (participants, interventions, outcome measures) are not impacting the observed treatment effect [71].

#### **Discussion**

We anticipate disseminating an objective review of the current available literature on the effectiveness of all

substitute opioid therapies for the treatment of opioid use disorder. This review will allow us to evaluate not only the relationship between all substitute opioid therapies and the patient important outcomes, but also, this review will allow us to evaluate the methodological quality of current available evidence. We seek to understand whether there are inconsistencies in the research and what reasons may account for them. Gaining insight into the predictors of patient response characteristics in opioid use disorder will help physicians develop patient-centered treatment regimes. This will be the first systematic review available in the literature looking at all possible substitute opioid therapies at one time. Thus, the dissemination of these results is imperative to the further enhancement of clinical practice through guideline development.

#### **Abbreviations**

OST: Opioid Substitution Treatment; MMT: Methadone Maintenance Therapy; WHO: World Health Organization; HAT: Heroin-assisted therapy; EMBASE: Excerpta Medica DataBase; RCT: Randomized controlled trial; MOOSE: Meta-analysis of Observational Studies in Epidemiology; PRISMA: Preferred Reporting Items for Systematic reviews and Meta-Analyses; NOS: Newcastle-Ottawa Scale.

#### **Competing interests**

The authors declare that they have no competing interests.

#### **Authors' contributions**

BBD, LN, ZS, and LT conceived the research question and designed the review protocol. BBD and LN completed the initial literature search, developed an electronic search strategy as well as designed and pilot tested the data extraction forms. BBD, AB, and LT developed the direct and multiple treatment comparison statistical analysis plan. BBD, LN, MB, AB, LT, ZS, CP, MV, JD, DCM, DD, GP, and AW contributed equally to writing and revision of the manuscript. The final version of the protocol submitted to BMC Systematic Reviews has been read and approved by all authors. All authors read and approved the final manuscript.

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# Online Supplement for Study 5: Network Meta-analysis

**eTable 1: Methodological Quality Assessment of Individual Trials Using the Cochrane Risk of Bias Tool (Web Appendix)**

Author Last Name, Year	Was the allocation sequence adequately generated?	Was allocation adequately concealed?	Was knowledge of the allocated intervention adequately prevented during the study?	Were incomplete outcome data adequately addressed?	Are reports of the study free of suggestion of selective outcome reporting?	Was the study apparently free of other problems that could put it at a high risk of bias?	Cochrane Score
Ahmadi, 2009	1	1	1	3	3	2	11
Comer, 2006	3	1	2	3	3	3	15
Haasen, 2007	2	2	2	3	3	3	15
Hartnoll, 1980	3	3	3	3	3	2	17
Johnson, 1992	3	3	3	3	2	3	17
Johnson, 1995	1	2	3	1	3	2	12
Kakko, 2003	3	3	3	2	3	3	17
Kamien, 2008	3	3	3	3	3	3	18
Krupitsky, 2006	3	3	3	3	3	3	18
Krupitsky, 2012	3	3	3	3	3	3	18
Ling, 1976	2	2	3	3	2	1	13
Ling, 1996	3	2	3	2	3	2	15
March, 2006	1	2	3	2	3	2	13
Mattick, 2003	3	3	3	3	2	3	17
Neri, 2005	3	3	3	2	2	3	16
Oviedo-Joekes, 2013	3	1	1	3	3	3	14
San, 1991	2	3	3	1	3	3	15
Saxon, 2013	3	2	3	2	2	3	15
Schottenfeld, 2008	3	3	3	3	3	3	18
Schuffman, 1994	3	3	3	2	2	3	16
Soyka, 2008	1	2	2	1	3	1	10
Strain, 1994	1	2	3	2	3	3	14
Strain, 1999	2	3	3	3	3	3	17
Strang, 2010	3	3	3	3	3	3	18
Van Den Brink, 2003	3	3	3	3	3	3	18
Wolstein, 2009	3	1	1	3	3	1	12
Woody, 2008	3	1	1	3	3	3	14
Zaks, 1972	2	1	1	1	3	2	10

\*Cochrane risk of bias scores are summed from individual ranking among multiple subdomains, giving a total score out of 18. Higher scores indicate increasing risk of bias

**eTable 2: GRADE Evaluation and Presentation of Direct, Indirect, and Network Estimates (Web Appendix)**

Interventions Compared	Number of Trials	I-Squared	Direct Evidence OR (95% CI)	Quality of Direct Evidence	Indirect Evidence OR (95% CI)	Quality of Indirect Evidence	Network OR (95% CI)	Quality of Network Evidence
Heroin vs High-dose Methadone	4	92.27	3.53 (1.28, 10.13)	Very Low <sup>1,3,5</sup>	-	-	-	-
Low-dose Methadone vs Heroin	1	0	0.28 (0.03, 2.97)	Very Low <sup>1,3,5,8</sup>	0.21 (0.04, 1.01)	Very Low <sup>6,8</sup>	0.23 (0.07, 0.80)	Very Low
High-dose Methadone vs High-dose Buprenorphine	3	92.29	1.70 (0.47, 5.84)	Low <sup>1,3,5</sup>	-	-	-	-
High-dose Heroin + Methadone vs High-dose Methadone	2	92.97	2.31 (0.49, 10.22)	Very Low <sup>1,3,5</sup>	-	-	-	-
High-dose Injectable Naltrexone (384 mg/day) vs Low-dose Injectable Naltrexone (192 mg)	1	-	-	-	-	-	-	-
High-dose Injectable Naltrexone (384 mg/day) vs Placebo	1	-	-	-	-	-	-	-
High-dose Methadone vs High-dose Suboxone <sup>®</sup>	1	-	-	-	-	-	-	-
Low-dose Buprenorphine vs High-dose Methadone	2	34.25	0.90 (0.20, 4.03)	Moderate <sup>1,5</sup>	0.48 (0.10, 2.16)	Low <sup>5,8</sup>	0.69 (0.24, 2.03)	Low
High-dose Methadone vs Low-dose LAAM	3	76.53	1.13 (0.30, 3.95)	Low <sup>1,5</sup>	-	-	-	-
High-dose Methadone vs Low-dose Methadone	6	0	1.20 (0.54, 2.73)	Low <sup>1,3,5</sup>	-	-	-	-
High-dose Methadone vs Low-dose Suboxone <sup>®</sup>	1	-	-	-	-	-	-	-
High-dose Naltrexone vs Low-dose Buprenorphine	1	-	-	-	-	-	-	-
High-dose Naltrexone vs Placebo	1	-	-	-	-	-	-	-
High-dose Suboxone <sup>®</sup> vs Low-dose Methadone	1	-	-	-	-	-	-	-
High-dose Suboxone <sup>®</sup> vs Low-dose Suboxone <sup>®</sup>	2	88.99	3.59 (0.80, 16.10)	Low <sup>1,3,5</sup>	-	-	-	-
Low-dose Buprenorphine vs Low-dose Methadone	5	68.07	0.83 (0.34, 2.05)	Low <sup>1,3,5</sup>	-	-	-	-
Low-dose Buprenorphine vs Low-dose Naltrexone	1	0	6.04 (0.81, 46.41)	Low <sup>1,3,5</sup>	3.73 (0.52, 32.28)	Very Low <sup>6,8</sup>	7.32 (1.86, 31.20)	Very Low
Low-dose Buprenorphine vs Placebo	3	79	7.56 (2.37, 25.53)	Low <sup>1,3,5</sup>	-	-	-	-
Low-dose Injectable Naltrexone (192 mg) vs	1	-	-	-	-	-	-	-

Placebo								
Low-dose Methadone vs Low-dose LAAM	1	40.02	0.94 (0.23, 3.64)	Low <sup>1,3,5</sup>	0.42 (0.05, 3.37)	Very Low <sup>6,8</sup>	0.93 (0.23, 3.65)	Very Low
Low-dose Naltrexone vs Low-dose Methadone	1	54.32	0.03 (0.00, 0.26)	Low <sup>1,3,5</sup>	0.31 (0.03, 2.86)	Very Low <sup>6,8</sup>	0.11 (0.02, 0.52)	Very Low
Low-dose Methadone vs Low-dose Suboxone <sup>®</sup>	1	-	-	-	-	-	-	-
Placebo vs Low-dose Naltrexone	2	79.84	0.67 (0.13, 3.42)	Low <sup>1,3,5</sup>	2.10 (0.19, 21.01)	Very Low <sup>6,8</sup>	0.97 (0.26, 3.66)	Very Low
Low-dose Oral vs Naltrexone Implant + Oral Naltrexone Placebo	1	-	-	-	-	-	-	-
Low-dose Oral Naltrexone vs Placebo	2	0	1.43 (0.28, 7.02)	Low <sup>1,3,5</sup>	-	-	-	-
Naltrexone Implant + Oral Naltrexone Placebo vs Placebo	1	-	-	-	-	-	-	-

\* 1 Limitations (risk of bias); 2 Inconsistency; 3 Imprecision; 4 Severe imprecision; 5 Contributing direct evidence of moderate quality; 6 Contributing direct evidence of low or very low quality; 7 Cannot be estimated because the drug was not connected in a loop in the evidence network. 8 Indirectness because of questionable comparability of trial populations to target population of network meta-analysis (patients failing methadone) or because of intransitivity

**eTable 3: Description of Effectiveness Outcome(s) Reported Across SOT Trials**

Interventions Compared	Effectiveness Outcome(s) Assessed	Treatment Effectiveness
High Dose Methadone (≥60 mg/day) vs. Heroin (Injectable and Inhaling arms) + High Dose Methadone (≥60 mg/day)	<ol style="list-style-type: none"> <li>1. Composite International Diagnostic Interview + European Addiction Severity Index (&gt;40% improvement in mental, physical, and social domains)<sup>1</sup></li> <li>2. HIV risk assessment measured using Opioid Treatment Index (OTI)<sup>2</sup></li> <li>3. Quality of Life measured using SF-12 for physical and mental<sup>2</sup></li> <li>4. General Health status measured using OTI<sup>2</sup></li> <li>5. Psychological Adjustment using Addiction Severity Index (family and social relations scores) and OTI social functioning scores<sup>2</sup></li> <li>6. Number of days involved in illegal activities<sup>2</sup></li> <li>7. Problems related to drug use measured using Composite ASI<sup>2</sup></li> </ol>	Heroin (injectable) + high-dose methadone showed significant benefit over high dose methadone for outcomes: 1, <sup>1</sup> 2, <sup>2</sup> 4, <sup>2</sup> 7 <sup>2</sup>
High and Low Dose Injectable Naltrexone (384mg and 192 mg) vs Placebo	<ol style="list-style-type: none"> <li>1. Mean number of negative opioid urine screens assessed per treatment arm<sup>3</sup></li> </ol>	Injectable naltrexone showed significant benefit over placebo for outcomes: 1 <sup>3</sup>
High-dose Levoacetylmethadol (LAAM) (≥ 85 mg/day) vs High Dose Methadone (>60 mg/day) <small>reference Anglin 2007 did not report by dose category</small>	<ol style="list-style-type: none"> <li>1. The percentage of urine screens positive for opioids assessed per treatment arm<sup>4,6</sup></li> <li>2. Percentage of urine screens positive for codeine assessed per treatment arm<sup>4</sup></li> <li>3. A composite score from the Addiction Severity Index (European Version) evaluating the frequency of drug and alcohol use as well as health and social status<sup>5</sup></li> <li>4. Physicians perception of disease severity and overall improvement compared to baseline measured using the Clinical Global Impressions Scale German Version<sup>5</sup></li> <li>5. Heroin craving measured using the Subjective Opiate Withdrawal Scale German Version<sup>5</sup></li> <li>6. Dirty rate measured using the number of opiate-positive urine screenings divided by the number of weeks of study participation<sup>5</sup></li> <li>7. Actual urine free rate measured using the number of opiate-free urine screens divided by the number of urine screens actually analyzed without a replacement of missing values<sup>5</sup></li> <li>8. Treatment effectiveness score (TES) evaluated by the number of opiate- free urine samples divided by the intended number of weeks of study treatment (24</li> </ol>	<p>LAAM showed benefit over methadone for outcomes: 1,<sup>4</sup> 2,<sup>4</sup> 10,<sup>5</sup> 13 (only vitality subscale),<sup>7</sup> 14,<sup>7</sup> 15,<sup>7</sup> 16,<sup>7</sup> 18,<sup>7</sup></p> <p>Methadone showed significant benefit over LAAM for outcomes: 22,<sup>8</sup> 23(only at 30 ms threshold)<sup>8</sup></p>

