CANNABIS USE AND METHADONE MAINTENANCE TREATMENT

CANNABIS USE AND METHADONE MAINTENANCE TREATMENT OUTCOMES IN PATIENTS WITH OPIOID USE DISORDER

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Abstract

Background: Methadone maintenance treatment (MMT) is a commonly prescribed therapy for patients with opioid use disorder, yet inter-individual variability in terms of treatment response is evident. Given the high prevalence of cannabis use in this population, this thesis aims to elucidate the association between cannabis use and MMT outcomes.

Methods: We conducted a systematic review and meta-analysis to comprehensively evaluate the literature and quality of evidence, as well as to identify gaps in the literature to inform future research. We then conducted a cross-sectional study investigating sex differences in the association between cannabis use and illicit opioid use in MMT patients. We employed a multivariable logistic regression analysis to assess the influence of any cannabis use as well as heaviness of cannabis use within men and women.

Results: The systematic review included 22 observational studies. Results revealed the low quality of available evidence as well as substantial heterogeneity among studies. We identified several limitations in the evidence base including reliance on crude measures of cannabis use and inadequate consideration of confounding variables. Our cross-sectional study included a sample of 777 patients on MMT. Consistent with previous research, we found cannabis use to be unrelated to illicit opioid use in the entire sample. However when we stratified the

analysis by sex, we found cannabis use was associated with increased odds of having concurrent illicit opioid use.

Conclusion: Results of this thesis suggest certain populations within MMT patients may be at higher risk of experiencing adverse effects of cannabis in terms of treatment outcomes. Future work can build on the results of these studies to identify unique risk factors for patients in order to inform the use of tailored treatment options to improve MMT effectiveness.

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List of Abbreviations

OUD	Opioid Use Disorder
MMT	Methadone Maintenance Treatment
RCT	Randomized-Controlled Trial
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
MOOSE	Meta-Analysis of Observational Studies In Epidemiology
NOS	Newcastle-Ottawa Scale
PRISMA-P	Preferred Reporting Items For Systematic Review And Meta-Analysis Protocols
OR	Odds Ratio
CI	Confidence Interval
UDS	Urine Drug Screen
CUD	Cannabis Use Disorder
GENOA	Genetics of Opioid Addiction
CATC	Canadian Addiction Treatment Centre
HIREB	Hamilton Integrated Research Ethics Board
MAP	Maudsley Addiction Profile
SD	Standard Deviation
VIF	Variance Inflation Factor
STROBE	Strengthening the Reporting of Observational Studies in

	Epidemiology
THC	Δ9-Tetrahydrocannabinol
CBD	Cannabidiol

Declaration of Academic Achievement

I am the primary author of all studies included in this thesis. I made substantial contributions to each study by conceiving of the study question, synthesizing data, performing statistical analyses, interpreting results, and writing the manuscripts. Detailed lists of author contributions are provided at the end of each study.

CHAPTER 1

Introduction

1.1 Background

1.1.1 Opioid Use Disorder

Opioids include any substances that act on the opioid receptor and not only include heroin, but also commonly prescribed analgesics such as morphine, oxycodone and fentanyl. The euphoric effects and susceptibility for physiological dependence make opioids highly liable for misuse and abuse [1]. High doses activate reward processes in the brain to release dopamine, which can lead to further drug-seeking behaviours in an attempt to continually experience these pleasurable feelings [2]. Repeated exposure to opioids causes a physiological tolerance, such that the brain adapts to escalating doses of opioids, and sudden elimination of opioid consumption can produce severe withdrawal symptoms [2]. The physiological tendency of opioids for abuse coupled with the increasing availability of prescription opioids are major contributing factors to the development of the current opioid crisis in North America [3,4].

One in six Canadians over the age of 14 reported using prescription opioids in the past year, with 5% of those individuals reporting opioid abuse [5]. Indeed, Canada has the second highest prevalence of prescription opioid use

worldwide, following only behind USA, and this is increasingly contributing to the overall morbidity and mortality rates [6].

A consequence of this increasing nonmedical use of opioids is a subsequent rise in the incidence of opioid use disorder (OUD) [7]. OUD, previously referred to as opioid abuse or dependence, is a chronic, relapsing disorder whereby individuals experience severe cravings and a persistent desire to obtain and use opioids, often at the expense of other important occupational and social obligations [8]. The severity of its impact on individual and public health has led Health Canada to develop a national action plan aimed at addressing this epidemic, which in addition to preventative measures, includes improving evidence-based treatment options for patients with OUD [9].

One of the most highly effective treatments for OUD is opioid substitution therapy, with the most thoroughly studied and commonly prescribed being methadone maintenance treatment (MMT) [10]. Methadone acts by blocking the opioid receptors in the brain to block the euphoric effects produced by exogenous opioids [11], and has shown effectiveness in retaining patients in treatment and reducing opioid use [12]. However, despite its overall effectiveness, there is a great amount of variability between individuals in terms of treatment response [13]. Because of the current shortcomings of treatment options for OUD, further research is necessary to identify risk factors for poor treatment outcomes in order to improve clinical practice.

1.1.2 Cannabis

Cannabis continues to be the most widely used illicit drug in Canada, with an estimated 43% of Canadians over 15 years of age having used cannabis in their lifetime [14]. Cannabis use is most prevalent amongst males and youth (15-24) within the general population [15]. With the impending legalization of cannabis in Canada, research from Colorado, USA suggests the prevalence of its use will increase even further due to factors such as better availability, as well criminal penalties no longer acting as a deterrent [16].

Compared to the general population, MMT patients show higher rates of cannabis use [17], and because of its association with polysubstance use [18,19], psychiatric disorders [20], and poor quality of life [21] , represents a potential risk factor for poor MMT outcomes. The impact of cannabis use on treatment outcomes in patients with OUD has been a point of contention in the literature, with studies showing conflicting results [22–25]. It remains unclear whether cannabis use is associated with MMT outcomes, and thus further research must be conducted.

1.2 Thesis Objectives

The objective of this thesis is to elucidate the nature of the association between cannabis use and methadone maintenance treatment outcomes through a series of three individual papers.

The first paper, Chapter 2, is a protocol for a systematic review and meta-analysis to investigate the relationship between cannabis use and MMT outcomes. It defines the research question and outlines detailed methods which will be used to evaluate the aforementioned association. This work is published in *Systematic Reviews.*

Chapter 3 is a systematic review summarizing all available evidence on the association between cannabis use and MMT outcomes. Using the methods described in Chapter 2, we conducted a thorough search of the literature to review the results and evaluate the quality of the literature. Meta-analyses were conducted on the two primary outcomes – illicit opioid use and treatment retention. We used the results of this systematic review and meta-analysis to identify gaps in the literature and propose areas for further research.

Chapter 4 is a primary study investigating sex differences in the association between cannabis use and illicit opioid use in a cohort of MMT patients. The aim of this study was to determine the influence of any cannabis use as well as heaviness of cannabis use, on continued opioid use during treatment in men and women. This paper has been submitted to *Biology of Sex Differences*.

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CHAPTER 2

Association between Cannabis Use and Treatment Outcomes in Patients Receiving Methadone Maintenance Treatment: A Systematic Review Protocol

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This work has been published in *Systematic Reviews*. The document has been reformatted from the original version for inclusion in this thesis. The published manuscript is available in Appendix I. The complete citation is included below.

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2.1 Abstract

Background: With the non-medical use of prescription opioids increasingly becoming a method of abuse in Canada, the number of patients requiring methadone maintenance treatment (MMT) for opioid use disorder has increased dramatically. The rate of cannabis use in this population is disproportionately high (~50%). Because its use is generally perceived as harmless, cannabis use is often not monitored during MMT. Current literature regarding the effects of cannabis use on MMT is conflicting, and the presence and nature of an association has not been clearly established. The primary objective of this review will be to conduct a systematic review of the literature and, if appropriate, a meta-analysis to determine whether there is an association between cannabis use and MMT outcomes. A secondary objective will be to perform subgroup analyses (by age, sex, method of cannabis measurement, and country) to determine whether cannabis use differentially influences MMT outcomes within these subgroups.

Methods/design: The search will be conducted on the following electronic databases using a predefined search strategy: MEDLINE, EMBASE, PsycINFO, and CINAHL. Two authors (LZ and MB) will independently screen articles using predetermined inclusion/exclusion criteria, and will extract data from included articles using a pilot tested data extraction form. Disagreements at all stages of the screening process will be settled through discussion, and when consensus cannot

be reached, a third author (ZS) will be consulted. An assessment of quality and risk of bias will be conducted on all included articles, and a sensitivity analysis will be used to compare results of studies with high and low risk of bias. We will perform a random and fixed effects meta-analyses, if appropriate, with heterogeneity calculated using the I^2 statistic, and formal evaluation of publication bias.

Discussion: Results of this systematic review will elucidate the association between cannabis use and methadone maintenance treatment outcomes. We will provide evidence that will be useful to clinicians regarding whether monitoring cannabis use during MMT is advantageous for optimizing MMT outcomes.

Systematic review registration: PROSPERO CRD42015029372

Keywords: Methadone maintenance treatment, MMT, cannabis, marijuana, systematic review, protocol

2.2 Background

There are an estimated 33 million opioid users globally [1], which is markedly contributing to the global burden of disease [2]. Illicit opioid use is associated with significant personal health risks such as accidental injury, dependency, infectious disease [3], and potential for fatal overdose, in addition to its effects on the social concerns of healthcare costs, criminal activity, and employment [2]. Although the prevalence of heroin use has remained constant in Canada, a dramatic rise in the use of prescription opioids has resulted in a surge in opioid detoxification admissions from 2000-2004 [4]. In both United States and Canada, illicit use of prescription opioids has become a significant contributor to emergency room visits and mortality[5]. This changing landscape and steady increase in problematic opioid use in North America signals an urgent need for evidence-based treatment practices.

Canada has witnessed a five-fold increase in patients on methadone maintenance treatment (MMT) since the mid-1990's [6]. MMT is an opioid substitution therapy and is the most widely researched pharmacological treatment for opioid use disorder [7]. Methadone is a long-acting synthetic opioid intended to reduce cravings and withdrawal symptoms without producing the euphoric effects associated with illicit opioids [8]. Studies have shown this treatment to be effective in decreasing illicit opioid use, reducing criminal activity, and reducing

mortality rates among patients [7]. Although an overall efficacious treatment for reducing illicit opioid use, MMT is limiting in that it has high attrition rates [9] because it often requires patients to be on the treatment for life [10].

Polydrug use is common amongst MMT patients [11,12], with cannabis consistently being the most commonly used illicit drug in this population [13–15]. This may be due to the fact that cannabis is generally perceived as harmless [16]. While it may be the case that mortality directly resulting from cannabis use is unlikely [2], associations with other adverse health outcomes have been found. In particular, regular cannabis use increases the risk of motor vehicle accidents and respiratory problems, and poses a risk for dependency [17]. Long term use is also associated with lower school performance and decreased life satisfaction [16]. Furthermore, cannabis use is associated with adverse mental health outcomes. The strongest evidence comes from studies on psychotic disorders, with a systematic review showing a strong, positive relationship between incidence of psychosis and cannabis use, which increases as frequency of cannabis use increases [18]. Studies have also found associations with other psychiatric illnesses including mood disorders (unipolar and bipolar) [19–21] and anxiety (particularly panic disorder and social anxiety) [22,23], however evidence for a directional association with these disorders is inconclusive. Nonetheless, it remains a possibility that cannabis use during the treatment of opioid addiction could influence its outcome

Studies on the association between cannabis use and MMT outcomes have produced conflicting results, with some demonstrating beneficial effects on outcomes [14] and others showing an association with adverse treatment outcomes. For example, Wasserman et al. (1998) found cannabis use at baseline and throughout the study period were significantly associated with subsequent heroin use during treatment [24], whereas Scavone et al. (2013) found patients using cannabis during the study reported significantly less daily expenditure on acquiring opioids [14]. Most studies, however, have failed to produce a statistically significant association between cannabis use and MMT retention or illicit opioid use [13,25–28]. Epstein and Preston (2003) found that cannabis use increased other outcomes such as jail time and family conflict [26], suggesting its use during MMT may act indirectly via social and lifestyle risk factors. The relationship between cannabis use and MMT outcomes may also include complex interactions with health behaviours. For instance, depressive symptoms and illicit substance use during MMT is significantly associated with a lack of HIV medication adherence [20], which may in turn affect MMT outcomes and overall health status among patients.

It remains unclear whether there is a true association between cannabis use and MMT outcomes and to what degree this association may be mediated by other confounding variables. A systematic investigation and evaluation of the studies is necessary, as well as the identification of any gaps in the literature. We

hypothesize that the use of cannabis in patients with opioid use disorder treated with methadone is associated with poor response to MMT as defined by illicit opioid use and length of treatment retention. Evidence indicates that treatment retention is a critical factor in MMT success, with research suggesting those in treatment for less than 90 days resemble those receiving no treatment at all [29]. Indeed, MMT dropout is significantly associated with drug use relapse and other high-risk health behaviours [11] and is a useful indicator of treatment response. We will also consider secondary outcomes to evaluate risky health and social behaviours including criminal activity, jail time, polydrug use, injection drug use, needle sharing, and unprotected sex. Isolating each outcome and controlling for potential confounders will help to clarify the association between cannabis use and MMT outcomes.

2.2.1 Objectives

The objective of this systematic review is to summarize the existing literature examining the effects of cannabis use on treatment outcomes during methadone maintenance treatment in patients with opioid use disorder by identifying and evaluating the current evidence. Specifically, our aims are as follows:

1. Summarize primary research to examine the relationship between cannabis use and primary methadone maintenance treatment outcomes (treatment

retention and illicit opioid use) and secondary outcomes (criminal activity, jail time, polydrug use, injection drug use, needle sharing, and unprotected sex).

2. Combine statistical outcomes of the primary studies in a meta-analysis, when appropriate.
3. Conduct subgroup analyses based on sex, method of cannabis measurement, and geographical region of study to explore potential confounders in the relationship.
4. Critically appraise the existing literature and identify areas requiring further research.