	<p>weeks)<sup>5</sup></p> <ol style="list-style-type: none"> <li>9. Time to relapse measured using the number of days between baseline and occurrence of the first opiate-positive urine screening<sup>5</sup></li> <li>10. Quality of life measured using the SCL-90-R subscales and the SCL-90-R global scores General Symptomatic Index, Positive Symptom Total and Positive Symptom Distress Index<sup>5</sup></li> <li>11. Opioid withdrawal measured using the Subjective Opiate Withdrawal Scale (German version: SOES)<sup>5</sup></li> <li>12. Heroin craving measured using the Visual Analog Scale for Heroin Craving<sup>5</sup></li> <li>13. Health and social functioning measured using SF-36 health survey<sup>7</sup></li> <li>14. Drug preferences measured using a visual analogue questionnaire of drug properties which required them to “rate each drug on six different factors: is the drug holding (suppressing withdrawal); how much buzz do you get from the drug; do you experience side effects, do the side effects bother you; do you like the drug, and do you feel more normal?”<sup>7</sup></li> <li>15. Illicit opioid use determined using hair samples<sup>7</sup></li> <li>16. Self-reported heroin use<sup>7</sup></li> <li>17. Self-reported poly-substance use (cocaine, benzodiazepines, illicit methadone)<sup>7</sup></li> <li>18. Final drug of choice (at end of cross-over trial participants could chose which therapy to remain on)<sup>7</sup></li> <li>19. Changes in vocational and social rehabilitation<sup>6</sup></li> <li>20. Degree of substance abuse measured using a global rating scale: rating of 2 marked an improvement in rehabilitation and substance use<sup>6</sup></li> <li>21. Opioid urinalysis to assess for poly-substance use (percentage of positive stimulants/benzodiazepines urine screens per treatment arm)<sup>6</sup></li> <li>22. Cardiac Function assessed with corrected QT interval measurements obtained from electrocardiographic analysis<sup>8</sup></li> <li>23. Evaluation of patients meetings the categorical QTc prolongation thresholds across treatment groups (more than 470 milliseconds for males and more than 490 milliseconds for females, as well as other sensitivity analyses such as 30 millisecond thresholds)<sup>8</sup></li> </ol>	
<p>High Dose Methadone (≥60mg) vs Low Dose Buprenorphine (&lt;16 mg)</p>	<ol style="list-style-type: none"> <li>1. The percentage of opioid positive urine screens reported per treatment arm<sup>9-16</sup></li> <li>2. Urinalysis for poly-substance use (benzodiazepine, cocaine, or cannabinoid) use per treatment arm<sup>15-17</sup></li> <li>3. Reported days of alcohol use per treatment arm<sup>15,17</sup></li> <li>4. Addiction Severity Index interview domain assessing number of days of</li> </ol>	<p>Low dose buprenorphine showed benefit over high dose methadone for outcomes: 1<sup>10,11</sup></p> <p>High dose methadone showed benefit over low dose buprenorphine for outcome: 1<sup>12,13,16</sup> 2,<sup>12,16</sup> 5,<sup>13</sup> 4,<sup>12</sup> 5<sup>12</sup></p>

	<p>opiate use in last month<sup>10,12</sup></p> <ol style="list-style-type: none"> <li>5. Opioid drug cravings<sup>13</sup></li> <li>6. Self-reported opioid use<sup>12,14,15</sup></li> <li>7. Self-reported amount of money spent on illicit opioid consumption per month measured using ASI<sup>12</sup></li> <li>8. Withdrawal symptoms measured using ASI<sup>12</sup></li> <li>9. To assess craving, patients were asked each week to estimate the maximum amount of opioid and cocaine craving at any time during the past 7 days by a mark on a 100 mm line VAS anchored by 'no craving' at one end a 'maximum craving ever experienced' at the other<sup>15</sup></li> <li>10. Substance use craving measured using a craving visual analogue scale (CVAS) (administered every week): a 10 cm line - with an end corresponding to 0 and the other to 100 - was used to record the extent of subjective cravings for heroin, cocaine and alcohol in the preceding week<sup>14</sup></li> <li>11. Psychiatric symptoms measured using Symptom checklist-90 (SCL-90) (administered every month): the SCL-90 (Derogatis, 1977) is an inventory composed of 90 items, with a point scale from 0 to 5, in terms of intensity<sup>14</sup></li> <li>12. Quality of Life measured using Lancashire Quality of Life Profile<sup>9</sup></li> </ol>	6 <sup>12</sup>
High Dose Suboxone® (buprenorphine ≥ 16 mg/day + naloxone) vs placebo	<ol style="list-style-type: none"> <li>1. Percentage of negative opioid urine screens per treatment arm<sup>18</sup></li> <li>2. Self-reported craving for opioids<sup>18</sup></li> </ol>	High dose Suboxone® (buprenorphine ≥ 16 mg/day + naloxone) showed significant benefit over placebo for outcomes: 1, <sup>18</sup> 2 <sup>18</sup>
High Dose Buprenorphine (≥ 16 mg/day) vs placebo	<ol style="list-style-type: none"> <li>1. Percentage of negative opioid urine screens per treatment arm<sup>18</sup></li> <li>2. Self-reported craving for opioids<sup>18</sup></li> <li>3. Composite ASI scores used to determine health, personal, and social functioning<sup>19</sup></li> <li>4. Compliance measured as the total number of doses taken<sup>20</sup></li> <li>5. Self reported drug use measured using a VAS (daily heavy drug abuse' was recorded as 10 and 'drug free' was recorded as 0)<sup>20</sup></li> <li>6. Subjective wellbeing was measured with a VAS (10 = very bad, 0 = very well) and with the temporal satisfaction with life scale (TSLs)<sup>20</sup></li> <li>7. Mental health (i.e. anxiety and depression) was measured with the symptom checklist (SCL-5)<sup>20</sup></li> </ol>	High dose buprenorphine (≥ 16 mg/day) showed significant benefit over placebo for outcomes: 1, <sup>18</sup> 2, <sup>18</sup> 3, <sup>19</sup> 5, <sup>20</sup> 6 <sup>20</sup>
Slow Release Oral Morphine vs Low Dose	<ol style="list-style-type: none"> <li>1. Opioid urinalysis, percentage of positive opioid urine screens per treatment arm<sup>9</sup></li> </ol>	Slow release oral morphine (mean dose 234.6 mg/day) showed significant benefit over Low Dose methadone

Methadone	2. Quality of Life measured using Lancashire Quality of Life Profile <sup>9</sup>	for outcomes: 1 <sup>9</sup>
Slow Release Oral Morphine (mean dose 234.6 mg/day) vs Low Dose Buprenorphine (<16 mg/day)	1. Opioid urinalysis, percentage of positive opioid urine screens per treatment arm <sup>9</sup> 2. Quality of Life measured using Lancashire Quality of Life Profile <sup>9</sup>	Low dose buprenorphine (<16 mg/day) showed benefit over slow release oral morphine (mean dose 234.6 mg/day) for outcomes: 1 <sup>9</sup>
Low Dose Buprenorphine (<16 mg/day) vs Low Dose Methadone (<60 mg/day)	1. Opioid urinalysis, percentage of positive opioid urine screens per treatment arm <sup>9,11-13,21-23</sup> 2. Quality of Life measured using Lancashire Quality of Life Profile <sup>9</sup> 3. Failure to maintain abstinence <sup>11</sup> 4. Addiction severity, measured using composite scores on Addiction Severity Index (ASI) <sup>21,23</sup> 5. Self-reported opioid drug cravings <sup>13,23</sup> 6. Heroin use in preceding month at three, six, and twelve month interviews using measures of self-reported frequency of use (measured using the Opiate Treatment Index) <sup>24</sup> 7. Cocaine urinalysis (percentage of cocaine positive urine screens per treatment arm) <sup>21-23</sup> 8. Benzodiazepine urinalysis (percentage of benzodiazepine positive urine screens per treatment arm) <sup>17,21,22</sup> 9. Days patients attended clinic as a measure of patient compliance <sup>22</sup> 10. Days patients were seen by counsellors <sup>22</sup> 11. Withdrawal symptoms assessed using The Withdrawal Symptoms Checklist <sup>23</sup> 12. Dose adequacy assessed using Dose Adequacy Questionnaire <sup>23</sup> 13. Weekly drug use behaviour assessed using the Weekly Drug Use Questionnaire <sup>23</sup> 14. Self-reported opioid use measured using ASI <sup>12</sup> 15. Self-reported amount of money spent on illicit opioid consumption per month measured using ASI <sup>12</sup> 16. Withdrawal symptoms measured using ASI <sup>12</sup> 17. Days of reported alcohol use <sup>17</sup>	Low dose buprenorphine (<16 mg/day) showed significant benefit over low dose methadone for outcomes: 1, <sup>9,11</sup> 3 <sup>11</sup>  Low dose methadone (<60 mg/day) showed significant benefit over low dose buprenorphine (<16 mg/day) for outcomes: 1, <sup>12</sup> 14, <sup>12</sup> 15, <sup>12</sup> 16 <sup>12</sup>
High Dose Heroin vs High	1. Mean number of days of heroin use over the last month per treatment arm <sup>25,26</sup>	High dose heroin showed significant benefit over high