2.3 Methods and Design

2.3.1 Search Strategy

An experienced health sciences librarian (NB) will be consulted when creating and implementing the search strategy. The following databases will be searched from their inception to present: MEDLINE/PubMed, EMBASE, PsycINFO, and Cumulative Index to Nursing and Allied Health Literature (CINAHL). Relevant articles will be identified from the comprehensive search strategy using all relevant search terms related to methadone maintenance treatment and cannabis, and their medical subject heading (MeSH) equivalents in varying combinations (Table 2.5.1). A wide search will be conducted to include

titles, abstracts, and keyword fields. Outcome variables will not be included in the search strategy so as not to impose unnecessary limitations on search results. The searches will all be limited to human studies. Grey literature will also be searched using ProQuest Dissertations and Theses Global database. Finally, we will conduct a thorough hand search of past reviews and reference lists of included studies to identify potentially relevant articles the initial search strategy may not have captured.

2.3.2 Inclusion/Exclusion Criteria

This review will include published observational studies or randomized controlled trials (RCTs) of the relationship between cannabis use and methadone maintenance treatment outcomes in any setting (hospital, outpatient, or community-based). Included studies will measure cannabis use at baseline for cross-sectional studies and during treatment for cohort studies and RCTs, which may be measured using objective measures (i.e. urine or hair analyses) or self-reports.

Studies will be excluded if they do not measure at least one of the primary or secondary outcomes of interest. If cannabis use is measured as an outcome rather than a predictor variable, it will be excluded. Many studies in this domain report frequency of cannabis use as part of the demographics of the sample, and as such, these will be excluded as we cannot make any conclusions regarding its

direct association with MMT outcomes. Studies including patients on opioid substitution therapy (i.e. buprenorphine or buprenorphine/naloxone) other than methadone will be excluded. Furthermore, studies looking at patients on methadone for anything other than treatment of opioid use disorder (i.e. illicit methadone use or chronic pain treatment) will be excluded. No age restrictions will be applied, as opioid addiction affects people of all age groups. There will be no other demographic limitations or language restrictions.

2.3.3 Outcome Measures

Two primary outcomes variables will be measured which evaluate the success of methadone maintenance treatment. These include illicit opioid use which may be measured in any way (self-reports, urine toxicology, hair analysis), as well as treatment retention. Treatment retention may be measured as either proportion of individuals remaining in treatment at the end of study or average length of time in treatment. In addition to the MMT outcomes, secondary outcomes will be considered which reflect the patients' social and personal functioning and other drug use behaviours. These include criminal activity, jail time, polydrug use, injection drug use, needle sharing, and unprotected sex.

2.3.4 Data Management

All articles retrieved during the initial search will be uploaded to Covidence, an online software system used to manage systematic reviews and

promotes collaboration amongst authors. Training will be provided to all members using the Covidence software. The review team will define a set of inclusion and exclusion criteria, and pilot test the title/abstract screening with the first 100 articles. Upon completion of title and abstract screening, full text articles will be uploaded to the Covidence system for purposes of the full text review.

2.3.5 Selection of Studies

Two independent reviewers (LZ and MB) will complete the initial title and abstract screening to identify eligible articles using a pre-determined criteria. Articles deemed eligible will be retrieved for a full-text review. Any disagreements during the screening process that cannot be settled through discussion will be resolved by a third party (ZS). Authors of the studies will be contacted if any clarification or additional data is needed during the full-text review to determine eligibility. For each phase of screening, a kappa statistic will be calculated to determine inter-rater agreements. A kappa value of 0.75 or greater reflects excellent agreement [30]. Studies determined to be ineligible will be excluded from the review. Reasons for ineligibility and exclusion will be reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [31] or Meta-analysis of Observational Studies in Epidemiology (MOOSE) [32] flow diagrams.

2.3.6 Data Extraction

The two reviewers (LZ and MB) will independently extract data from the included studies using a pilot-tested data extraction form (see Appendix I). To maximize consistency, a calibration exercise will be performed using articles not included in the review with the two reviewers prior to starting the data extraction phase. The authors will extract the following information from each study: publication details (name, author, year, journal, and country), study design (type of study, participant information, inclusion criteria, and length of study), demographics (mean age, ethnicity, and sex), measurement of cannabis (self-report, urinalysis, or hair analysis), outcome measures, the main findings, and statistical results (effect measures, p-values, confidence intervals, etc). If multiple outcomes are reported, all of them will be recorded so we can combine the studies with similar outcome measurements. Authors will be contacted in the case of missing or incomplete data.

2.3.7 Assessment of Quality

Risk of bias in will be assessed by two independent raters (LZ and MB) using the Newcastle-Ottawa Scale (NOS) [33]. An adapted version of a modified NOS was developed by Bawor et al. to be used to assess risk of bias in observational studies [34]. This version includes seven questions evaluating bias in four domains of biases: selection bias, performance bias, detection bias, and

information bias. Risk of bias is measured on a scale of 0 (high risk) to 3 (low risk). The adapted version has removed items regarding the comparability of groups and suitable follow-up for cohort and case-control studies, as these items are not relevant for our topic of interest. The Cochrane Collaboration's tool will be used for randomized-controlled trials which assesses risk of bias using six domains: selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias [35].

Quality of the literature will be measured using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) framework, which scores articles based on five domains – risk of bias, publication bias, consistency, directness, and precision [36]. These findings will be summarized in a table, allowing for an assessment of the confidence of the estimates. A summary of the findings will be provided in a table to easily compare the quality of studies included in this review and allow for confidence of estimates.

2.3.8 Statistical Analyses

All included studies will first be reviewed in a qualitative summary, followed by a meta-analysis if possible. Studies will be combined in a meta-analysis based on similarities in study design and outcomes measurements. Direct estimates will be pooled separately based on study design, as pooling data from

observational studies and RCTs is cautioned against due to the inherent susceptibility of observational studies to selection biases [37]. A random effects model for meta-analysis will be used to account for the expected heterogeneity in the literature, which assumes both within-study and between-study variability to provide a more conservative estimate compared to a fixed-effects model. These results will be presented in a forest plot. In the case of missing data, we will attempt to contact authors to obtain the relevant data. If the missing data cannot be obtained, we will employ an imputation method. We may also conduct a sensitivity analysis to assess the impact of missing data on the overall treatment effects. A sensitivity analysis will also be conducted to compare the overall results of studies with high or low risk of bias.

Heterogeneity will be calculated among pooled studies using the I^2 statistic. It is advised not to impose cut-off values because the importance of heterogeneity depends on a multitude of factors. However, Cochrane suggests a value <40% may not represent a notable amount of heterogeneity [37]. Thus, possible sources of clinical heterogeneity will be examined given an I^2 statistic >40%, and subgroup analyses will be performed. Possible sources of heterogeneity include age, sex, method of cannabis measurement, and country, and these will be investigated using subgroup analyses.

2.3.9 Subgroup Analyses

Subgroups are identified *a priori* so we can make stronger inferences about the effects of the subgroups [38]. Subgroup analyses will be conducted on the following variables: age, sex, method of cannabis measurement, and country. Drug addiction is a disorder that afflicts people of all ages, and thus no age restrictions will be placed on the articles in this review. However, there are differences in the biological and social mechanisms involved with youth and adults, so cannabis may differentially influence treatment outcomes in the two populations. Because a consistent age range is not used to define youth in MMT studies [28,39,40], they will be included in the subgroup analysis if the authors specify they are investigating youth or adolescents.

Methadone maintenance treatment has been found to differentially affect men and women [34], and prevalence of cannabis use tends to be higher in males [41]. However, females display a stronger dose-dependent effect from cannabis compared to males, with significantly lower mental quality of life as dosage increases [42]. Furthermore, women demonstrate a faster trajectory towards the development of cannabis use disorder [43]. Thus, particularly among heavy cannabis users, we expect treatment outcomes in women to be more negatively impacted by cannabis use. Stratifying these populations using a subgroup analysis

may reveal differences in the way cannabis use affects MMT outcomes for males and females.

We will also compare results of studies that use subjective or objective measures of drug use. Studies have shown that a large number of patients in treatment for addiction underreport drug use [44], whether intentionally or not, and thus objective measures of drug use, such as urine or hair analysis, may provide a more accurate estimate of cannabis use in the population. Therefore, we expect to find a stronger association between objective measures of cannabis and MMT outcomes compared to studies using subjective measures.

Finally, any potential differences found between studies from different regions of the world or different decades will be qualitatively commented on and compared to current literature on drug use patterns considering the varied pattern of drug use across the world [2]. Specifically, North America has the highest proportion of cannabis use and high rates of opioid use, largely due to the surge in non-medical use of prescription opioids [1]. Illicit drug use is considerably less in Europe, with lower rates of cannabis use compared to North America, as well as significantly less opioid use [1]. On the other hand, more than half of the world's opioid-using population lives in Asia, although cannabis rates are below the global average [1]. These different patterns of illicit drug use around the world

signify different societal mechanisms are at play, which may impact treatment outcomes for drug addiction.

2.3.10 Presenting and Reporting of Results

This systematic review will be reported in accordance with the PRISMA guidelines [31]. Additionally, we expect to include many observational studies, in which case these will be reported following the MOOSE guidelines [32]. A flow chart will be used to display the selection of articles with reasons for exclusion. Study characteristics and measured outcomes will be compiled into summary tables. An Egger's plot will be included to examine potential publication bias in the selected studies. If a meta-analysis is possible, results will be presented in a forest plot. The current protocol follows the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) statement (see Appendix I) [45].

2.4 Discussion

Using evidence from this systematic review, we expect to make conclusions regarding the presence of an association between cannabis use and methadone maintenance treatment outcomes. Systematically reviewing the literature will contribute to our understanding of the mechanisms involved in treatment retention and drug relapse in patients with opioid use disorder. We will

also be investigating cannabis use and its association with other outcomes related to overall social and physical well-being in MMT patients.

To our knowledge, this will be the first systematic review conducted on this topic. Given the current trend of cannabis being approved in many US states and the move towards a more liberal use in Canada, it is imperative these policy decisions are evidence-based. The findings of this systematic review will also be of value to clinicians administering methadone maintenance treatment to patients with opioid use disorder, as it will provide evidence regarding whether monitoring cannabis use during MMT is necessary, and how it may predict a patient's treatment outcomes.

2.5 Tables and Figures

Figure 2.5.1 Search Strategy

Database	Search Strategy
MEDLINE (n = 420)	1. exp Opiate substitution therapy/ 2. Methadone/ 3. Methadone.mp. 4. MMT.mp. 5. Cannabis/ 6. Marijuana Abuse/ 7. Marijuana Smoking/ 8. Medical Marijuana/ 9. Cannabis.mp. or marijuana*.mp. 10. THC.mp. or hash*.mp. or ganja.mp. or hemp.mp. or bhang*.mp. 11. 1 or 2 or 3 or 4 12. 5 or 6 or 7 or 8 or 9 or 10 13. 11 and 12 14. Limit 13 to humans
EMBASE (n = 1761)	1. exp opiate substitution treatment/ 2. exp methadone treatment/ 3. exp methadone/ 4. Methadone.mp. 5. MMT.mp. 6. exp cannabis/ 7. exp “cannabis use”/ 8. exp cannabis addiction/ 9. exp cannabis smoking/ 10. exp medical cannabis/ 11. Cannabis.mp. or marijuana*.mp. 12. THC.mp. or hash*.mp. or ganja.mp. or hemp.mp. or bhang*.mp. 13. 1 or 2 or 3 or 4 or 5 14. 6 or 7 or 8 or 9 or 10 or 11 or 12 15. 13 and 14 16. Limit 15 to humans
PsycINFO (n = 194)	1. exp methadone maintenance/ 2. methadone.mp. 3. MMT.mp. 4. exp cannabis/

	5. exp marijuana usage/ 6. cannabis.mp. or marijuana*.mp. 7. THC.mp. or hash*.mp. or ganja.mp. or hemp.mp. or bhang*.mp. 8. 1 or 2 or 3 9. 4 or 5 or 6 or 7 10. 8 and 9 11. Limit 10 to humans
CINAHL (n = 50)	1. (MH "Methadone") 2. "Methadone" 3. "MMT" 4. (MH "Cannabis") 5. (MH "Medical Marijuana") 6. "marijuana" or "cannabis" 7. "THC" or "hash*" or "ganja" or "hemp*" or "bhang*" 8. 1 or 2 or 3 9. 4 or 5 or 6 10. 7 and 8 (limiters – human)

2.6 Author Contributions and Acknowledgements

LZ: conception and design of study, development of data extraction forms and search strategy, manuscript writing, critical revision, and final review of the manuscript. MB: conception and design of study, development of search strategy, critical revision, and final review of the manuscript. RE: methodological design, critical revision, and final review of the manuscript. SP: methodological design, critical revision, and final review of the manuscript. NB: consultation for search strategy and quality assessment, and final review of the manuscript. JM: critical revision, and final review of the manuscript. MS: critical revision, and final review of the manuscript. SM: critical revision, and final review of the manuscript. LT: critical revision, and final review of the manuscript. ZS: conception and design of study, critical revision, and final review of the manuscript. All authors read and approved the final manuscript.

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CHAPTER 3

Cannabis Use and Treatment Outcomes in Methadone Maintenance Patients: A Systematic Review and Meta-Analysis

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3.1 Abstract

Introduction: Opioid use is substantially contributing to the global burden of disease, with opioid use disorder (OUD) being a major contributor to morbidity and mortality. Methadone maintenance treatment (MMT) is the most commonly prescribed pharmacological treatment for OUD, and despite its documented safety and effectiveness, a number of individuals experience poor treatment outcomes, highlighting the need for the identification of risk factors for poor MMT prognosis. The current review aims to investigate the influence of cannabis use on MMT outcomes.

Methods: We searched Medline/PubMed, EMBASE, PsycINFO, and CINAHL databases from inception to August 2016. We conducted title/abstract and full text screening, data extraction, and quality assessments in duplicate. Studies were summarized in terms of their outcomes, which included primary outcomes (illicit opioid use and treatment retention) and secondary outcomes (polydrug use, criminal activity, jail time, injection drug use, needle sharing, and unprotected sex). Meta-analyses were conducted on the primary outcomes using a random effects model.

Results: We retrieved 2,111 unique citations and included 22 observational studies after all phases of screening. Five studies were included in the illicit opioid meta-analysis, and the pooled estimate was not significant, OR=1.33, 95% CI=0.49-3.57, p = 0.58. Four studies were included in the treatment retention

meta-analysis, and was likewise not significant, OR=0.48, 95% CI=0.18-1.26, p = 0.14. When we conducted a subgroup analysis by country for treatment retention, we found cannabis use was significantly associated with decreased retention among studies from USA, OR=0.23, 95% CI=0.13-0.39, $p < .0001$, whereas it was significantly associated with increased retention among studies from Israel OR=1.44, 95% CI=1.17-1.78, $p < .0001$. Qualitative summaries of the secondary outcomes similarly showed inconsistent results.