<p>Dose Methadone (<math>\geq 60</math> mg/day)</p>	<ol style="list-style-type: none"> <li>2. Health Score on the Opioid Treatment Index (OTI)<sup>25</sup></li> <li>3. Reduction in illegal drug use, illegal activity, drug use, psychiatric symptoms, economic status, satisfaction with employment, family relations, social relations, and alcohol use measured using a composite score from the European Addiction Severity Index<sup>26</sup></li> <li>4. Mean number of day of illicit cocaine use over the last month per treatment arm<sup>26</sup></li> <li>5. Poly-substance use measured using urinalysis for cocaine, cannabis and barbiturates<sup>27</sup></li> <li>6. Injecting drug use behaviour<sup>27</sup></li> <li>7. Personal and social function measured by self-reported time spent with: people still abusing substances, selling drugs, engaging in illegal activity<sup>27</sup></li> <li>8. Social stability measured by self-reported consumption of meals, type of accommodation, and current employment activities<sup>27</sup></li> <li>9. Self reported health measured assessing symptoms, overdoses, and mortality<sup>27</sup></li> <li>10. Self-reported involvement in criminal activity<sup>27</sup></li> <li>11. Response to treatment measured as a reduction of regular use of street heroin, which was defined as 50% or more of negative specimens on urinalysis during weeks 14–26<sup>28</sup></li> <li>12. Self-reported abstinence from street heroin (zero use) in the past 30 days was obtained by independent researchers in face-to-face interviews<sup>28</sup></li> <li>13. Opioid urinalysis to assess for near (&lt;2 opioid positive urine screens) and full abstinence (0 opioid positive urine screens)<sup>28</sup></li> </ol>	<p>dose methadone for outcomes: 1,<sup>25,26</sup> 3 (illegal drug use, psychiatric symptoms, employment satisfaction),<sup>26</sup> 5,<sup>26</sup> 11,<sup>28</sup> 12,<sup>28</sup> 13 (near abstinence only)<sup>28</sup></p> <p>High dose methadone showed significant benefit over high dose heroin for outcomes: 6,<sup>27</sup> 7,<sup>27</sup></p> <p>2 year follow-up data from Andalusian trial<sup>29</sup> shows maintained difference, where by high-dose heroin group showed significant benefit for outcomes: 1,<sup>29</sup> 2,<sup>29</sup> 3 (psychiatric),<sup>29</sup> 5 (cannabis),<sup>29</sup> and SF-12 Mental Health Scores<sup>29</sup></p>
<p>Low Dose Methadone (&lt;60 mg/day) vs High Dose Methadone (<math>\geq 60</math> mg/day)</p>	<ol style="list-style-type: none"> <li>1. Opioid urinalysis, percentage of positive opioid urine screens per treatment arm<sup>11,13,30-33</sup></li> <li>2. Opioid drug cravings<sup>13,31</sup></li> <li>3. Percentage of participants per treatment arm who maintained 12 consecutive opioid-free urine screens<sup>30</sup></li> <li>4. The total number of doses taken per participant measured medication Compliance<sup>30</sup></li> <li>5. Successful medication induction was defined as at least one dose of medication by the 6<sup>th</sup> day of the study<sup>30</sup></li> <li>6. Urinalysis for poly-substance use (cocaine, cannabinoids, benzodiazepines)<sup>30-32</sup></li> <li>7. Psychological functioning assessed using multiple domains from the ASI<sup>30</sup></li> <li>8. Self-reported times of drug use since last visit<sup>31</sup></li> <li>9. Self-reported dollars spent on illicit substances and alcohol since last visit<sup>31</sup></li> </ol>	<p>High dose methadone showed significant benefit over low dose methadone for outcomes: 1,<sup>11,13,32,33</sup> 2,<sup>13,31</sup> 3,<sup>30</sup> 8,<sup>31</sup> 9,<sup>31</sup> 11<sup>32</sup></p>

	<ol style="list-style-type: none"> <li>10. Criminal activity and social functioning measured using the Lifestyle Changes Questionnaire (patients indicated whether they had engaged in any of 9 activities to stop, reduce, or avoid cocaine/heroin use during the past week and whether they had committed crimes)<sup>31</sup></li> <li>11. Self-reported opioid use over study period<sup>32</sup></li> <li>12. Physical health evaluation using self-report hematology tests, blood chemistry, vital signs, and weight<sup>33</sup></li> <li>13. Self-reported withdrawal symptoms<sup>33</sup></li> </ol>	
<p>Low Dose Oral Naltrexone (50mg) vs Placebo</p>	<ol style="list-style-type: none"> <li>1. Opioid urinalysis, percentage of positive opioid urine screens<sup>34-38</sup></li> <li>2. Poly-substance urinalysis, percentage of positive cannabinoid and benzodiazepine urine screens<sup>37</sup></li> <li>3. Self-reported poly-substance use by family members or friends watching the participant<sup>36,38</sup></li> <li>4. Relapse (self-reported everyday heroin use, three consecutive positive urine tests, or reported symptoms of withdrawal)<sup>35,36,38</sup></li> <li>5. Slip (self-reported occasional heroin use, less than three consecutive positive urine screens, and no symptoms of withdrawal)<sup>35,36,38</sup></li> <li>6. HIV risk assessed using Risk Assessment Battery (RAB) scores<sup>36,38</sup></li> <li>7. Psychiatric symptoms assessed using Beck Depression Inventory, Spielberger State-Trait Anxiety Test, and the Scale of Anhedonia Syndrome<sup>36,38</sup></li> <li>8. Days to heroin use measured as the first opiate positive urine test after randomization<sup>39</sup></li> <li>9. Days to heroin relapse (3 consecutive opiate-positive urine screens)<sup>39</sup></li> <li>10. Number of days a patient could remain abstinent measured by the longest duration of opiate negative urine screens<sup>39</sup></li> <li>11. Reductions in self-reported HIV risk behaviors<sup>39</sup></li> <li>12. Psychiatric symptoms measured using self-reported assessments (somatization, depression, hostility, anxiety, paranoid ideation, interpersonal sensitivity) assessed using the Brief Symptoms Inventory<sup>37</sup></li> <li>13. Addiction severity measured using composite ASI scores across different domains assessing personal, social, and physical functioning<sup>36,38</sup></li> <li>14. Self-reported euphoric feelings<sup>34</sup></li> <li>15. Duration of abstinence (opioid negative urine screens) across treatment arms<sup>34</sup></li> <li>16. Medication compliance was assessed in three ways: count of remaining capsules at each appointment; inclusion of riboflavin 50 mg in the active and placebo naltrexone capsules with visual inspection for its presence using ultraviolet light at the long wave setting (444 nm) in a room with low ambient light (O'Malley et al., 1992); and involvement of a significant other in</li> </ol>	<p>Low dose oral naltrexone showed significant benefit over placebo for outcomes: 1,<sup>34,35</sup> 4,<sup>36</sup> 12,<sup>37</sup> 19<sup>38</sup></p>

	<p>treatment who was asked to supervise and report on compliance at each study visit, either in person or by telephone<sup>35,36,38</sup></p> <ol style="list-style-type: none"> <li>17. Overall adjustment measured using the Clinical Global Impression as assessed by the Brief Psychiatric Rating Scale<sup>34,38</sup></li> <li>18. Alcohol consumption confirmed by breathalyser test<sup>34</sup></li> <li>19. Heroin craving assessed using Visual Analog Scale of Craving for heroin<sup>34,38</sup></li> <li>20. Physical Health: Immune system functioning as assessed by ALT/AST<sup>35,36</sup></li> <li>21. Percentage of patients in a drug free period, defined as time elapsed between the first day of Naltrexone administration and the first evidence of opiate abuse (day on which positive urine test for opiate was obtained, or alternatively, the day on which the patient reported on opiate abuse)<sup>37</sup></li> <li>22. Time until opioid relapse as assessed by urine toxicology screening<sup>37</sup></li> </ol>	
Naltrexone implant (1000mg) vs. Placebo	<ol style="list-style-type: none"> <li>1. Opioid urinalysis to assess for relapse in patients (percentage of positive opioid urine screens per treatment arm)<sup>35</sup></li> <li>2. Relapse (self-reported everyday heroin use, three consecutive positive urine tests, or reported symptoms of withdrawal)<sup>35,36</sup></li> <li>3. Slip (self-reported occasional heroin use, less than three consecutive positive urine screens, and no symptoms of withdrawal)<sup>35,36</sup></li> <li>4. Medication compliance was assessed in three ways: count of remaining capsules at each appointment; inclusion of riboflavin 50 mg in the active and placebo naltrexone capsules with visual inspection for its presence using ultraviolet light at the long wave setting (444 nm) in a room with low ambient light (O'Malley et al., 1992); and involvement of a significant other in treatment who was asked to supervise and report on compliance at each study visit, either in person or by telephone<sup>35,36</sup></li> </ol>	Naltrexone implant (1000mg) showed significant benefit over placebo for outcomes: 1 <sup>35</sup>
Naltrexone implant (1000mg) vs Oral Naltrexone (50 mg)	<ol style="list-style-type: none"> <li>1. Opioid urinalysis to assess for relapse in patients (percentage of positive opioid urine screens per treatment arm)<sup>35</sup></li> <li>2. Relapse (self-reported everyday heroin use, three consecutive positive urine tests, or reported symptoms of withdrawal)<sup>35,36</sup></li> <li>3. Slip (self-reported occasional heroin use, less than three consecutive positive urine screens, and no symptoms of withdrawal)<sup>35,36</sup></li> <li>4. Medication compliance was assessed in three ways: count of remaining capsules at each appointment; inclusion of riboflavin 50 mg in the active and placebo naltrexone capsules with visual inspection for its presence using ultraviolet light at the long wave setting (444 nm) in a room with low ambient light (O'Malley et al., 1992); and involvement of a significant other in treatment who was asked to supervise and report on compliance at each study visit, either in person or by telephone<sup>35,36</sup></li> </ol>	Naltrexone implant (1000mg) showed significant benefit over oral naltrexone for outcomes: 1 <sup>35</sup>

<p>Low Dose Buprenorphine (&lt;16mg) vs. Placebo</p>	<ol style="list-style-type: none"> <li>1. Opioid urinalysis to assess for relapse in patients (percentage of positive opioid urine screens per treatment arm)<sup>40</sup></li> <li>2. Days to heroin use measured as the first opiate positive urine test after randomization<sup>39</sup></li> <li>3. Days to heroin relapse (3 consecutive opiate-positive urine screens)<sup>39</sup></li> <li>4. Number of days a patient could remain abstinent measured by the longest duration of opiate negative urine screens<sup>39</sup></li> <li>5. Reductions in self-reported HIV risk behaviors<sup>39</sup></li> <li>6. Compliance measured as the total number of doses taken<sup>20</sup></li> <li>7. Self reported drug use measured using a VAS (daily heavy drug abuse' was recorded as 10 and 'drug free' was recorded as 0)<sup>20</sup></li> <li>8. Subjective wellbeing was measured with a VAS (10 = very bad, 0 = very well) and with the temporal satisfaction with life scale (TSLs)<sup>20</sup></li> <li>9. Mental health (i.e. anxiety and depression) was measured with the symptom checklist (SCL-5)<sup>20</sup></li> </ol>	<p>Low dose buprenorphine showed significant benefit over placebo for outcomes: 2,<sup>39</sup> 3,<sup>39</sup> 4,<sup>39</sup> 7,<sup>20</sup> 8<sup>20</sup></p>
<p>High Dose Methadone (≥60mg/day) vs. Waitlist</p>	<ol style="list-style-type: none"> <li>1. Opioid urinalysis to assess for heroin use (percentage of positive opioid urine screens per treatment arm)<sup>41</sup></li> <li>2. Cocaine urinalysis (percentage of cocaine positive urine screens across treatment arms)<sup>41</sup></li> </ol>	<p>High dose methadone showed significant benefit over waitlist for outcomes: 1<sup>41</sup></p>
<p>Slow Release Oral Morphine vs High Dose Methadone (≥60 mg/day)</p>	<ol style="list-style-type: none"> <li>1. Opioid urinalysis to assess for heroin use (percentage of positive opioid urine screens per treatment arm)<sup>42</sup></li> <li>2. Cocaine urinalysis (percentage of cocaine positive urine screens across treatment arms)<sup>42</sup></li> <li>3. Psychological well-being, evaluating depression and anxiety using the Beck Depression Inventory and the State-Trait Anxiety Inventory (STAI) respectively<sup>42</sup></li> <li>4. Withdrawal symptoms evaluated using The Wang Scale<sup>42</sup></li> </ol>	<p>Slow release oral morphine showed significant benefit over high dose methadone for outcomes: 3<sup>42</sup></p>
<p>Low Dose Levomethadyl Acetate Hydrochloride (LAAM) (&lt;85 mg/day) vs. High Dose LAAM (≥85 mg/day)</p>	<ol style="list-style-type: none"> <li>1. Opioid urinalysis to assess for heroin use (percentage of positive opioid urine screens per treatment arm)<sup>43</sup></li> <li>2. Self-reported heroin use<sup>43</sup></li> </ol>	<p>High dose LAAM showed significant benefit over low dose LAAM for outcomes: 1,<sup>43</sup> 2<sup>43</sup></p>