Discussion: The overall quality of evidence among the primary outcomes was very low and had substantial heterogeneity, likely due to methodological and clinical differences. Results of the current study suggest cannabis use may not be an independent predictor of MMT outcomes, however confidence in these results are low because of limitations in the quality and consistency of evidence.

Systematic review registration: PROSPERO CRD42015029372

Keywords: methadone maintenance treatment, cannabis, systematic review, meta-analysis

3.2 Introduction

With 33 million users worldwide, opioids are the third most commonly used illicit substance, following only cannabis and amphetamines [1]. Furthermore, opioids have a disproportionately high potential for misuse and abuse, and subsequent health and societal consequences [1]. Evidence continues to suggest that addiction to opioids is the main driver in morbidity and mortality due to opioid use [1–3]. In fact, over 75% of years lost due to premature death or disability worldwide from all drug-related causes was linked to opioid use disorders [1].

North America, in particular, is witnessing a dramatic rise in non-medical use of prescription opioids, with USA and Canada being the top two consumers of prescription opioids globally [4, 5]. Parallel to this rise in use, mortality rates due to opioids have dramatically increased in both countries [4, 6].

There is a clear and urgent need for effective treatments of OUD, reinforced addiction specialists have recently made an urgent call for increased access to evidence-based opioid agonist therapies [7]. Methadone maintenance treatment (MMT) is the most commonly prescribed treatment for OUD and despite its proven effectiveness, a significant degree of inter-individual variability exists in treatments outcomes [8, 9]. However, few risk factors for poor MMT prognosis have been established. With the emerging opioid crisis, it is more urgent than ever to identify effective treatment options for OUD.

Cannabis continues to be the most commonly used illicit drug worldwide, and the prevalence of its use is considerably higher in patients seeking treatment for opioid use disorder [10]. Studies investigating the influence of cannabis use on MMT outcomes have yielded conflicting results, and the nature of this association remains unclear.

The objective of the current review is to systematically summarize all literature investigating the association between cannabis use and MMT outcomes. In particular, we aim to identify whether cannabis use is associated with illicit opioid use and treatment retention, as these are direct measures of MMT success. Furthermore, we will consider secondary outcomes which reflect the overall health and functioning of a patient to assess the potential of harm reduction and changes in quality of life in MMT. These include polydrug use, criminal activity and jail time, injection drug use, needle sharing, and unprotected sex. We will also address gaps in the literature as well as consider risk of bias and overall quality of the literature to inform future work that should be conducted.

3.3 Methods

This review is presented in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [11]. It has been registered with PROSPERO (No. CRD42015029372). The detailed methods of the review have been published in a protocol in *Systematic Reviews* [12].

3.3.1 Search Strategy

The online databases MEDLINE/PubMed, EMBASE, PsycINFO, and CINAHL were searched from inception to August 2016. A detailed search strategy can be found in the published protocol [12]. Grey literature was also searched using the ProQuest Theses and Dissertations Global database. We also hand searched references lists of all included studies. No language or demographic restrictions were applied.

3.3.2 Study Selection

The current review included observational studies which look at the association between cannabis use and methadone maintenance treatment outcomes. The primary outcomes were illicit opioid use and treatment retention. We also included studies looking at the following secondary outcomes: criminal activity, jail time, polydrug use, injection drug use, needle sharing, and unprotected sex.

Studies were excluded if cannabis use was not measured as a predictor variable. Several studies reported cannabis use as part of baseline characteristics or measured change in cannabis use over time, and these studies were excluded. Many studies included a sample of patients of different opioid substitution therapies (i.e. buprenorphine and methadone), and these studies were excluded if they did not conduct the analysis on methadone patients separately. No other exclusion criteria were applied.

Two independent reviewers (LZ and MB) conducted title/abstract screening using the predetermined eligibility criteria. Full text screening was also performed in duplicate (LZ and XMZ). Any disagreements during screening unable to be resolved through discussion were settled by a third party (ZS). Inter-rater agreement for all screening phases was determined using the kappa statistic calculation.

3.3.3 Data Collection

Data extraction was performed in duplicate (LZ and MB) using a pilot-tested data extraction form (available as an additional file in the published protocol) [12].

3.3.4 Risk of Bias

Risk of bias for each included study was assessed in duplicate (LZ and MB) using the modified Newcastle-Ottawa Scale (NOS) and a kappa statistic was calculated to determine inter-rater agreement. Overall quality of literature was measuring using the grading of recommendations, assessment, development, and evaluation (GRADE) framework.

3.3.5 Data Synthesis

A meta-analysis was conducted on articles based on similarity in study design and outcome measurement using a random-effects model. A study was considered for inclusion if it produced, or included enough information to

generate an odds ratio, which was then calculated on RevMan version 5.3 software. If a study included multiple points of measurement for cannabis use, we used the baseline measurement. Some studies measured cannabis use both prior to treatment and during treatment, and we chose to use the in-treatment cannabis measurement to best answer our question. In studies that included multiple follow-up points for the outcome measurement, we included the latest follow-up time point in the meta-analysis. Due to significant heterogeneity, we were only able to conduct meta-analyses for the two primary outcomes – illicit opioid use and treatment retention.

Sensitivity analyses were conducted to compare results of studies with low and high risk of bias. Authors pre-specified studies would be excluded if they were given a score of 0 or 1 on the adapted NOS assessment for adjustment of potentially confounding variables (an item measuring performance bias) to determine whether results of these studies impacted the results of the meta-analysis. We specified this as a requirement because authors believed this bias was most likely to skew results, given the number of established confounders potentially affecting this specific relationship.

Furthermore, several a priori subgroup analyses were conducted which including method of cannabis measurement, and country in which the study was conducted. However, due to insufficient information reported in studies, we were

unable to perform several of the planned subgroup analyses, including stratifying by age and sex.

3.4 Results

After screening 2,111 unique citations, 22 observational studies were included in this review (Figure 3.7.1). Reasons for exclusion were wrong study design (i.e. qualitative, commentary, etc), some or all participants were on opioid substitution therapy other than methadone (eg. buprenorphine), cannabis was not measured as a predictor variable, or the wrong outcomes were measured. Inter-rater agreement was acceptable for both title/abstract, κ=0.63 (95% CI: 0.57-0.69) and full text screening, κ =0.60 (95% CI: 0.45-0.74).

3.4.1 Study Characteristics

Details of each included study are presented in Table 3.7.6A-E. There were a total of 11,137 participants, of which 69.6% were male (this percentage excludes one study which did not report the male to female ratio)[13]. The majority of studies were conducted in USA (n=13) and later than 2000 (n=13). Although we did not apply any age restrictions, all studies were conducted on an adult sample. Of samples that reported it in the entire sample, the mean age of participants ranged from 30.0 to 53.0.

15 studies dichotomized cannabis use, of which 13 defined cannabis use as any versus no use [14–26]. Lions et al. (2014) compared daily cannabis users to

other participants [9], while Joe et al. (1998) defined it as weekly marijuana use or not [27]. In addition to dichotomizing cannabis use, both Saxon et al. (1993) and Nirenberg et al. (1996) further analyzed cannabis use in multiple categories based on frequency of use. Three other studies also defined cannabis use categorically (>2 categories) [28–30]. The remaining three studies investigated the impact of cannabis use disorders (abuse or dependence) [13, 31, 32]. Peirce et al. (2009) looked at cannabis use disorder as well as cannabis use at intake [25]. Bell et al. (1997) was the only study to measure cannabis as a continuous measure, calculating average daily cannabis use for each participant [33].

In studies that reported the proportion of participants with any recent or current (i.e. not lifetime measurements) cannabis use, the prevalence ranged from 11.2% to 78.6%. Among these studies, the average prevalence of cannabis users was 32.9%, not adjusting for sample size.

3.4.2 Risk of Bias

We measured risk of bias using an adapted NOS scale [34] evaluating bias in four domains: selection bias, performance bias, detection bias, and information bias, each on a scale of 0 (high risk) to 3 (low risk). The NOS ratings for each study are presented in Table 3.7.7. All studies had moderate or high risk of bias for at least one criterion. The item with the highest risk of bias across studies was whether the study adjusted for important confounding variables, a measure of performance bias.

3.4.3 Illicit Opioid Use

11 studies examined the association between cannabis use and illicit opioid use or opioid relapse, which included four prospective cohort studies [15, 16, 26, 20], four retrospective cohort studies [14, 17–19], one cross sectional [29], and two secondary analyses of RCT data [28, 9]. Two studies defined illicit opioid use as relapse to opioids among patients who had achieved abstinence [28, 20].

Three studies found a positive association between cannabis use and illicit opioid use, while six found no significant association. Lions et al. (2014) measured both pre-treatment and in-treatment cannabis use, and found only in-treatment cannabis use was associated with continued opioid use [9]. Proctor et al. (2016) measured cannabis use at intake, 3, 6, 9, and 12 months in relation to opioid use at 3, 6, 9, and 12 months [17]. The only significant associations they found were 3-month positive cannabinoid UDS and 6-month opioid use (OR=2.03, 95% CI=1.03-3.98), and 9-month positive cannabinoid UDS and 12-month opioid use (OR=5.19, 95% CI: 1.26, 21.47) [17].

We were able to include five studies in the meta-analysis (Figure 3.7.2A). The pooled estimate was not significant, OR=1.33, 95% CI=0.49-3.57, $p = 0.58$, and there was significant heterogeneity with an I^2 of 70%, [$\chi^2(5)=16.81$, p=0.005]. Results did not change when excluding studies with high risk of bias. We conducted subgroup analyses by country and method of cannabis use measure

(i.e. objective vs. subjective), and neither yielded a significant estimate (Figure 3.7.2B,C).

The overall quality of evidence was very low (Table 3.7.8), with critical issues in inconsistency and imprecision, in addition to having moderate risk of bias. There was no evidence of publication bias (Figure 3.7.3).

3.4.4 Treatment Retention

11 studies investigated the influence of cannabis use on methadone maintenance treatment retention and consisted of six prospective cohort studies [13, 15, 26, 27, 21, 22], four retrospective cohort studies [14, 18, 23, 24], and one secondary analysis of an RCT [28].

Similar to illicit opioid use, the majority of studies found no significant association between cannabis use and treatment retention (n=8). Two studies found cannabis use to significantly decrease treatment retention, while one study found it to increase retention.

Upon including four studies in the meta-analysis (Figure 3.7.4A), the pooled analysis was not significant, OR=0.48, 95% CI=0.18-1.26, $p = 0.14$. This was also accompanied by significant heterogeneity, with an I^2 of 90%, [$\chi^2(5)=40.71$, $p<.0001$]. The sensitivity analysis conducted by excluding studies with high risk of bias did not change the result.

We did not stratify studies by cannabis measurement, as all studies used objective urine drug screens, however we conducted a subgroup analysis by

country. When stratifying results by country, we found studies conducted in USA showed cannabis use to be significantly associated with decreased retention rates, OR=0.23, 95% CI=0.13-0.39, $p < .0001$, while those conducted in Israel showed the opposite association, OR=1.44, 95% CI=1.17-1.78, $p < .0001$ (Figure 3.7.4B). Both subgroup analyses had an I^2 value of 0%, indicating no heterogeneity.

The overall quality of evidence was very low (Table 3.7.8), with quality issues related to inconsistency and imprecision. The funnel plot presented in Figure 3.7.5 displays slight asymmetry, however this is unlikely to be related to publication bias, as most studies included in the review had non-significant results.

3.4.5 Polydrug Use

When considering polydrug use, two studies found no association with cannabis use [30, 26], however another study found cannabis abuse was significantly associated with increased likelihood of having any other substance abuse diagnosis [13].

One study found cannabis use was associated with increased benzodiazepine use [18], and while another found no association [16]. A cannabis abuse diagnosis was found to be association with benzodiazepine abuse [13, 31], but one study found no such association [32].

Several studies assessed stimulant use (n=8), with 7 studies focusing specifically on crack or cocaine use. One study found a positive association [29],

while Nirenberg (1996) found no association [16]. Saxon et al. (1996) found pre-treatment cannabis use predicted less cocaine use during treatment [26]. When considering cannabis abuse or dependence, two studies showed an inverse association with cocaine/stimulant use [28, 25], whereas Weizman (2004) found the opposite, such that cannabis abusers showed higher rates of cocaine use [13]. One study found cannabis abuse was not associated with cocaine abuse [32].

When investigating its association with alcohol use, studies found cannabis use to be related to increased alcohol use [29] but not abuse [32].

3.4.6 Criminal Activity

Cannabis use was not shown to be associated with any criminal activity or jail time [28, 33]; however a lifetime diagnosis of cannabis abuse or dependence was significantly associated with more days in jail [28]. Cannabis use was also found to be predictive of future criminal activity measured at 12 months [33].

3.4.7 HIV Risk Behaviours (injection drug use, needle sharing, unprotected sex)

Only one study looked at HCV/HIV risk behaviours, including injecting drugs, needle sharing and safe sex, and found no significant relationship with cannabis abuse [13].

3.5 Discussion

To our knowledge, this is the first systematic review conducted investigating the use of cannabis during methadone maintenance treatment, and we included a total of 22 studies. The average prevalence of cannabis users in the MMT sample was 32.9%. This is notably higher than that seen in the general population, which shows the prevalence of past year use to be around 10% in North America [35, 36].

Of the included studies, we included five studies in the meta-analysis for the outcome, illicit opioid use and found no significant association. Four studies were included in the meta-analysis for the treatment retention outcome. The pooled estimate for this association was also not significant. Risk of bias due to performance bias was a significant issue across included studies, as most studies did not adjust for potential confounding variables. This can especially lead to spurious associations due to confounders such as age, sex, daily methadone dose and length of time in treatment that are known to influence the association between cannabis use and MMT outcomes. The overall quality of evidence was determined to be very low due to inconsistency related to substantial heterogeneity and imprecision of summary estimates.

The subgroup analysis stratifying by country for treatment retention showed that in USA, cannabis use was significantly associated with decreased retention whereas it was associated with increased retention for studies conducted

in Israel. This finding may reflect population differences, or differences in national policy or program characteristics. For example, the MMT programs in Israel used in the study were coupled with mandatory additional counselling, whereas it was either not offered or optional in MMT programs included in the USA studies.

Both meta-analyses were coupled with significant heterogeneity, which is likely the result of both clinical and methodological differences between studies. Unfortunately the limited number of studies included in the meta-analyses precluded us from conducting more subgroup analyses in an attempt to identify possible sources of heterogeneity. However, disparities were noted in factors such as definition of cannabis use and outcome, study design, study sample, and method of analysis, which may have all influenced the differences in results. The overall quality of evidence was very low for both primary outcomes which, coupled with the significant heterogeneity, makes it difficult to draw firm conclusions.

Despite being unable to conduct a meta-analysis on polydrug use, individual study results appeared similar to the primary outcomes in that there was little consistency within the literature. This could likely again, be explained by significant clinical and methodological heterogeneity between the studies. The majority of studies that looked at this outcome were conducted over 15 years ago, and further research in this area is merited.

Cannabis is seldom used in isolation [37], and there is some evidence to suggest it may be polydrug use so often coupled with cannabis use that is associated with poor outcomes. White et al. (2014) found baseline cannabis use to be significantly associated with treatment attrition, however when investigating patients who were positive for cannabis only at baseline, this association disappeared. When considering all non-opiate drugs together (benzodiazepines, amphetamines, and cocaine) as an outcome, Weizman (2004) found cannabis use to be significantly associated polydrug use.

A large epidemiological study conducted in the USA found cannabis use was independently associated with the prevalence and incidence of all substance use disorders [38]. Indeed, Weizman et al. (2004) found cannabis abuse specifically within the MMT population was also significantly associated with other substance use disorders (cocaine, benzodiazepines, and amphetamines). Studies suggest having comorbid substance use disorders negatively impacts quality of life [39] and increases risk of opioid relapse amongst patients receiving opioid substitution therapy [40], and as such this may represent a further confounding factor in this association.

A common finding in the literature was the differences between recreational cannabis use and cannabis use disorder (CUD). Some studies suggest cannabis use disorder is associated with less other drug use during treatment [25], whereas recreational cannabis use is associated with more; however that is not to

say CUD is benign. Patients with CUD may simply choose to use cannabis as opposed to any other drug, and this in and of itself may be related to other adverse health outcomes. For example, individuals with cannabis use disorder typically show high rates of comorbid psychiatric and personality disorders [41]. Those who use cannabis intermittently are perhaps more likely to be polydrug users who consume a variety of substances for recreational purposes.

Cannabis use was also found to not be associated with risky behaviours (criminal activity, injecting behaviours, needle sharing, and unsafe sexual behaviours); however this was based on very limited evidence. Results from the general population suggests cannabis use may increase the risk of criminal activity, particularly drug-based crimes [42] and impaired driving [43], as well as risky sexual behaviours [43].

3.5.1 Future Research

The current review is limited by the quality of studies included. Unfortunately the low quality of evidence and substantial heterogeneity for all outcomes renders the conclusions of this review fairly inconclusive; however it calls attention to the need for further research.

Because the majority of the studies did not identify cannabis use as their primary question of interest, they often crudely defined cannabis use. Most studies included in this review defined cannabis use as a binary variable, such that they compared patients with any cannabis use to those with none, and only one study

looked at it continuously [33]. This may be a major methodological issue itself, as this severely reduces the sensitivity of the findings. Research supports the notion that many harmful effects of cannabis are induced by heavy and chronic cannabis use [43, 44].

Future research should consider more sensitive definitions of cannabis use. The way the literature is currently defining cannabis use does not allow for the distinction between individuals who use it once a month recreationally and those who use it pathologically. Saxon et al. (1993) found evidence of a dose-dependent response, such that regular cannabis users had a smaller percentage of positive screens for other drugs of abuse, whereas intermittent users had higher percentages of positive screens [30]. More sensitive definitions can help determine whether heaviness and frequency of cannabis use can contribute to treatment outcomes.

Moreover, none of the studies considered mode of cannabis administration when defining cannabis use. Although not yet adequately studied, there is evidence to suggest some modes of administration are association with heavier patterns of drug use, in particular the use of water pipes [45]. The same study also found individuals who use multiple routes of administration have more problematic cannabis use [45], and as such there is reason to consider this factor in future research.

A further limitation is the lack of studies considering sex and gender differences in the relationship. Despite the well-established differences in substance use behaviours and MMT risk factors between men and women [46], few studies have stratified their analysis by sex. Levine et al. (2015) investigated the influence of cannabis use on MMT retention separately for men and women, and found the effect size was much greater in women [14]. In disorders like addiction where etiology and treatment outcomes are heavily influenced by both biological and social factors, an investigation into sex differences is crucial. In fact, guidelines have recently been developed in hopes of fostering a greater recognition of the importance of sex and gender in health research [47].

One of the major shortcomings noted across all studies was the inadequate control for clinically important confounding variables in the analysis. A large proportion of studies relied on univariate analyses, but even within studies who utilized more appropriate analyses, they often failed to adjust for documented risk factors for MMT outcomes.

It is well established that methadone dose has a considerable impact on MMT outcomes, with higher methadone doses related to higher retention rates [48, 49] and reductions in the use of illicit opioid use [48, 50], and other substances [51, 52]. Despite this fact, even among the studies utilizing adjusted analyses, few controlled for this known confounder which may have influenced the results.

3.6 Conclusion

Results of this review suggest cannabis use during MMT may not be a risk factor for poor treatment outcomes. However, the substantial heterogeneity and very low quality of evidence does not allow us to confirm the resultant estimates reflect the true association. Until further rigorous examinations of the effects of cannabis are conducted, its use during MMT should not be dismissed as benign at the present time.

Under certain circumstances, cannabis use may be a risk factor for poor treatment outcomes in MMT. Although perhaps not a direct risk factor for illicit opioid use or treatment retention, there is some evidence which suggests cannabis use may be related to more polydrug use and have a greater severity of addiction.

It is evident that further rigorous research needs to be conducted to identify sociodemographic and clinical profiles of patients at highest risk for any potential adverse effects of cannabis while in treatment for OUD. Future research should focus on differentiating between recreational cannabis use and cannabis use disorders, consider frequency and dose of cannabis use, and identify and adjust for potential confounding variables, as these may all be important factors influencing this association.

3.7 Figures and Tables

Figure 3.7.1 Flow Diagram of Included Studies

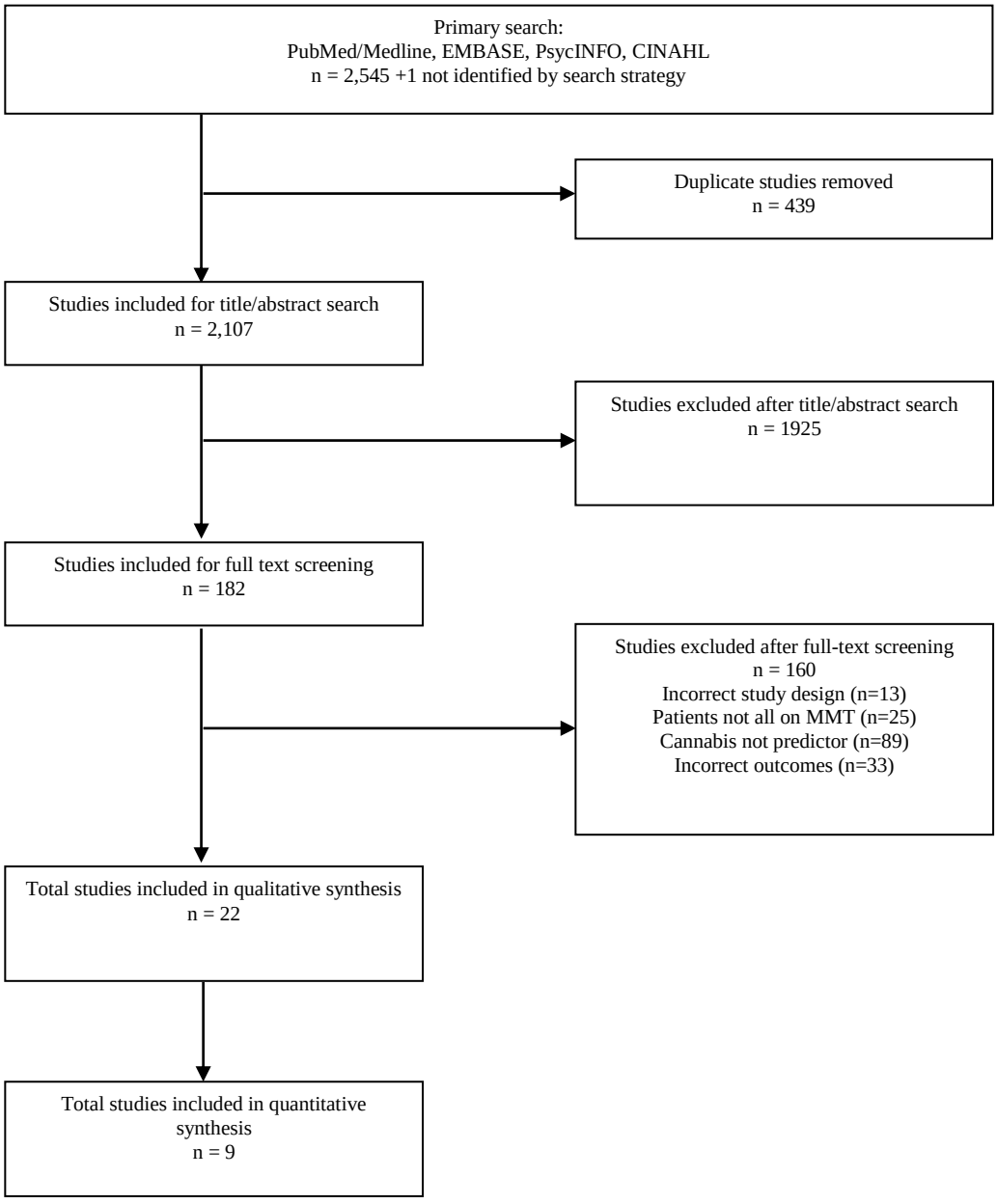
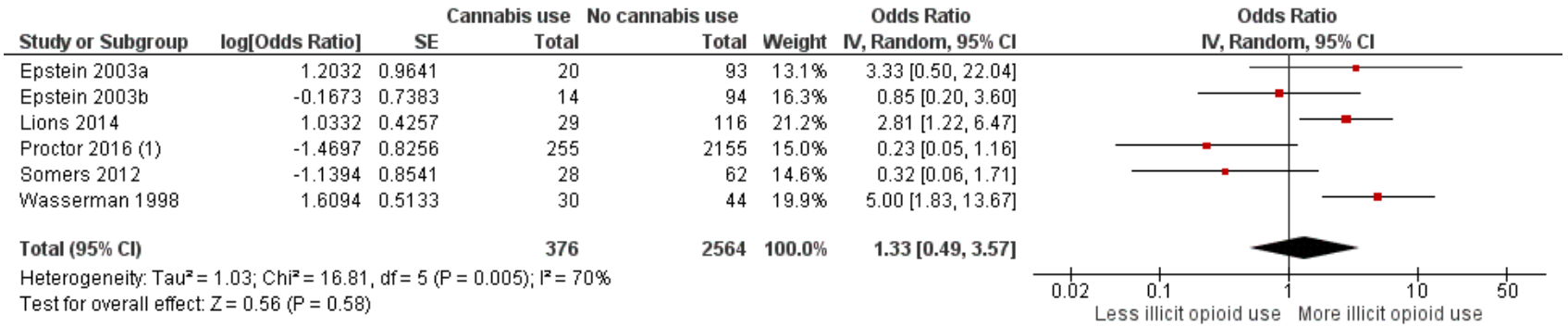


Figure 3.7.2

A. Meta-analysis forest plot for illicit opioid use.

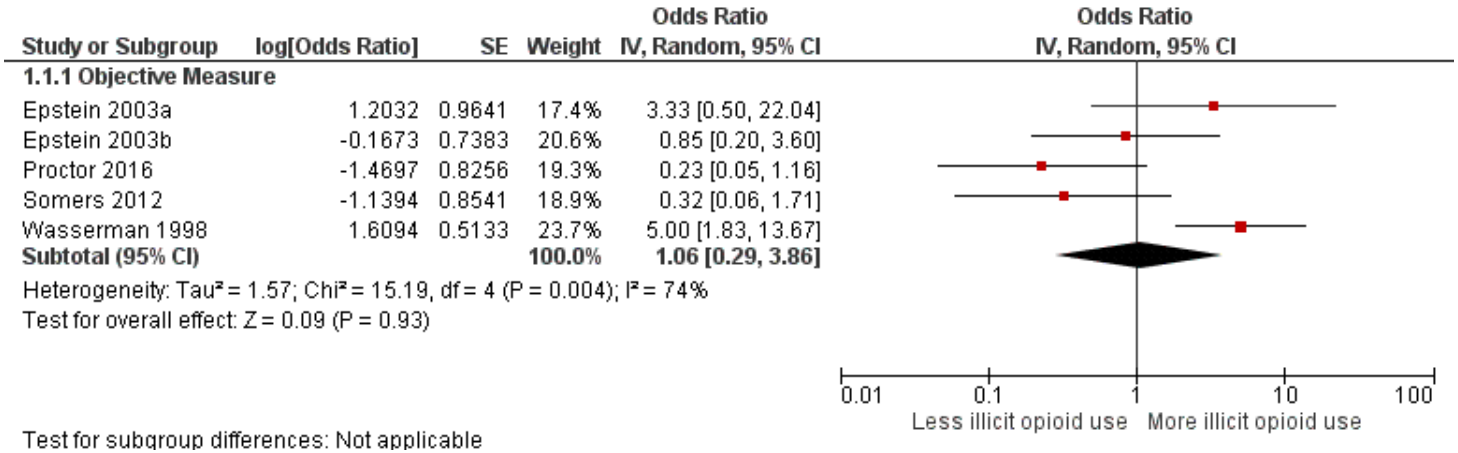


Study or Subgroup	log[Odds Ratio]	SE	Cannabis use Total	No cannabis use Total	Weight	Odds Ratio IV, Random, 95% CI
Epstein 2003a	1.2032	0.9641	20	93	13.1%	3.33 [0.50, 22.04]
Epstein 2003b	-0.1673	0.7383	14	94	16.3%	0.85 [0.20, 3.60]
Lions 2014	1.0332	0.4257	29	116	21.2%	2.81 [1.22, 6.47]
Proctor 2016 (1)	-1.4697	0.8256	255	2155	15.0%	0.23 [0.05, 1.16]
Somers 2012	-1.1394	0.8541	28	62	14.6%	0.32 [0.06, 1.71]
Wasserman 1998	1.6094	0.5133	30	44	19.9%	5.00 [1.83, 13.67]
Total (95% CI)			**376**	**2564**	**100.0%**	**1.33 [0.49, 3.57]**

Heterogeneity: Tau² = 1.03; Chi² = 16.81, df = 5 (P = 0.005); I² = 70%
Test for overall effect: Z = 0.56 (P = 0.58)

Footnotes
(1) Prevalence reflects 12 month cannabis use, as baseline prevalence was not reported.