<p>Levomethadyl acetate (range 30 – 80 mg/day) vs Methadone (range 36 to 80 mg)</p>	<ol style="list-style-type: none"> <li>1. Opioid urinalysis to assess for heroin use (percentage of positive opioid urine screens per treatment arm)<sup>44</sup></li> <li>2. Morphine and opioid withdrawal assessed using the Addiction Research Centre Inventory (ARCI)<sup>44</sup></li> <li>3. Illicit drug use, illegal activity and employment assessed using the a Weekly Activity Summary (WAS)<sup>44</sup></li> </ol>	<p>Methadyl acetate showed no significant benefit over methadone for any of the listed outcomes</p>
<p>Levomethadyl acetate (range 30 – 80 mg/day) vs waitlist</p>	<ol style="list-style-type: none"> <li>1. Morphine and opioid withdrawal assessed using the Addiction Research Centre Inventory (ARCI)<sup>44</sup></li> <li>2. Self-reported employment<sup>44</sup></li> </ol>	<p>Methadyl acetate showed no significant benefit over waitlist for any of the listed outcomes</p>
<p>Low Dose Suboxone® (buprenorphine &lt;16 mg/day + naloxone) vs. Low Dose Methadone (&lt;60 mg)</p>	<ol style="list-style-type: none"> <li>1. Opioid urinalysis to assess for illicit opioid use (percentage of positive opioid urine screens per treatment arm)<sup>30</sup></li> <li>2. Percentage of participants per treatment arm who maintained 12 consecutive opioid-free urine screens<sup>30</sup></li> <li>3. The total number of doses taken per participant measured medication Compliance<sup>30</sup></li> <li>4. Successful medication induction was defined as at least one dose of medication by the 6<sup>th</sup> day of the study<sup>30</sup></li> <li>5. Urinalysis for poly-substance use<sup>30</sup></li> <li>6. Psychological functioning assessed using multiple domains from the ASI<sup>30</sup></li> </ol>	<p>Outcomes did not significantly differ between treatment</p>
<p>High Dose Suboxone® (buprenorphine ≥ 16 mg/day + naloxone ) vs. High Dose Methadone (≥ 60 mg/day)</p>	<ol style="list-style-type: none"> <li>1. Opioid urinalysis to assess for illicit opioid use (percentage of positive opioid urine screens per treatment arm)<sup>30</sup></li> <li>2. Percentage of participants per treatment arm who maintained 12 consecutive opioid-free urine screens<sup>30</sup></li> <li>3. The total number of doses taken per participant measured medication Compliance<sup>30</sup></li> <li>4. Successful medication induction was defined as at least one dose of medication by the 6<sup>th</sup> day of the study<sup>30</sup></li> <li>5. Urinalysis for poly-substance use<sup>30</sup></li> <li>6. Psychological functioning assessed using multiple domains from the ASI<sup>30</sup></li> <li>7. Drug use history and routes of substance abuse measured using risk behaviour survey<sup>45</sup></li> <li>8. Severity of nicotine dependence assessed using The Fagerström Test for Nicotine Dependence<sup>45</sup></li> </ol>	<p>Outcomes did not significantly differ between treatment</p>

	<ol style="list-style-type: none"> <li>9. Quality of life (physical functioning, physical role limitations, bodily pain, general mental health, vitality, health perceptions) measured using the Short Form 36-item Health Survey<sup>45</sup></li> <li>10. Physical Health: Liver functioning as assessed by ALT/AST<sup>46</sup></li> <li>11. Self-reported 30 day history of opioid abuse<sup>45</sup></li> </ol>	
<p>Low Dose Suboxone® (buprenorphine &lt;16 mg/day + naloxone) vs. High Dose Methadone (≥ 60 mg/day)</p>	<ol style="list-style-type: none"> <li>1. Opioid urinalysis to assess for illicit opioid use (percentage of positive opioid urine screens per treatment arm)<sup>30</sup></li> <li>2. Percentage of participants per treatment arm who maintained 12 consecutive opioid-free urine screens<sup>30</sup></li> <li>3. The total number of doses taken per participant measured medication Compliance<sup>30</sup></li> <li>4. Successful medication induction was defined as at least one dose of medication by the 6<sup>th</sup> day of the study<sup>30</sup></li> <li>5. Urinalysis for poly-substance use<sup>30</sup></li> <li>6. Psychological functioning assessed using multiple domains from the ASI<sup>30</sup></li> </ol>	<p>Outcomes did not significantly differ between treatment</p>
<p>High Dose Suboxone® (buprenorphine ≥ 16 mg/day + naloxone) vs. Low Dose Methadone (&lt;60 mg)</p>	<ol style="list-style-type: none"> <li>1. Opioid urinalysis to assess for illicit opioid use (percentage of positive opioid urine screens per treatment arm)<sup>30</sup></li> <li>2. Percentage of participants per treatment arm who maintained 12 consecutive opioid-free urine screens<sup>30</sup></li> <li>3. The total number of doses taken per participant measured medication compliance<sup>30</sup></li> <li>4. Successful medication induction was defined as at least one dose of medication by the 6<sup>th</sup> day of the study<sup>30</sup></li> <li>5. Urinalysis for poly-substance use<sup>30</sup></li> <li>6. Psychological functioning assessed using multiple domains from the ASI<sup>30</sup></li> </ol>	<p>Outcomes did not significantly differ between treatment</p>
<p>High Dose Suboxone® (buprenorphine ≥ 16 mg/day + naloxone) vs. Low Dose Suboxone® (buprenorphine &lt;16 mg/day + naloxone)</p>	<ol style="list-style-type: none"> <li>1. Opioid urinalysis to assess for illicit opioid use (percentage of positive opioid urine screens per treatment arm)<sup>30</sup></li> <li>2. Percentage of participants per treatment arm who maintained 12 consecutive opioid-free urine screens<sup>30</sup></li> <li>3. The total number of doses taken per participant measured medication Compliance<sup>30</sup></li> <li>4. Successful medication induction was defined as at least one dose of medication by the 6<sup>th</sup> day of the study<sup>30</sup></li> <li>5. Urinalysis for poly-substance use<sup>30</sup></li> </ol>	<p>High dose Suboxone® showed significant benefit over low dose Suboxone® for outcomes: 2<sup>30</sup></p>

	6. Psychological functioning assessed using multiple domains from the ASI <sup>30</sup>	
Low Dose Oral Naltrexone (50mg) vs. Low Dose Buprenorphine (<16 mg)	<ol style="list-style-type: none"> <li>1. Days to heroin use measured as the first opiate positive urine test after randomization<sup>39</sup></li> <li>2. Days to heroin relapse (3 consecutive opiate-positive urine screens)<sup>39</sup></li> <li>3. Number of days a patient could remain abstinent measured by the longest duration of opiate negative urine screens<sup>39</sup></li> <li>4. Reductions in self-reported HIV risk behaviors used AIDS risk inventory<sup>39</sup></li> </ol>	Low dose buprenorphine showed significant benefit over low dose oral naltrexone for outcomes: 1, <sup>39</sup> 2, <sup>39</sup> 3 <sup>39</sup>
Dihydrocodiene (30 or 60 mg/day) vs Methadone (no specified dosing reported, range 40-150 mg)	<ol style="list-style-type: none"> <li>1. Opioid urinalysis to assess for illicit opioid use (percentage of positive opioid urine screens per treatment arm)<sup>47</sup></li> <li>2. Health risk behaviour (sexual behaviour, injecting drug use behaviour, HIV risk) measured using the Maudsley Addiction Profile<sup>47</sup></li> <li>3. Personal and social functioning (criminal activity, relationships) measured using the Maudsley Addiction Profile<sup>47</sup></li> <li>4. Physical health measured using Maudsley Addiction Profile<sup>47</sup></li> <li>5. Overdose<sup>47</sup></li> </ol>	Outcomes did not significantly differ between treatment
High Dose Buprenorphine (≥ 16 mg/day) vs Low Dose Buprenorphine (<16 mg/day)	<ol style="list-style-type: none"> <li>1. Opioid urinalysis to assess for illicit opioid use (percentage of positive opioid urine screens per treatment arm)<sup>48</sup></li> <li>2. Craving for heroin was measured weekly on a 10 cm visual analog scale labeled zero at one end (no craving for heroin) and 100 at the other end (the most intense craving ever experienced for heroin)<sup>48</sup></li> <li>3. The global severity of all aspects of their current drug problem measured on a scale of 0 (no problem) to 100 (very severe)<sup>48</sup></li> </ol>	High dose buprenorphine showed significant benefit over low dose buprenorphine for outcomes: 1, <sup>48</sup> 2 <sup>48</sup>
High Dose Buprenorphine (≥ 16 mg/day) vs High Dose Methadone (≥ 60 mg/day)	<ol style="list-style-type: none"> <li>1. Opioid urinalysis to assess for illicit opioid use (percentage of positive opioid urine screens per treatment arm)<sup>49</sup></li> <li>2. Urinalysis to assess for poly-substance use (percentage of positive stimulants/cannabinoids/benzodiazepines urine screens per treatment arm)<sup>49</sup></li> <li>3. Psychiatric depressive symptoms measured using a self-rating depression (SRD) questionnaire<sup>49</sup></li> <li>4. Heroin craving was measured using the Tiffany Heroin Craving Questionnaire<sup>49</sup></li> <li>5. Immune system response was measured using plasma concentrations of TNF-alpha, IL-2 beta, IL-1beta and CD14 lymphocyte<sup>49</sup></li> <li>6. Heroin use in preceding month at three, six, and twelve month interviews using measures of self-reported frequency of use (measured using the Opiate Treatment Index)<sup>50</sup></li> </ol>	High dose buprenorphine showed significant benefit in comparison to high dose methadone for outcomes: 1, <sup>49</sup> 2, <sup>49</sup> 3, <sup>49</sup> 4, <sup>49</sup> 8, <sup>8</sup> 9 <sup>8</sup>