B. Subgroup meta-analysis stratified by measure of cannabis use



Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
1.1.1 Objective Measure				
Epstein 2003a	1.2032	0.9641	17.4%	3.33 [0.50, 22.04]
Epstein 2003b	-0.1673	0.7383	20.6%	0.85 [0.20, 3.60]
Proctor 2016	-1.4697	0.8256	19.3%	0.23 [0.05, 1.16]
Somers 2012	-1.1394	0.8541	18.9%	0.32 [0.06, 1.71]
Wasserman 1998	1.6094	0.5133	23.7%	5.00 [1.83, 13.67]
Subtotal (95% CI)			**100.0%**	**1.06 [0.29, 3.86]**

Heterogeneity: Tau² = 1.57; Chi² = 15.19, df = 4 (P = 0.004); I² = 74%
Test for overall effect: Z = 0.09 (P = 0.93)

Test for subgroup differences: Not applicable

C. Subgroup meta-analysis stratified by country

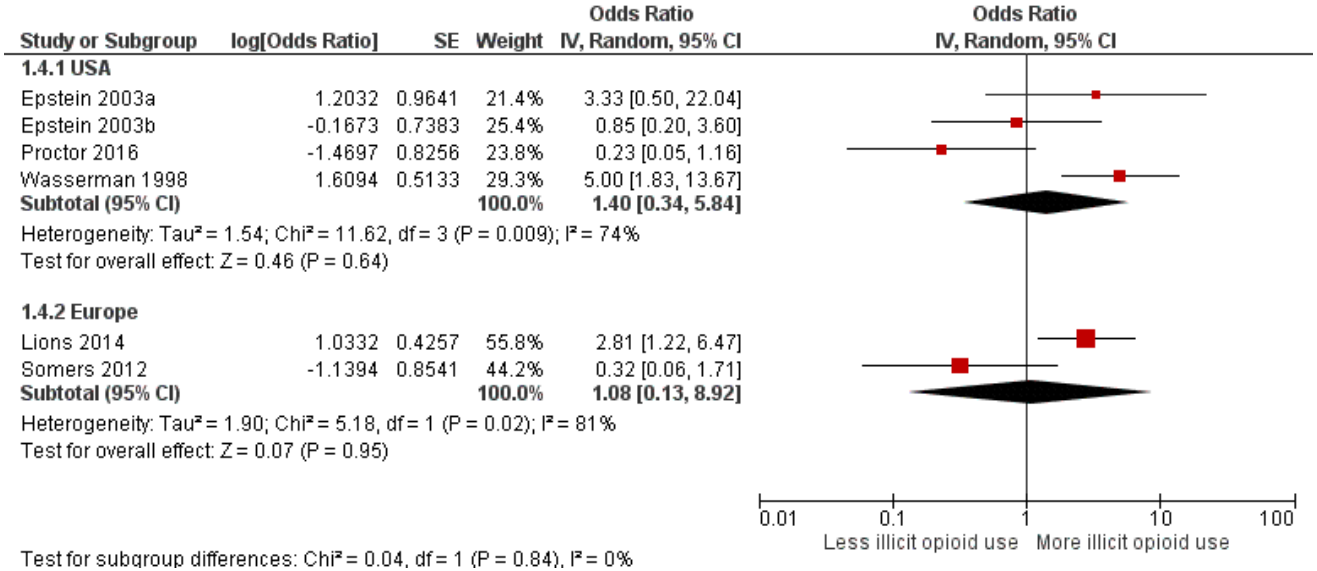


Figure 3.7.3 Funnel plot evaluating publication bias for illicit opioid use.

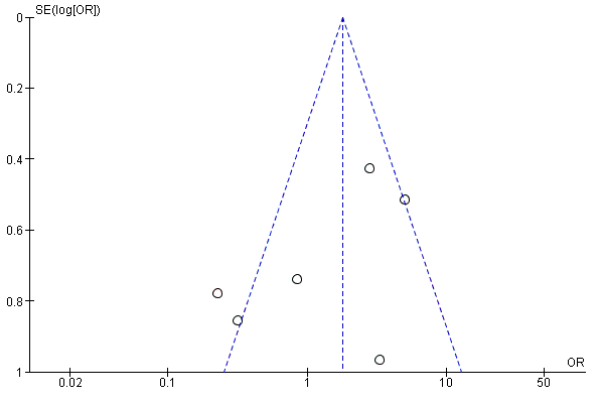
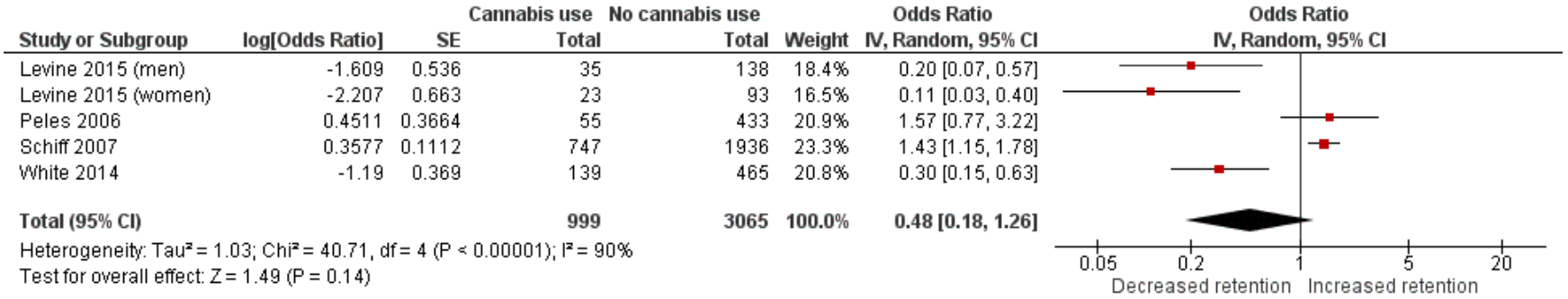


Figure 3.7.4

A. Meta-analysis forest plot for treatment retention



B. Subgroup meta-analysis stratified by country

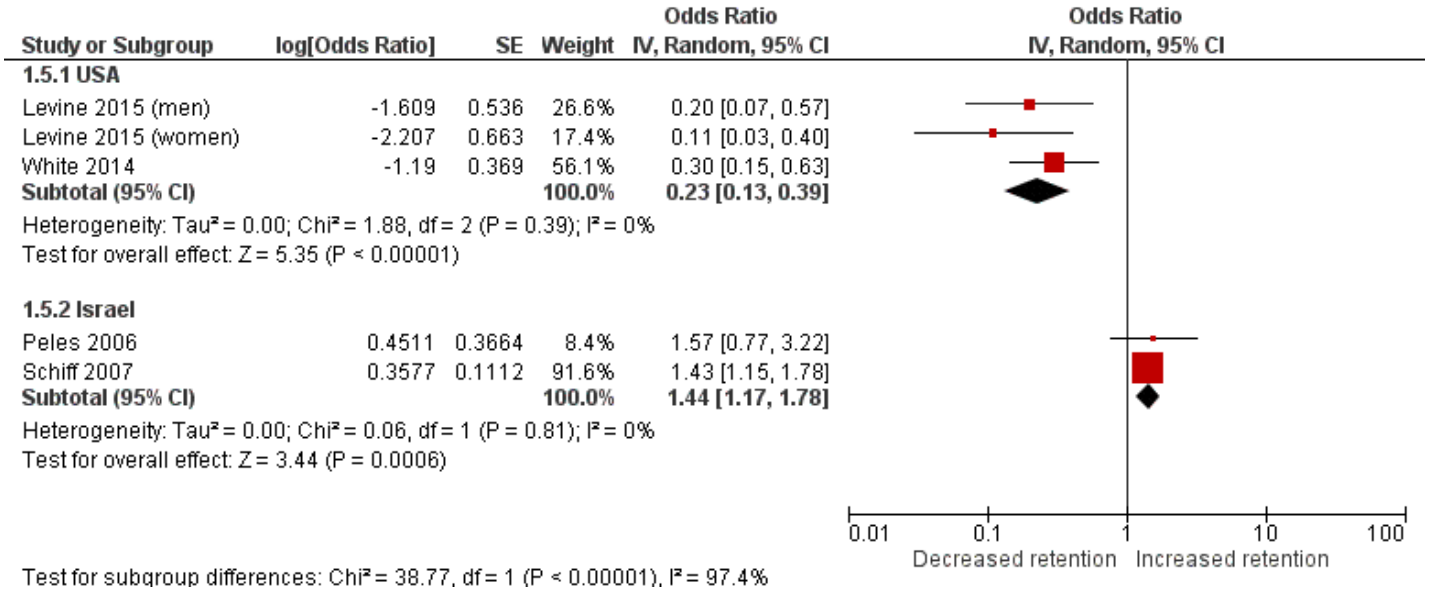


Figure 3.7.5 Funnel plot evaluating publication bias for treatment retention

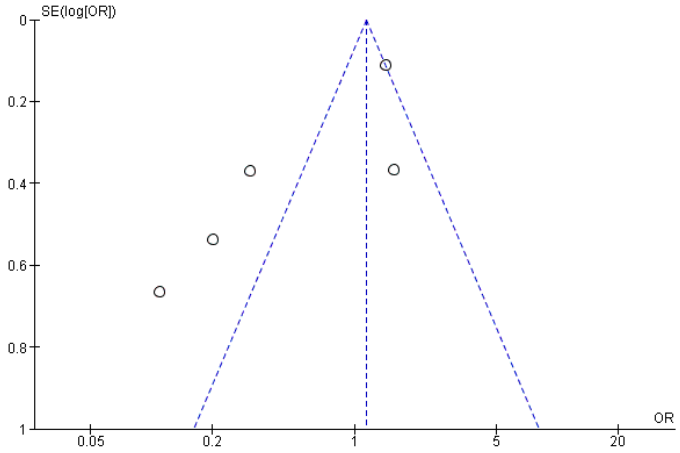


Table 3.7.6 Characteristics of Individual Studies

A. Outcome: Illicit Opioid Use

Study	Country	Study Design	Sample Size (% Female)	Cannabis Use Definition	Outcome	Statistical Analysis	Results
Best, 1999	UK	Cross sectional	200 (30%)	**Method:** MAP **Definition:** Categorical; daily users, occasional users (used cannabis but not on all 30 days in previous months), and non-users **Timing:** Baseline	**Method:** MAP **Definition:** Continuous; Mean number of days of heroin use in the past 30 days from MAP **Timing:** Baseline	ANOVA; post-hoc Scheffe test	F=11.07, p<.0001, such that non-users had more occasions of heroin use than occasional and daily users
Epstein, 2003	USA	Secondary RCT analysis, 12 months	408 (40.44%)	**Method:** Diagnostic Interview and urinalysis **Definition:** Dichotomized cannabis use and cannabis abuse/dependence diagnosis **Timing:** Baseline and 12 months	**Method:** Urinalysis **Definition:** Relapse to heroin among patients who achieved abstinence (3 consecutive weeks of opioid abstinence) **Timing:** Time to lapse	Cox proportional-hazard regression	**Cannabis use:** First two trials: HR = 1.54 (0.93–2.56) ; χ^2=2.78, p=0.095 Third trial: HR = 0.90 (0.48-1.65) ; χ^2=0.41, p=0.52 **Cannabis abuse/dependence:** First two trials: HR = 1.16 (0.63-2.13); χ^2=0.22, p=0.64 Third trial: HR = 2.09 (0.76-5.76); χ^2=1.66, p=0.19
Levine, 2015	USA	Retrospective cohort, 1 year	290 (40.34%)	**Method:** Urinalysis **Definition:** Dichotomized cannabis use **Timing:** Baseline within the First month of drug testing upon entry into MMT	**Method:** Urinalysis **Definition:** Continuous; Proportion of UDS results negative for opioids was calculated within the first year **Timing:** 12 months in treatment	Logistic Regression	Not significant, but statistics not reported.
Lions, 2014	France	Secondary RCT analysis, 45 weeks	158 (15.19%)	**Method:** Opiate Treatment Index **Definition:** Dichotomous; Daily users vs. non-daily users **Timing:** Baseline and 12 months	**Method:** Opiate Treatment Index **Definition:** Dichotomous; Opiate users vs. non-opiate users (used opiates at least once in the past month) **Timing:** 12 months	Multiple logistic regression	**Pre-treatment daily cannabis:** OR=1.46 (0.61-3.77), ns **In-treatment daily cannabis:** OR=2.81 (1.22-6.48), p<.05
Nava, 2007	Italy	Prospective cohort, 12 months	121 (13%)	**Method:** Self report, Urinalysis **Definition:** Dichotomous; long term users (more than 6 months) and currently smoking at least 7 times per week vs. non-users never exposed to marijuana smoking. **Timing:** Baseline	**Method:** Urinalysis **Definition:** Continuous; Percentage positive opioid screens (missing specimens considered positive) **Timing:** Urine samples were collected once a week	Hierarchical linear modelling	**Marijuana users:** z=-3.42, p<.001, such that there was a reduced percentage of positive opioid urines. **Non-marijuana users:** z=-3.18, p<.001, such that there was a reduced percentage of positive opioid urines.
Nirenberg, 1996	USA	Prospective cohort, 6 months	70 (1.42%)	**Method:** Urinalysis **Definition:** Dichotomized cannabis use; and Categorical 4 groups: Group 1 - cannabis abstainers (0 positive screens); Group 2 - intermittent cannabis users (0%-33.3% positive screens); Group 3 - moderate	**Method:** Urinalysis; **Definition:** Continuous; Percentage positive opioid UDS **Timing**: 45 weeks	ANOVA	**Dichotomized cannabis use:** F(1,68)=0.90, p=.35, ns **Four groups:** F(3,66)=1.13, p=.34, ns

				cannabis users (33.3% to 66.6% positive screens); Group 4 - consistent cannabis users (66.6%-100% positive screens) **Timing:** 45 weeks			
Proctor, 2016*	USA	Retrospective cohort, 12 months	2410 (40.41%)	**Method:** Urinalysis **Definition:** Dichotomized cannabis use **Timing:** Intake, 3, 6, 9, and 12 months	**Method:** Urinalysis **Definition:** Dichotomous; users vs. nonusers **Timing:** 3, 6, 9, 12 months	Logistic Regression	**3 months:** Intake cannabis: OR=1.17 (0.83-1.63) **6 months:** Intake cannabis: OR=0.59 (0.32-1.10) **9 months**: Intake cannabis: OR=0.63 (0.24-1.66) **12 months:** Intake cannabis: OR=0.23 (0.05-1.16)
Saxon, 1996	USA	Prospective cohort, 18 months	353 (38.20%)	**Method:** Self report; seven-point scale ranging from 0 "never" to 6 "four or more times per day". **Definition:** Categorical **Timing:** 6 months prior to baseline	**Method:** Urinalysis **Definition**: Dichotomous; Considered opioid users if at any visit reported use of any opioid drug other than their prescribed OMT medication, or if they reported having administered their prescribed OMT by snorting or injection in the previous 6 months. Percentage of opioid positive urine screens over 18 months **Timing:** 18 months	Cox regression model	r=0.06; B=0.05, ns
Scavone, 2013	USA	Retrospective cohort, 9 months	91 (36.56%)	**Method:** Self-report, Urinalysis **Definition:** Dichotomized cannabis use **Timing:** Baseline (self-report) and In-treatment (initial 9 months of MMT enrolment)	**Method:** Urinalysis **Definition:** Continuous **Timing:** 9 months	ANCOVA	r(82)=.018, p=.873, such that there was no significant relationship between frequency of cannabis use in treatment and opiate use.
Somers, 2012	Ireland	Retrospective cohort, 15 months	123	**Method:** Urinalysis **Definition:** Dichotomous cannabis use **Timing:** Baseline and in-Treatment; intake, 3, 9 and 15 months	**Method:** Urinalysis **Definition:** Dichotomous; Subjects with less than 20 % of samples positive for heroin **Timing:** 3,9,15 months	Logistic regression	**Baseline:** OR: 0.88 (.67-1.15) **3 month:** OR: 0.79 (.58, 1.1) **9 month:** OR: 0.78 (.55, 1.2) **15 months:** OR: 1.45 (.82, 2.5) **Total:** AOR: 32 (.06, 1.66)
Wasserman, 1998	USA	Prospective cohort, 6 months	74 (40.54%)	**Method:** Urinalysis **Definition:** Dichotomized cannabis use **Timing:** Baseline cannabis (first week) and cannabis as a time-dependent variable included in analyses	**Method:** Self-report or urinalysis; **Definition:** Dichotomous; Participants dichotomized as having used heroin during the period from week 2 through the 6-month follow-up assessment or not. **Timing:** 6 month follow-up	Cox proportional hazards regression	χ^2=8.39, p<0.004., such that baseline marijuana use significantly increased the risk of a lapse to heroin. χ^2=7.62, p<0.006, such that marijuana as a time-dependent variable significantly increased the risk of a lapse to heroin. **6-month follow-up:** χ^2=7.9, p<0.005, such that such that baseline marijuana use significantly increased the risk of a lapse to heroin

Notes: "Dichotomized cannabis use" means users vs. non-users or at least one positive urine screen vs. none unless otherwise specified.

*Proctor et al. (2016) had too many results to present in this table, so we included only intake cannabis values in relation to opioid use at all time points. See study for more results.

B. Treatment Retention

Study	Country	Study Design	Sample size (% female)	Cannabis Measurement	Outcome	Statistical Analysis	Results
Epstein, 2003	USA	Secondary RCT analysis, 12 months	408 (40.44%)	**Method:** Diagnostic Interview and urinalysis **Definition:** Categorical; Non-users, occasional users and frequent users **Timing:** Time to dropout	**Definition:** Retention in clinical trials up till follow up **Timing:** Did they complete the follow ups to 12 months	Survival Analysis for Treatment Retention for all 3 trials	In all 3 trials, p-values ranged from p=.69 to p=.72 Further statistics not reported.
Joe, 1998	USA	Prospective cohort, 360 days	981 (39%)	**Method:** Self-report **Definition:** Dichotomous; At least weekly marijuana use or not **Timing:** Baseline	**Definition:** Whether clients stayed at least 360 days in outpatient methadone treatment. **Timing**: 360 days into treatment	Hierarchical linear regression model	b=0.13, SE=0.16, t=0.79, OR=1.14, ns
Levine, 2015	USA	Retrospective cohort, 1 year	290 (40.34%)	**Method:** Urinalysis **Definition:** Dichotomized cannabis use **Timing:** Baseline within the First month of drug testing upon entry into MMT	**Definition:** Dichotomized into two groups: less than a year and more than a year **Timing:** 12 months after treatment	Logistic regression	**Men:** cannabinoid-negative: OR=5.00 (1.61-14.29), p=.01, such that less cannabis use predicted >1 year retention **Women** cannabinoid-negative: OR=9.09 (2.33-33.33), p<.001, such that less cannabis use predicted >1 year retention
Nava, 2007	Italy	Prospective cohort, 12 months	121 (13.22%)	**Method:** Self report, Urinalysis **Definition:** Dichotomous; long term users (more than 6 months) and currently smoking at least 7 times per week vs. non-users never exposed to marijuana smoking. **Timing:** Baseline	**Definition:** Percentage dropout from treatment measured **Timing:** 2 weeks, 3 months, and 12 months	Kaplain-Meier survival analysis	No significant association (values not reported).
Peles, 2006	Israel	Prospective cohort, 11 years	492 (27.24%)	**Method:** Urinalysis **Definition:** Dichotomized cannabis use **Timing:** 13 months or month before dropout	**Definition:** Continuous; The number of days in clinic from first admission until the patient quit treatment or until the end of follow-up (11 years) **Timing:** 132 months	Fishers exact test	**Cannabis use on admission:** p=0.3, ns
Peles, 2008	USA and Israel	Prospective cohort, 12 months	794 (30.98%)	**Method:** Weekly urinalysis; **Definition:** Dichotomized cannabis use **Timing:** Baseline and in-treatment For follow-up, recorded cannabis use month after completion or one month before if early dropout	**Definition:** Continuous; Duration in clinic from first admission until the patient stopped treatment or until the end of the follow-up **Timing:** Analyzed 6 months retention and 1 year retention in treatment	Kaplan-Meier survival analysis with log rank for cumulative retention.	**Tel Aviv:** Positive THC on admission: log rank=0.2, p=.8 Positive THC after 1 year: log rank=1.8, p=.2 **Las Vegas:** Positive THC on admission: log rank=4.2, p=.04 Positive THC after 1 year: log rank=0.8, p=.4 Included in multivariate analysis but not significant (values not provided)
Saxon, 1996	USA	Prospective cohort, 18 months	353 (38.20%)	**Method:** Self-reported seven-point scale ranging from 0 "never" to 6 "four or more times per day". **Definition:** Categorical **Timing:** 6 months prior to baseline	**Definition:** subjects remaining in treatment continuously after enrolment and those not remaining **Timing:** 18 months after enrolment	Cox regression analysis	r=0.06; B=1.08 (0.97-1.2), ns

Scavone, 2013	USA	Retrospective cohort, 9 months	91 (39.56%)	**Method:** Self-report, Urinalysis **Definition:** Dichotomized cannabis use **Timing:** Baseline (self-report) and In-treatment (urinalysis from initial 9 months of MMT enrolment)	**Definition:** Mean number of patients dropped out **Timing:** 9 months into treatment	Pearson correlation, chi square	Unfavourable discharge status: r(80)=.069, p=.567, ns Premature discharge status: χ^2 = 3.009, p=.222, ns
Schiff, 2007	Israel	Retrospective cohort, 13 months	2,683 (14.07%)	**Method:** Urinalysis; **Definition:** Dichotomized cannabis use **Timing:** Baseline and in-treatment; 13 months into treatment	**Definition:** Dichotomized patients as 100% retention vs. lower **Timing:** 13 months into treatment	Logistic regression	OR=1.43 (1.15, 1.78), p<.001, such that there was a significant relationship between cannabis use and increased retention.
Weizman, 2004	Israel	Prospective cohort, 12 months	283 (NR)	**Method:** Urinalysis **Definition:** Dichotomous; Cannabis abuse vs. not; First assessed the percentage of tests positive for a given month (first month and 12th month); second considered that is a patient tested positive for cannabis for any consecutive 3 months during the first year of MMT, was considered a potential cannabis abuser. SCID used to confirm or disconfirm cannabis abuse status. **Timing:** Baseline and 12 months	**Definition:** Treatment tenure was calculated based upon the overall number of days patients remained in treatment; Continuous **Timing:** 12 months into treatment	Cox regression survival analysis	Non-CAs vs CAs, B=-0.17; SE=0.13; Wald=1.57, p=0.21; r=0.00; Exp(B)=0.84 Analysis with heroin, cocaine, and BZD abuse as covariates did not significantly change the results.
White, 2014	USA	Retrospective cohort, 15-17 months	604 (39.40%)	**Method:** Urinalysis **Definition:** Dichotomized cannabis use **Timing:** First 3 months	**Definition:** Dichotomized retention as left MMT or remained in MMT **Timing:** 15-17 months	Chi square Fishers Exact Test	**Baseline cannabis use:** OR: 3.3 (1.6-6.8), p<.01, such that cannabis use was significantly associated with increased attrition rates. **Positive ONLY for cannabis at baseline:** 5% OR: 0.5 (0.7-9.8), p=1.00, ns

Notes: "Dichotomized cannabis use" means users vs. non-users or at least one positive urine screen vs. none unless otherwise specified.

C. Polydrug Use

Study	Country	Study Design	Sample size (% female)	Cannabis Measurement	Outcome	Statistical Analysis	Results
Best, 1999	UK	Cross sectional	200 (30%)	**Method:** MAP **Definition:** Classified participants as daily users, occasional users, and non-users; categorical **Timing:** Baseline	**Method:** MAP **Definition:** Measured alcohol and crack cocaine use; continuous **Timing:** 30 days after MAP	ANOVA; post-hoc Scheffe test	**Alcohol:** F=5.24, p<.01 Scheffe test: significant difference such that non-users of cannabis consumed more alcohol than occasional and daily users **Crack cocaine:** F=4.67, p<.05 Scheffe test: significant difference such that non-users of cannabis consumed more alcohol than occasional and daily users
Bleich, 1999	Israel	Prospective cohort, 12 months	148 (29.82%)	**Method:** Urinalysis **Definition:** A positive urine test for cannabis. A drug abuser for any substance of abuse was defined as having a positive urine test for that substance during the 12th month of treatment. **Timing:** 12 months into treatment	**Method:** Urinalysis **Definition:** Benzodiazepines; A positive urine test for benzodiazepines non-abusers vs. abusers **Timing:** 12 months into treatment	Chi square	**Benzodiazepine:** χ^2 = 7.77, p=0.005, such that benzodiazepine abusers were more likely to currently abuse cannabis that non abusers of benzodiazepine
Epstein, 2003	USA	Secondary RCT analysis, 12 months	408 (40.44%)	**Method:** Diagnostic Interview and urinalysis **Definition:** Categorical; Non-users, occasional users and frequent users **Timing:** Baseline and 12 months	**Method:** Urinalysis **Definition:** Continuous; Cocaine use from urinalysis **Timing:** Entire study duration	Multiple linear regression	**Cocaine abstinence:** Parameter estimate +/- SEM: 11.49 +/- 5.68, t=2.02, p=0.0438
Nirenberg, 1996	USA	Prospective cohort, 45 weeks	70 (1.43%)	**Method:** Urinalysis **Definition:** Dichotomous and Categorical; 4 groups: Group 1 - cannabis abstainers (0positive screens); Group 2 - intermittent cannabis users (0%-33.3% positive screens); Group 3 - moderate cannabis users (33.3% to 66.6% positive screens); Group 4 - consistent cannabis users (66.6%-100% positive screens) **Timing:** 45 weeks	**Method:** Urinalysis **Definition:** Continuous; Cocaine and benzodiazepine use **Timing:** 45 weeks	ANOVA	**Cocaine:** F(3,66)=1.17, p=.33 such that there was no significant difference between the 4 cannabis groups and their use of cocaine. **Benzodiazepines:** F(3,66)=2.10, p=.11, such that there was no significant difference between the 4 cannabis groups and their use of benzodiazepine.
Peirce, 2009	USA	Secondary RCT analysis, 12 weeks	386 (44%)	**Method:** Urinalysis. breath sample **Definition:** Cannabis use defined as positive urine/breath sample given at study intake **Timing:** at intake Cannabis use disorder defined as the interview administered checklist of DSM-IV substance use disorder symptoms	**Method:** Urinalysis, breath sample **Definition:** Stimulant use measured as number of stimulant-negative urine results provided **Timing:** Throughout the 12 week study intervention	Mixed-model regression	**Cannabis use at intake:** B(SE) = -3.27 (1.33), p=0.014, such that participants showed more stimulant use (less negative urine tests). **Cannabis use disorder:** B(SE) = 3.89(1.49), p=0.010, such that participants showed less stimulant use (more negative urine tests).
Saxon, 1996	USA	Prospective cohort, 18 months	353 (38.20%)	**Method:** Self-reported seven-point scale ranging from 0 "never" to 6 "four or more times per day". **Definition:** Categorical; **Timing:** 6 months prior to baseline	**Method:** Urinalysis **Definition:** Continuous; percentage positive urine screens for any drug use then cocaine use, specifically **Timing:** 18 months in treatment	Cox regression model	**Any drug use:** Model 1: r=-0.05; B=0.06 Not included in second model. **Cocaine use:** Model 1: r=-0.08; B=-0.09 Model 2: B=-0.11, p<0.05, such that pre-treatment frequency of cannabis use predicted less cocaine use
Saxon, 1993	USA	Cross sectional	98 (0%)	**Method:** Urinalysis;	**Method:** Urinalysis	Mann-Whitney	**THC+ vs. THC-:**