	<ol style="list-style-type: none"> <li>7. HIV-risk taking behaviour, social functioning, criminality, physical health and psychological status measured using the Opiate Treatment Index)<sup>50</sup></li> <li>8. Cardiac Function assessed with corrected mean QT interval measurements obtained from electrocardiographic analysis over the study period<sup>8</sup></li> <li>9. Evaluation of patients meeting the categorical QTc prolongation thresholds across treatment groups (more than 470 milliseconds for males and more than 490 milliseconds for females)<sup>8</sup></li> </ol>	
Low Dose Methadone (<60 mg/day) vs. Placebo	<ol style="list-style-type: none"> <li>1. Opioid urinalysis to assess for illicit opioid use (percentage of positive opioid urine screens per treatment arm)<sup>51</sup></li> <li>2. Urinalysis to assess for poly-substance use (percentage of positive stimulants/benzodiazepines urine screens per treatment arm)<sup>51</sup></li> <li>3. Compliance with treatment was assessed through treatment attendance, the number of days medicated divided by days in treatment, and counselling contacts, which were based on the length (minutes) and number of contacts the patient had with either individual or group treatments<sup>51</sup></li> </ol>	Low dose methadone showed significant benefit over placebo for outcomes: 1, <sup>51</sup> 2(cocaine), <sup>51</sup> 3 <sup>51</sup>
High Dose Injectable Methadone (≥60mg/day) vs High Dose Injectable Heroin	<ol style="list-style-type: none"> <li>1. Response to treatment measured as a reduction of regular use of street heroin, which was defined as 50% or more of negative specimens on urinalysis during weeks 14–26<sup>28</sup></li> <li>2. Self-reported abstinence or near abstinence from street heroin (zero use) in the past 30 days was obtained by independent researchers in face-to-face interviews<sup>28</sup></li> </ol>	High dose injectable heroin showed significant difference over high dose injectable methadone for outcomes: 1 <sup>28</sup>
High-dose Injectable Methadone (≥60mg/day) vs. High-dose Oral Methadone (≥60 mg/day)	<ol style="list-style-type: none"> <li>1. Response to treatment measured as a reduction of regular use of street heroin, which was defined as 50% or more of negative specimens on urinalysis during weeks 14–26<sup>28</sup></li> <li>2. Opioid urinalysis to assess for near (&lt;2 opioid positive urine screens) and full abstinence (0 opioid positive urine screens)<sup>28</sup></li> <li>3. Self-reported abstinence or near abstinence from street heroin (zero use) in the past 30 days was obtained by independent researchers in face-to-face interviews<sup>28</sup></li> </ol>	Outcomes did not significantly differ between treatment
Low Dose Levoacetylmethadol (LAAM) (< 85 mg/day) vs High Dose Methadone (>60 mg/day)	<ol style="list-style-type: none"> <li>1. Changes in vocational and social rehabilitation<sup>6</sup></li> <li>2. Degree of substance abuse measured using a global rating scale: rating of 2 marked an improvement in rehabilitation and substance use<sup>6</sup></li> <li>3. Opioid urinalysis to assess for illicit opioid use (percentage of positive opioid urine screens per treatment arm)<sup>6,33</sup></li> <li>4. Opioid urinalysis to assess for poly-substance use (percentage of positive</li> </ol>	Outcomes only reported using descriptive statistics, no tests made across treatment groups

	<p>stimulants/benzodiazepines urine screens per treatment arm)<sup>6</sup></p> <ol style="list-style-type: none"> <li>5. Mortality<sup>33</sup></li> <li>6. Physical health evaluation using self-report hematology tests, blood chemistry, vital signs, and weight<sup>33</sup></li> <li>7. Self-reported withdrawal symptoms<sup>33</sup></li> </ol>	
High Dose Oral Naltrexone (≥50 mg/day) vs. Placebo	<ol style="list-style-type: none"> <li>1. Opioid urinalysis to assess for illicit opioid use (percentage of positive opioid urine screens per treatment arm)<sup>52</sup></li> <li>2. Urinalysis to assess for poly-substance use (percentage of positive stimulants/benzodiazepines urine screens per treatment arm)<sup>52</sup></li> <li>3. Psychiatric symptoms assessed using the Minnesota Multifactorial Personality Inventory (MMPI); a specific questionnaire for measuring anxiety, the State-Trait Anxiety Inventory (STAI); and a personality questionnaire, the Sensation Seeking Scale (SSS)<sup>52</sup></li> <li>4. Acceptance of treatment was measured as “therapeutic success,” which was defined when patients had regularly taken the treatment for 6 months and had attended all the scheduled visits without presenting side effects of toxicity that forced patients to discontinue the therapy<sup>52</sup></li> </ol>	Placebo showed benefit over Naltrexone for Outcomes: 3 <sup>52</sup>
High-dose Methadone (≥60 mg/day) vs 180 day High-dose Methadone detoxification + Psychosocial Services	<ol style="list-style-type: none"> <li>1. Opioid use as assessed by self-report and confirmed by urine toxicology screening<sup>53</sup></li> <li>2. Cocaine use as assessed by self-report and confirmed by urine toxicology screening<sup>53</sup></li> <li>3. HIV risk behaviour as assessed by RAB<sup>53</sup></li> <li>4. Addiction severity measured using composite ASI scores across different domains assessing personal, social, and physical functioning<sup>53</sup></li> <li>5. Self-reported days of heroin use in the previous month<sup>53</sup></li> </ol>	<p>High-dose Methadone showed significant benefit over 180 day High-dose Methadone detoxification + Psychosocial Services for outcomes: 3,<sup>53</sup> 5<sup>53</sup></p> <p>High-dose Methadone detoxification + Psychosocial Services showed significant benefit over High-dose MMT for outcomes: 2<sup>53</sup></p>
High-dose Methadone (≥60mg/day) vs High-dose Methadone Medical Maintenance (≥60 mg/day, offered at methadone clinic and physicians office, patients allowed 1 month reporting and dispensed methadone for 27 days at a time)	<ol style="list-style-type: none"> <li>1. Opioid use as assessed by urine toxicology screening<sup>54</sup></li> <li>2. Addiction severity measured using composite ASI scores across different domains assessing personal, social, and physical functioning<sup>54</sup></li> <li>3. Medication Monitoring: all study patients were required to respond to a random medication recall once each 4 weeks to monitor and deter potential misuse of methadone<sup>54</sup></li> <li>4. Medication preference as assessed by the Client Satisfaction Questionnaire (CSQ), a self-administered questionnaire that assesses overall satisfaction with treatment<sup>54</sup></li> <li>5. Medication preference as assessed by the Helping Alliance Questionnaire II (HAQ-II; patient version), which is a 19-question self-administered instrument</li> </ol>	High-dose Methadone Medical Maintenance showed significant benefit over routine High-dose Methadone for outcomes: 4 <sup>54</sup>

	<p>that measures the quality of therapeutic alliance between patients and therapists from the point of view of the patients<sup>54</sup></p> <p>6. Personal and Social Functioning as assessed by behavioural observation where the research assistant recorded (yes/no) if patients had initiated new activities or increased the amount of time spent in any of three activity categories: (1) employment; (2) family/social; and (3) personal (spiritual, counseling or psychotherapy, physical fitness)<sup>54</sup></p>	
High-dose Methadone (≥60 mg/day) vs. High-dose Interim Methadone	<ol style="list-style-type: none"> <li>1. Addiction severity measured using composite ASI scores across different domains assessing personal, social, and physical functioning<sup>55</sup></li> <li>2. Opioid use as assessed by self-report and confirmed by urine toxicology screening<sup>55</sup></li> <li>3. Cocaine use as assessed by self-report and confirmed by urine toxicology screening<sup>55</sup></li> <li>4. Self-reported opioid use (number of times of use in the previous 30 days)<sup>55</sup></li> <li>5. Self-reported cocaine use (number of times of use in the previous 30 days)<sup>55</sup></li> <li>6. Self-reported illegal activity in preceding month<sup>55</sup></li> <li>7. Self-reported money spent on drugs in preceding month<sup>55</sup></li> <li>8. Self-reported money gained from illegal activity in previous month<sup>55</sup></li> </ol>	High-dose Interim Methadone showed significant benefit over High-dose Methadone for outcomes: 7, <sup>55</sup> 8 <sup>55</sup>
High-dose Interim Methadone (≥60 mg/day) vs Waitlist	<ol style="list-style-type: none"> <li>1. Addiction severity measured using composite ASI scores across different domains assessing personal, social, and physical functioning<sup>56</sup></li> <li>2. Opioid use as assessed by self-report and confirmed by urine toxicology screening<sup>56</sup></li> <li>3. Cocaine use as assessed by self-report and confirmed by urine toxicology screening<sup>56</sup></li> <li>4. Self-reported opioid use (number of times of use in the previous 30 days)<sup>56</sup></li> <li>5. Self-reported cocaine use (number of times of use in the previous 30 days)<sup>56</sup></li> <li>6. Self-reported illegal activity in preceding month<sup>56</sup></li> <li>7. Self-reported money spent on drugs in preceding month<sup>56</sup></li> <li>8. Self-reported money gained from illegal activity in previous month<sup>56</sup></li> </ol>	High-dose Interim Methadone showed significant benefit over Waitlist: 2, <sup>56</sup> 4, <sup>56</sup> 7, <sup>56</sup> 8 <sup>56</sup>
High-dose Levomethadyl Acetate Hydrochloride (LAAM) (≥85 mg/day) vs. High Dose Buprenorphine (≥ 16 mg/day)	<ol style="list-style-type: none"> <li>1. Cardiac Function assessed with corrected QT interval measurements obtained from electrocardiographic analysis<sup>8</sup></li> <li>2. Evaluation of patients meeting the categorical QTc prolongation thresholds across treatment groups (more than 470 milliseconds for males and more than 490 milliseconds for females, as well as other sensitivity analyses such as 30 sec thresholds)<sup>8</sup></li> </ol>	High-dose Buprenorphine showed significant benefit over High-dose LAAM for outcomes: 1, <sup>8</sup> 2 <sup>8</sup>
High Dose Buprenorphine	<ol style="list-style-type: none"> <li>1. Opioid Use assessed by urine toxicology screening<sup>57</sup></li> </ol>	High Dose Buprenorphine showed significant benefit

<p>(≥ 16 mg/day) vs High-dose Buprenorphine Taper Program</p>	<ol style="list-style-type: none"> <li>2. Opioid Use assessed by self-report<sup>57</sup></li> <li>3. Poly-substance use (cocaine, benzodiazepine, methamphetamines, and cannabis) as assessed by urine toxicology screening<sup>57</sup></li> <li>4. Poly-substance use (cocaine, benzodiazepine, methamphetamines, and cannabis) as assessed by self-report<sup>57</sup></li> <li>5. Self-reported injecting drug use behavior<sup>57</sup></li> <li>6. Self-reported participation in other treatment programs<sup>57</sup></li> </ol>	<p>over high-dose Buprenorphine taper program for outcomes: 1 (only at week 4, 8, and 12),<sup>57</sup> 3,<sup>57</sup> 4,<sup>57</sup> 5,<sup>57</sup> 6<sup>57</sup></p>
<p>Low Dose Levoacetylmethadol (LAAM) (&lt; 85 mg/day) vs Low Dose Methadone (&gt;60 mg/day)</p>	<ol style="list-style-type: none"> <li>1. Opioid urinalysis to assess for illicit opioid use (percentage of positive opioid urine screens per treatment arm)<sup>33</sup></li> <li>2. Physical health evaluation using self-report hematology tests, blood chemistry, vital signs, and weight<sup>33</sup></li> <li>3. Self-reported withdrawal symptoms<sup>33</sup></li> </ol>	<p>Low Dose Levoacetylmethadol (LAAM) showed significant benefit over Low-dose Methadone for outcomes: 1<sup>33</sup></p>