				Definition: Dichotomized cannabis use **Timing:** During the study period, specimens were periodically tested for THC. The number of tests for THC per subject varied from 1 to 17 (median=4). THC testing was generally spread over the duration of the study so that subjects were tested periodically over a span of months.	**Definition:** Continuous; screened for opiates, cocaine, and benzodiazepines. **Timing:** Weekly tests during entire treatment	U-test	Percentage of urinalysis positive for other drugs of abuse was not significantly different between THC+ (median=6.5, mean rank=50.74) and THC- patients (median-6.3, mean rank=48.0; z=-0.48). **Consistently THC+:** Participants consistently THC+ had a smaller percentage of urinalysis positive for other drugs of abuse (median=3.25, mean rank=21.7) than those who were intermittently THC+ (median=8.2, mean rank=31.5; z=-2.27, p<0.05).
Scavone, 2013	USA	Retrospective cohort, 9 months	91 (39.56%)	**Method:** Self-report, Urinalysis **Definition:** Dichotomized cannabis use **Timing:** Baseline (self-report) and In-treatment (urinalysis from initial 9 months of MMT enrolment)	**Method:** Urinalysis **Definition:** Any **i**llicit benzodiazepine use Timing: In-treatment (Initial 9 months of MMT enrolment)	Correlation	**Benzodiazepine:** r(91)=.374, p<.01, such that there was a positive correlation between rates of cannabis use and illicit benzodiazepine use during the initial nine months in treatment
Strain, 1991	USA	Cross sectional	66 (45%)	**Method:** Alcohol Research Center Intake Interview (ARC) **Definition:** Dichotomous; those with versus those without a history of a cannabis use diagnosis **Timing:** Interviews and assessments done in a series of two to three sessions	**Method:** Alcohol Research Center Intake Interview (ARC) **Definition:** Cocaine, sedative, and alcohol abuse/dependence diagnoses **Timing:** Interviews and assessments done in a series of two to three sessions	Z-Test	**Cocaine diagnosis:** RR=0.69, ns **Sedative diagnosis:** RR=1.67, ns **Alcohol diagnosis:** RR=0.83, ns
Weizman, 2004	Israel	Prospective cohort, 12 months	283 (NR)	**Method:** Urinalysis **Definition:** Dichotomous; Cannabis abuse vs. not; First assessed the percentage of tests positive for a given month (first month and 12th month); second considered that is a patient tested positive for cannabis for any consecutive 3 months during the first year of MMT, was considered a potential cannabis abuser. SCID used to confirm or disconfirm cannabis abuse status. **Timing:** Baseline and 12 months	**Method:** Urinalysis; **Definition:** Measured heroin, benzodiazepines, amphetamine, and cocaine abuse (they do not specify if they used SCID or something else to define abuse) **Timing:** 12 months	ANOVA	**Benzodiazepine:** F=18.48, p=0.000, such that CAs abused more benzodiazepines **Amphetamines:** F=9.29, p=0.003, such that CAs abused more amphetamines **Cocaine:** F=4.06, p=0.045, such that CAs abused more cocaine **All abuse and dependency diagnoses:** F=7.5, p=0.007, such that CAs had more other drug abuse and dependency diagnoses

Notes: "Dichotomized cannabis use" means users vs. non-users or at least one positive urine screen vs. none unless otherwise specified.

D. Criminal activity, jail time

Study	Country	Study Design	Sample size (% female)	Cannabis Measurement	Outcome	Statistical Analysis	Results
Bell, 1997	Australia	Prospective cohort, 12 months	304 (43.09%)	**Method:** Self-report **Definition:** Continuous; average daily use of cannabis in past month **Timing:** Baseline	**Method**: Crime scale of the Opiate Treatment Index; property offenses confirmed using police records **Definition:** Continuous; amount of criminal activity in past month **Timing:** Baseline and 12 months	Multiple linear regression	**Baseline**: Not significant, but statistics not provided **12 months**: Cannabis was a significant predictor, p=0.0001
Epstein, 2003	USA	Secondary RCT analysis, 12 months	408 (40.44%)	**Method:** Diagnostic Interview and urinalysis **Definition:** Categorical; Non-users, occasional users and frequent users; Cannabis abuse/dependence diagnosis **Timing:** Baseline and 12 months	**Method:** ASI **Definition:** Illegal income, days of illegal activity, days in jail **Timing:** Baseline	Mixed-regression	**Cannabis use:** Cannabis use category not associated with any differences in criminal activity, statistics not provided **Cannabis abuse/dependence:** Days in jail: $F(1,258)=8.58$, $p<0.0037$ Other measures were not significant

E. HIV Risk behaviours (injection drug use, needle sharing, unprotected sex)

Study	Country	Study Design	Sample size (% female)	Cannabis Measurement	Outcome	Statistical Analysis	Results
Weizman, 2004	Israel	Prospective cohort, 12 months	283 (NR)	**Method:** Urinalysis **Definition:** Dichotomous; Cannabis abuse vs. not; First assessed the percentage of tests positive for a given month (first month and 12th month); second considered that is a patient tested positive for cannabis for any consecutive 3 months during the first year of MMT, was considered a potential cannabis abuser. SCID used to confirm or disconfirm cannabis abuse status. **Timing:** Baseline and 12 months	**Method:** Clinic questionnaire **Definition:** Dichotomous; Whether the patient injected drugs, shared needles, performed safe sex, had sex for drugs, and had a partner who abused drugs during the past year. **Timing:** 12 months	ANOVA	Cannabis abuse was not related to any of the risk behaviours. Statistics not provided.

Table 3.7.7. Risk of bias assessment using modified NOS.

	SELECTION BIAS	PERFORMANCE BIAS		DETECTION BIAS		INFORMATION BIAS		
Study	**Is the source population representative?**	**Is the sample size sufficient and is there sufficient power?**	**Did the study adjust for confounders?**	**Did the study use appropriate statistical analysis?**	**Is there little missing data and was it handled appropriately?**	**Is the outcome measurement appropriate?**	**Is there an objective assessment of the outcome of interest?**	**Total Score**
Bell 1997	2	2	3	3	2	2	2	**16**
Best 1999	2	3	0	1	1	2	0	**9**
Bleich 1999	1	1	0	1	1	1	3	**8**
Epstein 2003	0	1	2	3	2	3	3	**16**
Joe 1998	3	3	2	3	2	3	3	**19**
Levine 2015	2	2	3	2	1	3	3	**16**
Lions 2014	1	2	0	2	1	3	2	**11**
Nava 2007	0	1	0	2	1	2	3	**9**
Nirenberg 1996	2	1	0	1	1	3	3	**11**
Peirce 2009	1	3	3	3	3	3	3	**19**
Peles 2006	3	3	0	3	3	3	3	**18**
Peles 2008	3	3	1	3	3	3	3	**19**
Proctor 2016	3	3	2	1	1	3	3	**16**
Saxon 1993	1	1	0	1	1	2	3	**9**
Saxon 1996	2	2	3	2	2	2	3	**16**
Scavone 2013	1	1	0	1	2	1	2	**8**
Schiff 2007	3	3	2	3	2	3	3	**19**
Somers 2012	2	1	1	1	2	1	3	**11**
Strain 1991	2	0	0	1	2	2	1	**8**
Wasserman 1998	2	0	3	3	3	3	3	**17**
Weizman 2004	2	2	0	1	1	1	3	**10**
White 2014	2	3	0	1	2	2	3	**13**

Note: 0=definitely no (high risk of bias); 1=mostly no; 2=mostly yes; 3=definitely yes (low risk of bias). Maximum total score=21.

Table 3.7.8 GRADE Evidence Profile.

Quality assessment							Quality	Importance
# of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**		
Illicit Opioid Use								
5	observational studies	serious [a]	very serious [b, c]	not serious	very serious [d]	none	⊕◯◯◯ VERY LOW	CRITICAL
Retention								
4	observational studies	not serious	serious [b]	not serious	very serious [d]	none	⊕◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **OR:** Odds ratio

a. Moderate risk of bias across studies

b. Point estimates vary widely across studies, little overlap between individual confidence intervals

c. Heterogeneity not explained by subgroup analyses

d. Small sample sizes, wide pooled 95% confidence interval

3.8 Author Contributions and Acknowledgements

LZ conceived of the question and study design, screened articles for inclusion, assisted with data extraction and synthesis, conducted quality assessments, assisted with statistical analysis and interpretation of results, and drafted the initial manuscript. MB screened articles for inclusion, assisted with data extraction and synthesis, conducted quality assessments, and assisted with statistical analysis and interpretation of results. XMZ screened articles for inclusion. NS contributed to data extraction and synthesis. JM, MS, and LT contributed to the statistical analysis and interpretation of results. ZS helped conceive of the question and study design, and assisted with statistical analysis and interpretation of results. All authors contributed to the critical revision and final approval of the manuscript.

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CHAPTER 4

Association between Cannabis Use and Methadone Maintenance Treatment Outcomes: An Investigation into Sex Differences

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4.1 Abstract

Background: Cannabis will soon become legalized in Canada, and it is currently unclear how this will impact public health. Methadone maintenance treatment (MMT) is the most common pharmacological treatment for opioid use disorder (OUD), and despite its documented effectiveness, a large number of patients respond poorly and experience relapse to illicit opioids. Some studies implicate cannabis use as a risk factor for poor MMT response. Although it is well established that substance use behaviours differ by sex, few of these studies have considered sex as a potential moderator. The current study aims to investigate sex differences in the association between cannabis use and illicit opioid use in a cohort of MMT patients.

Methods: This multicentre study recruited participants on MMT for OUD from Canadian Addiction Treatment Centre sites in Ontario, Canada. Sex differences in the association between any cannabis use and illicit opioid use were investigated using multivariable logistic regression. A secondary analysis was conducted to investigate the association with heaviness of cannabis use.

Results: The study included 414 men and 363 women with OUD receiving MMT. Cannabis use was significantly associated with illicit opioid use in women only (OR = 1.82, 95% CI: 1.18, 2.82, p=0.007). Heaviness of cannabis use was not associated with illicit opioid use in men or women.

Conclusions: This is the largest study to date examining the association between cannabis use and illicit opioid use. Cannabis use may be a sex-specific predictor of poor response to MMT, such that women are more likely to use illicit opioids if they also use cannabis during treatment. Women may show improved treatment outcomes if cannabis use is addressed during MMT.

Keywords: Cannabis, opioid, opioid use disorder, methadone maintenance treatment, sex differences

4.2 Background

Canada is currently developing legislation for the legalization of cannabis [1]. The rationale is that legalization would have social and economic advantages by generating revenue and deterring such crimes as illegal drug dealing [2]. Prohibition has been ineffective, with data suggesting this policy option has created more societal costs by way of excessive incarceration, largely involving already marginalized individuals [3], and no evidence to suggest these criminal penalties have any substantial effect on public health [4].

Colorado, USA has recently legalized cannabis, and while it remains premature to assess the public health impact of this policy, data show that the commercialization of medical marijuana in 2009 led to a 20% increase in college age (18-25 years) monthly marijuana use and a 36% increase in adult (26+ years) monthly marijuana use in the following three years [5]. Legalizing cannabis will almost certainly increase its availability and accessibility; plausible mechanisms for increasing recreational use include reduced prices, ease of access, criminal penalties no longer acting as a deterrent, and increased social acceptability [6]. It is reasonable to expect Canada will observe a similar increase in the prevalence of cannabis use, though its public health impact remains uncertain.

Despite the commonly held perception that cannabis is relatively harmless [7], its use has been linked to adverse consequences such as cognitive impairment,

lower life satisfaction, respiratory problems, and increased risk of developing psychotic episodes and disorders [8]. Those with a history of psychiatric or substance use disorders can experience worsened symptoms from cannabis use [1]. Cannabis users are also at heightened risk for developing other substance use disorders [9]. However, the current system of criminalization is similarly associated with individual and public risks. For example, individuals with a criminal record from minor possession charges often experience considerable difficulties in finding employment or housing leading to further social and health risks [1]. Public costs of criminalization are also substantial, with an estimated $2.3 billion spent annually on enforcement and prosecution [1].

While public health risks of cannabis legalization may by and large be minimal, certain vulnerable populations are more susceptible to the deleterious effects of its use. One such population are those with substance use disorders. North America is currently in the midst of an opioid crisis [10], in which we are witnessing a dramatic increase in non-medical use of opioids and subsequently the incidence of opioid use disorder (OUD). While opioid abuse is associated with serious adverse outcomes, it has been shown that the development of addiction is a major driver in the increase in opioid-related morbidity and mortality [11], indicating the extent to which OUD negatively impacts public health.

Because of the ongoing opioid epidemic in Canada, we must remain mindful of how increasing accessibility of cannabis will impact this population, in particular. Currently, the most commonly prescribed treatment for OUD is methadone maintenance treatment (MMT), an opioid substitution therapy [12]. MMT has proven to be effective in retaining patients in treatment and reducing opioid use and mortality [13], and this effectiveness has led to a steep increase in patients on MMT. In Ontario, Canada, the number of patients receiving MMT has nearly doubled since 2010 [12]. Despite its effectiveness, a significant number of patients respond poorly to treatment and experience relapse [14]. Illicit opioid use in combination with MMT is of immense concern, as it is a substantial risk factor for overdose and death [15].

Recent studies point to a changing landscape of OUD and those in treatment, one that includes a higher percentage of women, older aged patients, and more individuals abusing prescription opioids rather than heroin [16]. These sociodemographic changes warrant a re-evaluation of risk factors associated with poor MMT outcomes.

Several studies have investigated the influence of cannabis use on MMT outcomes in humans, though the results are mixed. Some studies have indicated cannabis use is associated with poorer treatment outcomes [17–19] while others looking at illicit opioid use found no significant association [20–23]. Although

this is the case, confidence in these diverging results is reduced by methodological limitations such as small sample size and subjective outcome measures, making further investigations merited.

Furthermore, few studies have considered sex as a potential moderator. It is well established that substance use behaviours differ by sex and different social and biological factors contribute to the development of substance use disorders between men and women [24]. Although a higher proportion of men use cannabis, women who use cannabis are more likely to experience adverse outcomes such as development of cannabis use disorder, and may also be more likely to show negative outcomes from cannabis in other domains [25]. Additionally, a large survey of cannabis users, for example, found a larger proportion of men use cannabis for recreational purposes while more women reported using it for purposes of self-medication [26]. Thus motivational processes for drug use may differ between men and women.