\*Significant benefit assessed from direct comparison made in study, p<0.05

**eTable 4: Summary of Findings for all SOT Comparisons Reported Across Outcome Domains**

Intervention A	Intervention B	Number of Trials Evaluating Comparison	Number of Patients in Comparison	Domain: Outcome Domain	Number of Trials for Showing Benefit for Intervention A	Number of Trials showing Benefit for Intervention B	Final Evaluation
High-dose Methadone	Injectable High-dose Heroin + High-dose Methadone	2 <sup>1,2</sup>	236	Global Quality of Life and Addiction Severity Assessment: Composite Addiction Severity Scores	0	2 <sup>1,2</sup>	Intervention B Superior <sup>1,2</sup>
High-dose Methadone	Injectable High-dose Heroin + High-dose Methadone	1 <sup>2</sup>	62	Global Quality of Life and Addiction Severity Assessment: Global Quality of Life	0	0	N/A
High-dose Methadone	Injectable High-dose Heroin + High-dose Methadone	1 <sup>2</sup>	62	Psychiatric Health and Symptoms: Psychological Adjustment	0	0	N/A
High-dose Methadone	Injectable High-dose Heroin + High-dose Methadone	1 <sup>2</sup>	62	Physical Health: General Physical Health	0	1 <sup>2</sup>	N/A
High-dose Methadone	Injectable High-dose Heroin + High-dose Methadone	1 <sup>2</sup>	62	Abstinence and Substance Use Behaviour: Health Risk Behaviour (related to substance use)	0	1 <sup>2</sup>	N/A
High-dose Methadone	Injectable High-dose Heroin + High-dose Methadone	1 <sup>2</sup>	62	Personal and Social Functioning: Criminal Behaviour	0	1 <sup>2</sup>	N/A
High-dose Injectable Naltrexone	Placebo	1 <sup>3</sup>	40	Abstinence and Substance Use Behaviour: Illicit Opioid Use	1 <sup>3</sup>	0	N/A
Low-dose Injectable Naltrexone	Placebo	1 <sup>3</sup>	38	Abstinence and Substance Use Behaviour: Illicit Opioid Use	1 <sup>3</sup>	0	N/A
High-dose Levoacetylmethadol (LAAM)	High-dose Methadone	4 <sup>4-7</sup>	481	Abstinence and Substance Use Behaviour: Illicit Opioid Use	2 <sup>4,7</sup>	0	Intervention A Superior <sup>4,7</sup>
High-dose Levoacetylmethadol (LAAM)	High-dose Methadone	1 <sup>5</sup>	84	Physical Health: Drug Craving	0	0	N/A
High-dose Levoacetylmethadol (LAAM)	High-dose Methadone	1 <sup>5</sup>	84	Physical Health: Withdrawal Symptoms	0	0	N/A
High-dose Levoacetylmethadol (LAAM)	High-dose Methadone	2 <sup>5,8</sup>	184	Physical Health: General Physical Health	0	1	N/A
High-dose Levoacetylmethadol	High-dose Methadone	1 <sup>5</sup>	84	Global Quality of Life and Addiction Severity Assessment: Composite Addiction Severity Scores	0	0	N/A
High-dose Levoacetylmethadol (LAAM)	High-dose Methadone	1 <sup>5</sup>	84	Global Quality of Life and Addiction Severity Assessment: Global Quality of Life	0	0	N/A
High-dose Levoacetylmethadol	High-dose Methadone	1 <sup>7</sup>	62	Intervention Acceptance: Intervention Preference	1 <sup>7</sup>	0	N/A

dol (LAAM)							
High-dose Levoacetylmethadol (LAAM)	High-dose Methadone	1 <sup>7</sup>	62	Personal and Social Functioning: Employment and Social Involvement	0	0	N/A
High-dose Levoacetylmethadol (LAAM)	High-dose Methadone	1 <sup>7</sup>	62	Personal and Social Functioning Relationships	0	0	N/A
High-dose Levoacetylmethadol (LAAM)	High-dose Methadone	2 <sup>6,7</sup>	82	Abstinence and Substance Use Behaviour: Illicit Non-Opioid Substance Use	0	0	N/A
High-dose Methadone	Low-dose Buprenorphine	8 <sup>9-16</sup>	780	Abstinence and Substance Use Behaviour: Illicit Opioid Use	3 <sup>12,13,16</sup>	2 <sup>10,11</sup>	Inconclusive <sup>10-13,16</sup>
High-dose Methadone	Low-dose Buprenorphine	3 <sup>15-17</sup>	306	Abstinence and Substance Use Behaviour: Non-Opioid Substance Use	2 <sup>12,16</sup>	0	Intervention A Superior <sup>12,16</sup>
High-dose Methadone	Low-dose Buprenorphine	3 <sup>13-15</sup>	280	Physical Health: Drug Craving	1 <sup>13</sup>	0	Inconclusive <sup>13</sup>
High-dose Methadone	Low-dose Buprenorphine	1 <sup>13</sup>	91	Physical Health: Withdrawal Symptoms	0	0	N/A
High-dose Methadone	Low-dose Buprenorphine	1 <sup>13</sup>	91	Abstinence and Substance Use Behaviour: Money Spent on Illicit Opioid Consumption	0	0	N/A
High-dose Methadone	Low-dose Buprenorphine	1 <sup>13</sup>	91	Psychiatric Health and Symptoms: Psychiatric Symptoms	0	0	N/A
High-dose Suboxone	Placebo	1 <sup>18</sup>	218	Abstinence and Substance Use Behaviour: Illicit Opioid Use	1 <sup>18</sup>	0	Intervention A Superior <sup>18</sup>
High-dose Suboxone	Placebo	1 <sup>18</sup>	218	Physical Health: Drug Craving	1 <sup>18</sup>	0	Intervention A Superior <sup>18</sup>
High-dose Buprenorphine	Placebo	2 <sup>18,20</sup>	324	Abstinence and Substance Use Behaviour: Illicit Opioid Use	2 <sup>18,20</sup>	0	Intervention A Superior <sup>18,20</sup>
High-dose Buprenorphine	Placebo	1 <sup>20</sup>	106	Abstinence and Substance Use Behaviour: Non-Opioid Substance Use	1 <sup>20</sup>	0	N/A
High-dose Buprenorphine	Placebo	1 <sup>18</sup>	218	Physical Health: Drug Craving	1 <sup>18</sup>	0	Intervention A Superior <sup>18</sup>
High-dose Buprenorphine	Placebo	1 <sup>20</sup>	106	Intervention Adherence: Intervention Compliance	0	0	N/A
High-dose Buprenorphine	Placebo	1 <sup>20</sup>	106	Global Quality of Life and Addiction Severity Assessment: Composite Quality of Life Scores	1 <sup>20</sup>	0	N/A
High-dose	Placebo	1 <sup>20</sup>	106	Psychiatric Health and Symptoms:	0	0	N/A

				Psychiatric Symptoms			
High-dose Buprenorphine	Placebo	1 <sup>19</sup>	40	Global Quality of Life and Addiction Severity Assessment: Composite Addiction Severity Scores	1 <sup>19</sup>	0	N/A
Low-dose Buprenorphine	Low-dose Methadone	8 <sup>9,11-13,21-24</sup>	961	Abstinence and Substance Use Behaviour: Illicit Opioid Use	2 <sup>9,11</sup>	1 <sup>12</sup>	Inconclusive <sup>9,11,12</sup>
Low-dose Buprenorphine	Low-dose Methadone	2 <sup>21,23</sup>	226	Global Quality of Life and Addiction Severity Assessment: Composite Addiction Severity Scores	0	0	No Difference <sup>2</sup> <sub>1,23</sub>
Low-dose Buprenorphine	Low-dose Methadone	2 <sup>13,23</sup>	236	Physical Health: Drug Craving	0	0	No Difference <sup>1</sup> <sub>3,23</sub>
Low-dose Buprenorphine	Low-dose Methadone	4 <sup>17,21-23</sup>	478	Abstinence and Substance Use Behaviour: Illicit Non-Opioid Substance Use	0	0	Inconclusive <sup>e</sup> <sub>17,21-23</sub>
Low-dose Buprenorphine	Low-dose Methadone	2 <sup>12,23</sup>	180	Physical Health: Withdrawal Symptoms	0	1 <sup>12</sup>	N/A
Low-dose Buprenorphine	Low-dose Methadone	1 <sup>22</sup>	164	Intervention Adherence: Intervention Compliance	0	0	N/A
Low-dose Buprenorphine	Low-dose Methadone	1 <sup>22</sup>	164	Intervention Acceptance: Intervention Preference	0	0	N/A
Low-dose Buprenorphine	Low-dose Methadone	1 <sup>12</sup>	94	Abstinence and Substance Use Behaviour: Money Spent on Illicit Opioid Consumption	0	1 <sup>12</sup>	N/A
Low-dose Buprenorphine	Low-dose Methadone	1 <sup>9</sup>	80	Global Quality of Life and Addiction Severity Assessment: Composite Quality of Life	0	0	N/A
High-dose Heroin	High-dose Methadone	3 <sup>25,26,28</sup>	1368	Abstinence and Substance Use Behaviour: Illicit Opioid Use	3 <sup>25,26,28</sup>	0	Intervention A Superior <sup>25,26,28</sup>
High-dose Heroin	High-dose Methadone	2 <sup>26,27</sup>	322	Abstinence and Substance Use Behaviour: Illicit Non-Opioid Substance Use	1 <sup>26,27</sup>	0	Intervention A Superior <sup>26,27</sup>
High-dose Heroin	High-dose Methadone	1 <sup>27</sup>	96	Abstinence and Substance Use Behaviour: Health Risk Behaviour (related to substance use)	0	1 <sup>27</sup>	N/A
High-dose Heroin	High-dose Methadone	2 <sup>26,27</sup>	322	Personal and Social Functioning: Employment and Social Involvement	1 <sup>26</sup>	0	Intervention A Superior
High-dose Heroin	High-dose Methadone	1 <sup>27</sup>	96	Personal and Social Functioning Relationships	0	1 <sup>27</sup>	N/A
High-dose Heroin	High-dose Methadone	1 <sup>26</sup>	226	Psychiatric Health and Symptoms: Psychiatric Symptoms	1 <sup>26</sup>	0	Intervention A Superior <sup>26</sup>
High-dose Heroin	High-dose Methadone	1 <sup>25</sup>	1015	Physical Health: General Physical Health	0	0	No

							Difference <sup>2</sup> <sub>5</sub>
High-dose Heroin	High-dose Methadone	1 <sup>27</sup>	96	Physical Health: Overdose	0	0	N/A
High-dose Heroin	High-dose Methadone	1 <sup>27</sup>	96	Personal and Social Functioning: Criminal Behaviour	0	0	N/A
Low-dose Methadone	High-dose Methadone	6 <sup>11,13,30-33</sup>	771	Abstinence and Substance Use Behaviour: Illicit Opioid Use	0	5 <sup>11,13,30-33</sup>	Intervention B Superior <sup>2</sup> 11,13,30-33
Low-dose Methadone	High-dose Methadone	2 <sup>13,31</sup>	209	Physical Health: Drug Craving	0	2 <sup>13,31</sup>	Intervention B Superior <sup>2</sup> 13,31
Low-dose Methadone	High-dose Methadone	1 <sup>33</sup>	153	Physical Health: Withdrawal Symptoms	0	0	N/A
Low-dose Methadone	High-dose Methadone	1 <sup>33</sup>	153	Physical Health: General Physical Health	0	0	N/A
Low-dose Methadone	High-dose Methadone	3 <sup>30-32</sup>	379	Abstinence and Substance Use Behaviour: Illicit Non-Opioid Substance Use	0	0	No Difference <sup>3</sup> 0-32
Low-dose Methadone	High-dose Methadone	1 <sup>30</sup>	128	Psychiatric Health and Symptoms: Psychiatric Symptoms	0	0	N/A
Low-dose Methadone	High-dose Methadone	1 <sup>31</sup>	59	Abstinence and Substance Use Behaviour: Money Spent on Illicit Opioid Consumption	0	1 <sup>31</sup>	N/A
Low-dose Methadone	High-dose Methadone	1 <sup>31</sup>	59	Personal and Social Functioning: Criminal Behaviour	0	0	N/A
Low-dose Methadone	High-dose Methadone	1 <sup>30</sup>	128	Intervention Adherence: Intervention Compliance	0	0	N/A
Low-dose Methadone	High-dose Methadone	1 <sup>30</sup>	128	Intervention Adherence: Successful Medication Induction	0	0	N/A
Low-dose Oral Naltrexone	Placebo	6 <sup>34-39</sup>	812	Abstinence and Substance Use Behaviour: Illicit Opioid Use	2 <sup>34,35</sup>	0	Inconclusive <sup>3</sup> 34,35
Low-dose Oral Naltrexone	Placebo	2 <sup>37,38</sup>	84	Abstinence and Substance Use Behaviour: Illicit Non-Opioid Substance Use	0	0	N/A
Low-dose Oral Naltrexone	Placebo	2 <sup>36,38</sup>	134	Abstinence and Substance Use Behaviour: Health Risk Behaviour (related to substance use)	0	0	N/A
Low-dose Oral Naltrexone	Placebo	2 <sup>37,38</sup>	84	Psychiatric Health and Symptoms: Psychiatric Symptoms	1 <sup>37</sup>	0	N/A
Low-dose Oral Naltrexone	Placebo	3 <sup>35,36,38</sup>	396	Physical Health: General Physical Health	0	0	No Difference <sup>3</sup> 5,36
Low-dose Oral Naltrexone	Placebo	2 <sup>34,38</sup>	84	Physical Health: Drug Craving	1	0	Intervention A Superior

Low-dose Oral Naltrexone	Placebo	1 <sup>34</sup>	302	Intervention Acceptance: Intervention Preference	0	0	No Difference <sup>3</sup> <sub>4</sub>
Low-dose Oral Naltrexone	Placebo	3 <sup>35,36,38</sup>	396	Intervention Adherence: Intervention Compliance	0	0	No Difference <sup>3</sup> <sub>5,36</sub>
Naltrexone Implant	Placebo	1 <sup>35</sup>	204	Abstinence and Substance Use Behaviour: Illicit Opioid Use	1 <sup>35</sup>	0	Intervention A Superior <sup>35</sup>
Naltrexone Implant	Placebo	1 <sup>35</sup>	204	Intervention Adherence: Intervention Compliance <sup>35</sup>	0	0	No Difference <sup>3</sup> <sub>5</sub>
Naltrexone Implant	Oral Naltrexone	1 <sup>35</sup>	204	Abstinence and Substance Use Behaviour: Illicit Opioid Use	1 <sup>35</sup>	0	Intervention A Superior <sup>35</sup>
Naltrexone Implant	Oral Naltrexone	1 <sup>35</sup>	204	Intervention Adherence: Intervention Compliance	0	0	No Difference <sup>3</sup> <sub>5</sub>
Low-dose Buprenorphine	Placebo	2 <sup>39,40</sup>	233	Abstinence and Substance Use Behaviour: Illicit Opioid Use	1 <sup>39</sup>	0	Intervention A Superior <sup>39</sup>
Low-dose Buprenorphine	Placebo	1 <sup>39</sup>	83	Abstinence and Substance Use Behaviour: Health Risk Behaviour (related to substance use)	0	0	N/A
High-dose Methadone	Waitlist	1 <sup>41</sup>	301	Abstinence and Substance Use Behaviour: Illicit Opioid Use	1 <sup>41</sup>	0	Intervention A Superior <sup>41</sup>
High-dose Methadone	Waitlist	1 <sup>41</sup>	301	Abstinence and Substance Use Behaviour: Illicit Non-Opioid Substance Use	0	0	No Difference <sup>4</sup> <sub>1</sub>
Slow Release Oral Morphine	High-dose Methadone	1 <sup>42</sup>	64	Abstinence and Substance Use Behaviour: Illicit Opioid Use	0	0	N/A
Slow Release Oral Morphine	High-dose Methadone	1 <sup>42</sup>	64	Abstinence and Substance Use Behaviour: Illicit Non-Opioid Substance Use	0	0	N/A
Slow Release Oral Morphine	High-dose Methadone	1 <sup>42</sup>	64	Psychiatric Health and Symptoms: Psychiatric Symptoms	1 <sup>42</sup>	0	N/A
Slow Release Oral Morphine	High-dose Methadone	1 <sup>42</sup>	64	Physical Health: Withdrawal Symptoms	0	0	N/A
Low-dose LAAM	High-Dose LAAM	1 <sup>43</sup>	121	Abstinence and Substance Use Behaviour: Illicit Opioid Use	0	1 <sup>43</sup>	N/A
Methadyl acetate (range 30-80 mg)	Methadone (range 36-90 mg)	1 <sup>44</sup>	34	Abstinence and Substance Use Behaviour: Illicit Opioid Use	0	0	N/A
Methadyl acetate (range 30-80 mg)	Methadone (range 36-90 mg)	1 <sup>44</sup>	34	Abstinence and Substance Use Behaviour: Illicit Non-Opioid Substance Use	0	0	N/A

Methadyl acetate (range 30-80 mg)	Methadone (range 36-90 mg)	1 <sup>44</sup>	34	Physical Health: Withdrawal Symptoms	0	0	N/A
Methadyl acetate (range 30-80 mg)	Waitlist	1 <sup>44</sup>	31	Physical Health: Withdrawal Symptoms	0	0	N/A
Methadyl acetate (range 30-80 mg)	Waitlist	1 <sup>30,44</sup>	31	Personal and Social Functioning: Employment and Social Involvement	0	0	N/A
Low-dose Suboxone	Low-dose Methadone	1 <sup>30</sup>	134	Abstinence and Substance Use Behaviour: Illicit Opioid Use	0	0	N/A
Low-dose Suboxone	Low-dose Methadone	1 <sup>30</sup>	134	Abstinence and Substance Use Behaviour: Illicit Non-Opioid Substance Use	0	0	N/A
Low-dose Suboxone	Low-dose Methadone	1 <sup>30</sup>	134	Intervention Adherence: Successful Medication Induction	0	0	N/A
Low-dose Suboxone	Low-dose Methadone	1 <sup>30</sup>	134	Intervention Adherence: Intervention Compliance	0	0	N/A
Low-dose Suboxone	Low-dose Methadone	1 <sup>30</sup>	134	Psychiatric Health and Symptoms: Psychiatric Symptoms	0	0	N/A
High-dose Suboxone	High-dose Methadone	2 <sup>30,43</sup>	1303	Abstinence and Substance Use Behaviour: Illicit Opioid Use	0	0	No Difference <sup>3</sup> <sub>043</sub>
High-dose Suboxone	High-dose Methadone	2 <sup>30,45</sup>	1303	Abstinence and Substance Use Behaviour: Illicit Non-Opioid Substance Use	0	0	No difference <sup>3</sup> <sub>043</sub>
High-dose Suboxone	High-dose Methadone	1 <sup>46</sup>	1269	Physical Health: General Physical Health	0	0	No Difference <sup>3</sup> <sub>043</sub>
High-dose Suboxone	High-dose Methadone	1 <sup>30</sup>	134	Intervention Adherence: Successful Medication Induction	0	0	N/A
High-dose Suboxone	High-dose Methadone	1 <sup>30</sup>	134	Intervention Adherence: Intervention Compliance	0	0	N/A
High-dose Suboxone	High-dose Methadone	2 <sup>30,45</sup>	1303	Psychiatric Health and Symptoms: Psychiatric Symptoms	0	0	No difference <sup>4</sup> <sub>5</sub>
High-dose Suboxone	High-dose Methadone	1 <sup>30</sup>	134	Abstinence and Substance Use Behaviour: Health Risk Behaviour (related to substance use)	0	0	N/A
High-dose Suboxone	High-dose Methadone	2 <sup>30,45</sup>	1303	Global Quality of Life and Addiction Severity Assessment: Global Quality of Life	0	0	No Difference <sup>4</sup> <sub>5</sub>
Low-dose Suboxone	High-dose Methadone	1 <sup>30</sup>	158	Abstinence and Substance Use Behaviour: Illicit Opioid Use	0	0	N/A
Low-dose Suboxone	High-dose Methadone	1 <sup>30</sup>	158	Abstinence and Substance Use Behaviour: Illicit Non-Opioid Substance Use	0	0	N/A
Low-dose Suboxone	High-dose Methadone	1 <sup>30</sup>	158	Intervention Adherence: Successful Medication Induction	0	0	N/A
Low-dose	High-dose Methadone	1 <sup>30</sup>	158	Intervention Adherence: Intervention	0	0	N/A

				Compliance			
Suboxone							
Low-dose Suboxone	High-dose Methadone	1 <sup>30</sup>	158	Psychiatric Health and Symptoms: Psychiatric Symptoms	0	0	N/A
High-dose Suboxone	Low-dose Suboxone	1 <sup>30</sup>	140	Abstinence and Substance Use Behaviour: Illicit Opioid Use	0	0	N/A
High-dose Suboxone	Low-dose Suboxone	1 <sup>30</sup>	140	Abstinence and Substance Use Behaviour: Illicit Non-Opioid Substance Use	0	0	N/A
High-dose Suboxone	Low-dose Suboxone	1 <sup>30</sup>	140	Intervention Adherence: Successful Medication Induction	0	0	N/A
High-dose Suboxone	Low-dose Suboxone	1 <sup>30</sup>	140	Intervention Adherence: Intervention Compliance	0	0	N/A
High-dose Suboxone	Low-dose Suboxone	1 <sup>30</sup>	140	Psychiatric Health and Symptoms: Psychiatric Symptoms	0	0	N/A
High-dose Suboxone	Low-dose Methadone	1 <sup>30</sup>	134	Abstinence and Substance Use Behaviour: Illicit Opioid Use	0	0	N/A
High-dose Suboxone	Low-dose Methadone	1 <sup>30</sup>	134	Abstinence and Substance Use Behaviour: Illicit Non-Opioid Substance Use	0	0	N/A
High-dose Suboxone	Low-dose Methadone	1 <sup>30</sup>	134	Intervention Adherence: Successful Medication Induction	0	0	N/A
High-dose Suboxone	Low-dose Methadone	1 <sup>30</sup>	134	Intervention Adherence: Intervention Compliance	0	0	N/A
High-dose Suboxone	Low-dose Methadone	1 <sup>30</sup>	134	Psychiatric Health and Symptoms: Psychiatric Symptoms	0	0	N/A
Low-dose Oral Naltrexone	Low-dose Buprenorphine	1 <sup>39</sup>	87	Abstinence and Substance Use Behaviour: Illicit Opioid Use	1 <sup>39</sup>	0	N/A
Low-dose Oral Naltrexone	Low-dose Buprenorphine	1 <sup>39</sup>	87	Abstinence and Substance Use Behaviour: Health Risk Behaviour (related to substance use)	1 <sup>39</sup>	0	N/A
Dihydrocodiene (30 or 60 per day)	Methadone (no specified dosing)	1 <sup>47</sup>	218	Abstinence and Substance Use Behaviour: Illicit Opioid Use	0	0	No Difference <sup>4</sup> <sub>7</sub>
Dihydrocodiene (30 or 60 per day)	Methadone (no specified dosing)	1 <sup>47</sup>	218	Abstinence and Substance Use Behaviour: Health Risk Behaviour (related to substance use)	0	0	No Difference <sup>4</sup> <sub>7</sub>
Dihydrocodiene (30 or 60 per day)	Methadone (no specified dosing)	1 <sup>47</sup>	218	Personal and Social Functioning Relationships	0	0	No Difference <sup>4</sup> <sub>7</sub>
Dihydrocodiene (30 or 60 per day)	Methadone (no specified dosing)	1 <sup>47</sup>	218	Personal and Social Functioning: Criminal Behaviour	0	0	No Difference <sup>4</sup> <sub>7</sub>
Dihydrocodiene (30 or 60 per day)	Methadone (no specified dosing)	1 <sup>47</sup>	218	Personal and Social Functioning: Employment and Social Involvement	0	0	No Difference <sup>4</sup> <sub>7</sub>
Dihydrocodiene (30 or 60 per day)	Methadone (no specified dosing)	1 <sup>47</sup>	218	Physical Health: General Physical Health	0	0	No Difference <sup>4</sup> <sub>7</sub>

							7
Dihydrocodiene (30 or 60 per day)	Methadone (no specified dosing)	1 <sup>47</sup>	218	Physical Health: Overdose	0	0	No Difference <sup>4</sup> <sub>7</sub>
High-dose Buprenorphine	Low-dose Buprenorphine	1 <sup>48</sup>	736	Abstinence and Substance Use Behaviour: Illicit Opioid Use	1 <sup>48</sup>	0	Intervention A Superior <sup>48</sup>
High-dose Buprenorphine	Low-dose Buprenorphine	1 <sup>48</sup>	736	Physical Health: Drug Craving	1 <sup>48</sup>	0	Intervention A Superior <sup>48</sup>
High-dose Buprenorphine	High-dose Methadone	2 <sup>49,50</sup>	456	Abstinence and Substance Use Behaviour: Illicit Opioid Use	1 <sup>49</sup>	0	Intervention A Superior <sup>49</sup>
High-dose Buprenorphine	High-dose Methadone	1 <sup>49</sup>	62	Abstinence and Substance Use Behaviour: Illicit Non-Opioid Substance Use	1 <sup>49</sup>	0	N/A
High-dose Buprenorphine	High-dose Methadone	1 <sup>49</sup>	62	Psychiatric Health and Symptoms: Psychiatric Symptoms	1 <sup>49</sup>	0	N/A
High-dose Buprenorphine	High-dose Methadone	1 <sup>49</sup>	62	Physical Health: Drug Craving	1 <sup>49</sup>	0	N/A
High-dose Buprenorphine	High-dose Methadone	1 <sup>50</sup>	394	Abstinence and Substance Use Behaviour: Health Risk Behaviour (related to substance use)	0	0	No Difference <sup>5</sup> <sub>0</sub>
High-dose Buprenorphine	High-dose Methadone	2 <sup>8,49</sup>	162	Physical Health: General Physical Health	1	0	N/A
Low-dose Methadone	Placebo	1 <sup>51</sup>	165	Abstinence and Substance Use Behaviour: Illicit Opioid Use	1 <sup>51</sup>	0	N/A
Low-dose Methadone	Placebo	1 <sup>51</sup>	165	Abstinence and Substance Use Behaviour: Illicit Non-Opioid Substance Use	1 <sup>51</sup>	0	N/A
Low-dose Methadone	Placebo	1 <sup>51</sup>	165	Intervention Adherence: Intervention Compliance	1 <sup>51</sup>	0	N/A
High-dose Injectable Methadone	High-dose Injectable Heroin	1 <sup>28</sup>	85	Abstinence and Substance Use Behaviour: Illicit Opioid Use	0	0	N/A
High-dose Injectable Methadone	High-dose Methadone	1 <sup>28</sup>	84	Abstinence and Substance Use Behaviour: Illicit Opioid Use	0	0	N/A
High-dose Oral Naltrexone	Placebo	1 <sup>52</sup>	50	Abstinence and Substance Use Behaviour: Illicit Opioid Use	0	0	N/A
High-dose Oral Naltrexone	Placebo	1 <sup>52</sup>	50	Abstinence and Substance Use Behaviour: Illicit Non-Opioid Substance Use	0	0	N/A
High-dose Oral Naltrexone	Placebo	1 <sup>52</sup>	50	Psychiatric Health and Symptoms: Psychiatric Symptoms	0	1 <sup>52</sup>	N/A
High-dose Oral Naltrexone	Placebo	1 <sup>52</sup>	50	Intervention Acceptance: Intervention Preference	0	0	N/A
Slow Release	Low-dose Methadone	1 <sup>9</sup>	80	Abstinence and Substance Use Behaviour:	1	0	N/A

				Illicit Opioid Use			
Oral Morphine				Global Quality of Life and Addiction Severity Assessment: Global Quality of Life	0	0	N/A
Slow Release Oral Morphine	Low-dose Methadone	1 <sup>9</sup>	80	Abstinence and Substance Use Behaviour: Illicit Opioid Use	1 <sup>9</sup>	0	N/A
Slow Release Oral Morphine	Low-dose Buprenorphine	1 <sup>9</sup>	80	Global Quality of Life and Addiction Severity Assessment: Global Quality of Life	0	0	N/A
Slow Release Oral Morphine	Low-dose Buprenorphine	1 <sup>9</sup>	80	Abstinence and Substance Use Behaviour: Illicit Opioid Use	0	0	N/A
Low-dose LAAM	High-dose Methadone	2 <sup>6,33</sup>	180	Global Quality of Life and Addiction Severity Assessment: Global Quality of Life	0	0	N/A
Low-dose LAAM	High-dose Methadone	1 <sup>33</sup>	183	Abstinence and Substance Use Behaviour: Illicit Opioid Use	0	0	N/A
Low-dose LAAM	High-dose Methadone	1 <sup>33</sup>	183	Physical Health: General Physical Health	0	0	N/A
Low-dose LAAM	High-dose Methadone	1 <sup>33</sup>	183	Physical Health: Withdrawal Symptoms	0	0	N/A
Low-dose LAAM	High-dose Methadone	1 <sup>6</sup>	14	Abstinence and Substance Use Behaviour: Non-Opioid Substance Use	0	0	N/A
Low-dose LAAM	High-dose Methadone	1 <sup>6</sup>	14	Personal and Social Functioning: Employment and Social Involvement	0	0	N/A
High-dose Methadone	180 day High-dose Methadone detoxification + Psychosocial Services	1 <sup>53</sup>	179	Abstinence and Substance Use Behaviour: Illicit Opioid Use	1 <sup>53</sup>	0	N/A
High-dose Methadone	180 day High-dose Methadone detoxification + Psychosocial Services	1 <sup>53</sup>	179	Abstinence and Substance Use Behaviour: Illicit Non-Opioid Substance Use	0	1 <sup>53</sup>	N/A
High-dose Methadone	180 day High-dose Methadone detoxification + Psychosocial Services	1 <sup>53</sup>	179	Abstinence and Substance Use Behaviour: Health Risk Behaviour (related to substance use)	1 <sup>53</sup>	0	N/A
High-dose Methadone	180 day High-dose Methadone detoxification + Psychosocial Services	1 <sup>53</sup>	179	Global Quality of Life and Addiction Severity Assessment: Composite Addiction Severity Scores	0	0	N/A
High-dose Methadone	High-dose Methadone Medical Maintenance (>60 mg/day, offered at methadone clinic and physicians office, patients allowed 1 month reporting and dispensed methadone for 27 days at a time)	1 <sup>54</sup>	92	Abstinence and Substance Use Behaviour: Illicit Opioid Use	0	0	N/A
High-dose Methadone	High-dose Methadone Medical Maintenance (>60 mg/day, offered at methadone clinic and physicians office, patients allowed 1 month reporting and dispensed methadone for 27 days at a time)	1 <sup>54</sup>	92	Intervention Acceptance: Intervention Preference	0	1	N/A
High-dose Methadone	High-dose Methadone Medical Maintenance (>60 mg/day, offered at methadone clinic and physicians office, patients	1 <sup>54</sup>	92	Intervention Adherence: Intervention Compliance	0	0	N/A

	allowed 1 month reporting and dispensed methadone for 27 days at a time)						
High-dose Methadone	High-dose Methadone Medical Maintenance (>60 mg/day, offered at methadone clinic and physicians office, patients allowed 1 month reporting and dispensed methadone for 27 days at a time)	1 <sup>54</sup>	92	Personal and Social Functioning Relationships	0	1	N/A
High-dose Methadone	High-dose Methadone Medical Maintenance (>60 mg/day, offered at methadone clinic and physicians office, patients allowed 1 month reporting and dispensed methadone for 27 days at a time)	1 <sup>54</sup>	92	Global Quality of Life and Addiction Severity Assessment: Composite Addiction Severity Scores	0	0	N/A
High-dose Methadone	Interim Methadone	1 <sup>55</sup>	203	Global Quality of Life and Addiction Severity Assessment: Composite Addiction Severity Scores	0	0	No difference
High-dose Methadone	Interim Methadone	1 <sup>55</sup>	203	Abstinence and Substance Use Behaviour: Illicit Opioid Use	0	0	No difference
High-dose Methadone	High-dose Interim Methadone	1 <sup>55</sup>	203	Abstinence and Substance Use Behaviour: Illicit Non-Opioid Use	0	0	No difference
High-dose Methadone	High-dose Interim Methadone	1 <sup>55</sup>	203	Abstinence and Substance Use Behaviour: Money Spent on Illicit Substance Consumption	0	1 <sup>55</sup>	Intervention B Superior <sup>55</sup>
High-dose Methadone	High-dose Interim Methadone	1 <sup>55</sup>	203	Personal and Social Functioning: Criminal Behavior	0	1 <sup>55</sup>	Intervention B Superior <sup>55</sup>
High-dose Interim Methadone	Waitlist	1 <sup>56</sup>	319	Global Quality of Life and Addiction Severity Assessment: Composite Addiction Severity Scores	0	0	No Difference
High-dose Interim Methadone	Waitlist	1 <sup>56</sup>	319	Abstinence and Substance Use Behaviour: Illicit Opioid Use	1 <sup>56</sup>	0	Intervention A Superior <sup>56</sup>
High-dose Interim Methadone	Waitlist	1 <sup>56</sup>	319	Abstinence and Substance Use Behaviour: Illicit Non-Opioid Use	0	0	No Difference

High-dose Interim Methadone	Waitlist	1 <sup>56</sup>	319	Abstinence and Substance Use Behavior: Money Spent on Illicit Substance Consumption	1 <sup>56</sup>	0	Intervention A Superior <sup>56</sup>
High-dose Buprenorphine	High-dose LAAM	1 <sup>8</sup>	101 <sup>8</sup>	Physical Health: General Physical Health	1 <sup>8</sup>	0	N/A
High-dose Suboxone	High-dose Suboxone with early tapering	1 <sup>57</sup>	152	Abstinence and Substance Use Behaviour: Illicit Opioid Use	1 <sup>57</sup>	0	N/A
High-dose Suboxone	High-dose Suboxone with early tapering	1 <sup>57</sup>	152	Abstinence and Substance Use Behaviour: Illicit Non-Opioid Use	1 <sup>57</sup>	0	N/A
High-dose Suboxone	High-dose Suboxone with early tapering	1 <sup>57</sup>	152	Abstinence and Substance Use Behaviour: Health Risk Behavior	1 <sup>57</sup>	0	N/A
High-dose Suboxone	High-dose Suboxone with early tapering	1 <sup>57</sup>	152	Personal and Social Functioning: Employment and Social Involvement	1 <sup>57</sup>	0	N/A
Low-dose Levoacetylmethadol (LAAM) (< 85 mg/day)	Low-dose Methadone	1 <sup>33</sup>	183	Abstinence and Substance Use Behaviour: Illicit Opioid Use	1 <sup>33</sup>	0	N/A
Low-dose Levoacetylmethadol (LAAM) (< 85 mg/day)	Low-dose Methadone	1 <sup>33</sup>	183	Physical Health: General Physical Health	0	0	N/A
Low-dose Levoacetylmethadol (LAAM) (< 85 mg/day)	Low-dose Methadone	1 <sup>33</sup>	183	Physical Health: Withdrawal Symptoms	0	0	N/A