The objective for this study is to investigate sex differences in the association between cannabis use and illicit opioid use during methadone maintenance treatment. We will build on previous research by including a large, representative sample of MMT patients to ensure adequate power and generalizability of findings. Our secondary objective is to determine whether

heaviness of cannabis use is associated with illicit opioid use amongst male and female cannabis users.

4.3 Methods

4.3.1 Participants and Procedure

Data were collected as part of the GENetics of Opioid Addiction (GENOA) program, an ongoing prospective cohort study conducted in collaboration with the Population Genomics Program at McMaster University, and the Canadian Addiction Treatment Centre (CATC) [27]. We recruited participants from 16 CATC sites across Ontario, Canada from 2013-2016. Patients were eligible for participation if they were ≥18 years old, on methadone maintenance treatment for OUD, and able to provide informed written consent. Individuals were excluded if they did not speak English, were on an opioid substitution therapy other than methadone, or refused to provide blood or urine samples. Eligible participants provided informed written consent and underwent a face-to-face interview administered by trained research staff. This study was approved by the Hamilton Integrated Research Ethics Board (HIREB; Study ID 11-056).

4.3.2 Data Collection

The study participants provided sociodemographic and clinical information during an interview. We collected information regarding current

methadone maintenance treatment – methadone dose, duration of current treatment, and information about any past treatments for opioid use disorder.

The Maudsley Addiction Profile (MAP) [28] was administered to retrieve information about substance use, health risk behaviours, physical and psychological health, and personal and social functioning in the past 30 days. Substance use data included information on number of days used in the past 30, typical dose used, and route of administration. We also used the physical and psychological health sections of the MAP to compare general health and well-being among participants. These sections comprised of eight questions each and were scored using a Likert scale ranging from 0-4 (never-always) to produce a maximum score of 40 per section.

All study data were collected and managed by trained researchers using REDCap electronic data capture tools [29].

4.3.3 Drug Use Measurements

In addition to self-reported use of drugs using the MAP, all study participants underwent routine weekly or biweekly urine toxicology screens at the clinical sites part of routine clinical care as per CATC management protocol.

Cannabis Use

Cannabis use, the primary predictor variable, was measured using urinalysis (cutoff = 50 ng/ml for tetrahydrocannabinol) in the past 3 months. We

intended to use results of the urinalysis to quantify cannabis use, however several clinics discontinued screening for cannabis during urine testing, with only 45.0% of participants being tested as the primary purpose of urine drug screens for the clinical sites was to test for illicit opioid use and not cannabis use. Therefore, we opted to use self-reported cannabis use from the MAP. To verify the validity of self-reports, we calculated the sensitivity and specificity using participants who had data for both urinalysis and MAP (n=349). The sensitivity was 79.9% (95% CI: 72.7, 85.8) and specificity was 80.0% (95% CI: 73.6, 85.4), and thus we deemed self-reported cannabis use an appropriate measure of cannabis use.

For the primary regression analysis, we dichotomized cannabis use as any reported use versus no use in the past 30 days for our main predictor variable. We defined heaviness of cannabis use as the product of number of days used in the past 30 days by the typical dose per use (measured in grams) as reported on the MAP.

Many participants reported doses in values other than grams, and thus we utilized the quantification of common "marijuana measurements" to convert self-reported doses into grams as determined by Mariani et al. (2011). In this study, authors determined the following values as typical quantities of cannabis: pipe = 0.39g (SD = 0.64); joint = 0.66g (SD = 0.45); blunt = 0.97g (SD = 0.47) [30]. Furthermore, many participants reported values such as "less than one joint" or

"couple of puffs of a joint", and we coded all of these reports as equivalent to one half of a joint (0.33g). For all other reported quantities, we consulted an addiction expert to estimate the average dose per route of administration based on clinical experience. We used the following quantifications: bowl = 0.25g and cookie = 2g.

Illicit Opioid Use

Illicit opioid use during MMT was the primary outcome which was measured in the 3 months prior to baseline interview using urinalysis, with participants averaging 16 screens per 3 months. The cut-off concentration was 300 ng/mL for opiates and 100 ng/mL for oxycodone. We dichotomized illicit opioid use to reflect no positive screens versus any positive screens during a 3-month duration. This dichotomized variable is a patient-important treatment outcome, as the ultimate goal of MMT is complete abstinence of opioids. Individuals were excluded from analysis if they were currently prescribed any opioid medications, as these compromise the results of urine screens.

4.3.4 Statistical Analysis

Descriptive statistics were reported to compare demographic characteristics between men and women. Continuous variables were expressed as mean (standard deviation) and categorical variables were expressed as number (percent).

A multivariable logistic regression analysis was performed to investigate the association between cannabis and illicit opioid use, including an interaction term, sex by cannabis use, to investigate between-group sex differences. In the analysis, we controlled for age, sex, methadone dose, and treatment duration. Two multivariable logistic regression analyses were also performed for men and women separately to investigate within-group sex differences, controlling for the same covariates.

We conducted a secondary analysis on cannabis users to determine whether it is only the presence of cannabis use that influences treatment outcome or the heaviness of use that drives the association. For this, we replaced the binary cannabis variable with the continuous measurement of cannabis use heaviness. Multivariable logistic regression analyses were employed for male and female users, controlling for the same covariates as in the initial analysis.

Variables were assessed for collinearity using the variance inflation factor (VIF), and variables with VIF>10 were excluded from the analysis. Adjusted odds ratios (OR), 95% confidence intervals (CI), and p-values generated from the regression models are reported. The level of significance for hypothesis testing was set at alpha=0.05 for the main analysis and alpha = 0.025 for analyses performed separately on men and women.

The general requirement for logistic regression is to have a minimum of 10 events per predictor variable [31]. We included 212 men and 183 women with the event (presence of at least one positive opioid urine screen), and we included four predictor variables therefore the study was adequately powered for analysis. When isolating cannabis users for the secondary analysis, there were 133 men and 91 women with the event, demonstrating adequate power.

All analyses were performed using IBM SPSS version 20. This study is reported in adherence to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [32].

4.4 Results

4.4.1 Participants' Characteristics

The total sample comprised of 777 participants including 414 men and 363 women (Figure 4.7.1). Ages varied from 18-65 years with a mean age of 38.05 years (*SD* =11.11). The mean daily methadone dose was 75.44mg (*SD* = 45.84), and the average duration of current MMT was 48.55 months (*SD* = 49.53).

Sociodemographic and clinical characteristics of cannabis users and non-users are compared in Table 4.7.2. The mean age for cannabis users, 36.46 (10.94), was lower relative to non-users 39.78 (11.05), and a higher proportion of cannabis users were male. Cannabis users had a lower average methadone dose (72.36mg vs. 78.77mg) and shorter treatment duration (46.18 months vs. 51.14

months). Cannabis users also showed worse physical (16.02 vs. 15.06) and psychological functioning (14.27 vs. 12.90) compared to non-users as based on the MAP.

4.4.2 Illicit Opioid Use

The primary logistic regression analysis did not yield a significant association between cannabis use and illicit opioid use (Table 4.7.3), after adjusting for age, sex, methadone dose, and treatment duration (OR = 1.16, 95% CI: 0.77, 1.75, p=0.49). The interaction of sex and cannabis use also did not show a significant association with illicit opioid use in the regression model (OR = 1.52, 95% CI: 0.84, 2.77, p=0.17).

4.4.3 Sex Differences

59.7% of males and 43.5% of females reported using cannabis. Furthermore, men on average used cannabis more often in the past 30 days (11.97 days vs. 7.44 days) and at a higher average dose (1.48g vs. 1.04g). Women, on average, had lower methadone doses (72.34mg vs. 78.15mg) and were on their current MMT for a shorter duration (47.82 months vs. 49.18 months). Women also had worse physical (16.79 vs. 14.45) and psychological functioning (15.11 vs. 12.33) compared to men.

After adjusting for age, methadone dose, and treatment duration, any cannabis use in the past 30 days was significantly associated with illicit opioid use

(OR = 1.82, 95% CI: 1.18, 2.82, p=0.007) in women but not in men (OR = 1.11, 95% CI: 0.73, 1.69, p=0.62) (Table 4.7.4).

4.4.4 Heaviness of Cannabis Use

Among cannabis users, the mean number of days of cannabis use in the past 30 days was 18.91 days (*SD* = 12.46) and the mean daily dose was 1.31g (*SD* = 1.50), varying from 0.10-14.00g. The logistic regression analysis showed the heaviness of cannabis use to be unrelated to illicit opioid use in both women (OR = 1.00, 95% CI: 0.99, 1.01, p=0.92) and men (OR = 1.01, 95% CI: 1.00-1.01, p=0.07) (Table 4.7.5).

4.5 Discussion

The current study sought to investigate sex differences in the association between cannabis use and illicit opioid use in a cohort of MMT patients. Our results suggest that cannabis use during treatment may be a predictor of illicit opioid use in women. This could help explain why previous studies investigating this relationship provided conflicting results due to the lack of consideration of sex effect on the association between cannabis use and continued opioid use in MMT [20,33].

To our knowledge, this is the largest study conducted to date investigating the relationship between cannabis use and illicit opioid use in men and women on MMT. While some studies have indicated cannabis use is associated with poor

MMT treatment outcomes [17–19], several previous studies looking at illicit opioid use have not found significant results [20–23]. These inconsistent reports could be explained by methodological limitations such as the selection of the study participants [20] and insufficient investigations into sex differences in cannabis use and MMT treatment outcomes.

Despite the well-documented sex differences in the sociodemographic and clinical profiles of patients in MMT [34], there has been little research conducted on sex-specific predictors of MMT outcomes. Women are more sensitive to the subjective effects of cannabis (i.e. subjective ratings of intoxication and other drug effects like altered mood and sociability) and consequently show a faster trajectory to cannabis use disorder [25], indicating they may be have a higher proclivity to problematic cannabis use. Furthermore, cannabis use has consistently been shown to be associated with worse mental health outcomes in women compared to men [35,36].

Preclinical research points to many important developmental and biological sex differences which suggest females are more susceptible to the deleterious effects of cannabis use. Studies in rodents have found females exposed to Δ9-tetrahydrocannabinol (THC) were more susceptible to the reinforcing effects of cannabinoids, such that female rats more quickly acquired self-administration and were more sensitive to drug- and cue-induced reinstatement of

the drug [37]. These behavioural observations may be explained by the findings that prolonged exposure to THC led to a much greater cannabinoid receptor desensitization in female rats compared to their male counterparts [37]. It was also found significantly greater concentrations of THC and its metabolites in the female rat brain compared to males [38]. Despite this evidence, there is a paucity of research looking into the sexually-dimorphic effects of cannabis in humans [39].

While there is reason to consider biological mechanisms as explanation for the differential consequences of cannabis use in men and women, other clinical and social factors should not be overlooked. Women in MMT tend to show a higher prevalence of comorbid psychiatric and physical illnesses [16,40,41], as well as more severe opioid craving upon treatment entry [42] which may represent confounding factors that serve to increase rates of both cannabis and opioid use during MMT. As such, these patients may have motivation to use both drugs for purposes of self-medication. Indeed a survey of cannabis users found men were more likely to use cannabis recreationally while women were more likely to use it for purposes of self-medication for conditions such as anxiety and headaches [26].

Unexpectedly, when looking at cannabis users only, we failed to find an association between severity of cannabis use and illicit opioid use in either sex. It

is currently unclear why this is the case. A study by Saxon et al. (1993) found that MMT patients who had intermittent positive cannabis urine screens had a significantly higher percentage of positive screens for other drugs of abuse compared to those who consistently had positive screens [43]. Thus the relationship between severity of cannabis use and illicit opioid use may not be linear, but rather parabolic in nature whereby the recreational cannabis users show worse outcomes than either abstinent or daily users. However, our data seems to suggest that simply any cannabis use may be a risk factor for poor MMT outcomes in women.

Several studies also indicate a distinct difference between recreational cannabis users and those with cannabis use disorder, regardless of frequency of use, such that patients with a cannabis use disorder actually show less polysubstance use during MMT [20,44,45]. It is unclear why this is the case, but it may represent a confounding effect such as having cannabis use disorder may be associated with lack of means to obtain further drugs and lack of will or time to use other drugs while on MMT. In this study we did not find a significant association between the amount or frequency of cannabis use and illicit opioid use. However our study lacks the ability to distinguish cannabis use disorder from recreational use.

Another consideration is to account for the potency of cannabis used by patients, which was not measured in this study. Research on opioid-dependent rats suggests cannabidiol (CBD) and THC, the two main active ingredients in cannabis, actually generate opposing response. Administration of CBD extinguishes cue-induced heroin-seeking behaviours following periods of abstinence [46], whereas THC administration seems to heighten opioid sensitivity and increase heroin self-administration [47,48]. This antagonism is further supported by imaging studies in humans, which suggest CBD attenuates the neurotoxic and adverse psychiatric effects of THC [49,50]. Because of these differential effects, those who use cannabis for medicinal purposes may choose higher CBD concentrations while those who use it for recreational purposes may prefer greater amounts of THC. Therefore, depending on ratio of CBD to THC in the ingested cannabis, an individual may become more or less susceptible to further drug use, and this distinction should be investigated further.

Some limitations of this study should be noted. The cross-sectional nature of the analysis prevents any causal inferences from being made. Self-reported cannabis use, despite its adequate sensitivity and specificity may also be a biased estimate. However, there is evidence to suggest self-report use may be a more valid and sensitive indicator of cannabis use compared to urine screening. For example, patients enrolled in methadone maintenance treatment are required to provide urine samples at least one or two times per week, however studies have

shown the average time for the first negative result in urine screening for THC metabolites following a single dose of THC was 8.5 days following ingestion for infrequent users and 19.1 days for chronic users [51]. This suggests that urine data may overestimate the frequency of cannabis use.

4.6 Conclusions

This study suggests cannabis use is a potential sex-specific predictor of poor outcome during MMT. It will be important to look at the impact of cannabis use on women by systematically screening for cannabis use in women with OUD and providing addiction counselling to address not only opioid use but also cannabis use in this vulnerable group. This study also showed women with OUD experienced physical and psychological symptoms more frequently than men; these symptoms may be the underlying cause of cannabis use in women in this study and addiction services should consider sex specific treatment programs to manage symptoms and co-substance use.

4.7 Figures and Tables

Figure 4.7.1 Flow diagram for eligibility and screening of participants

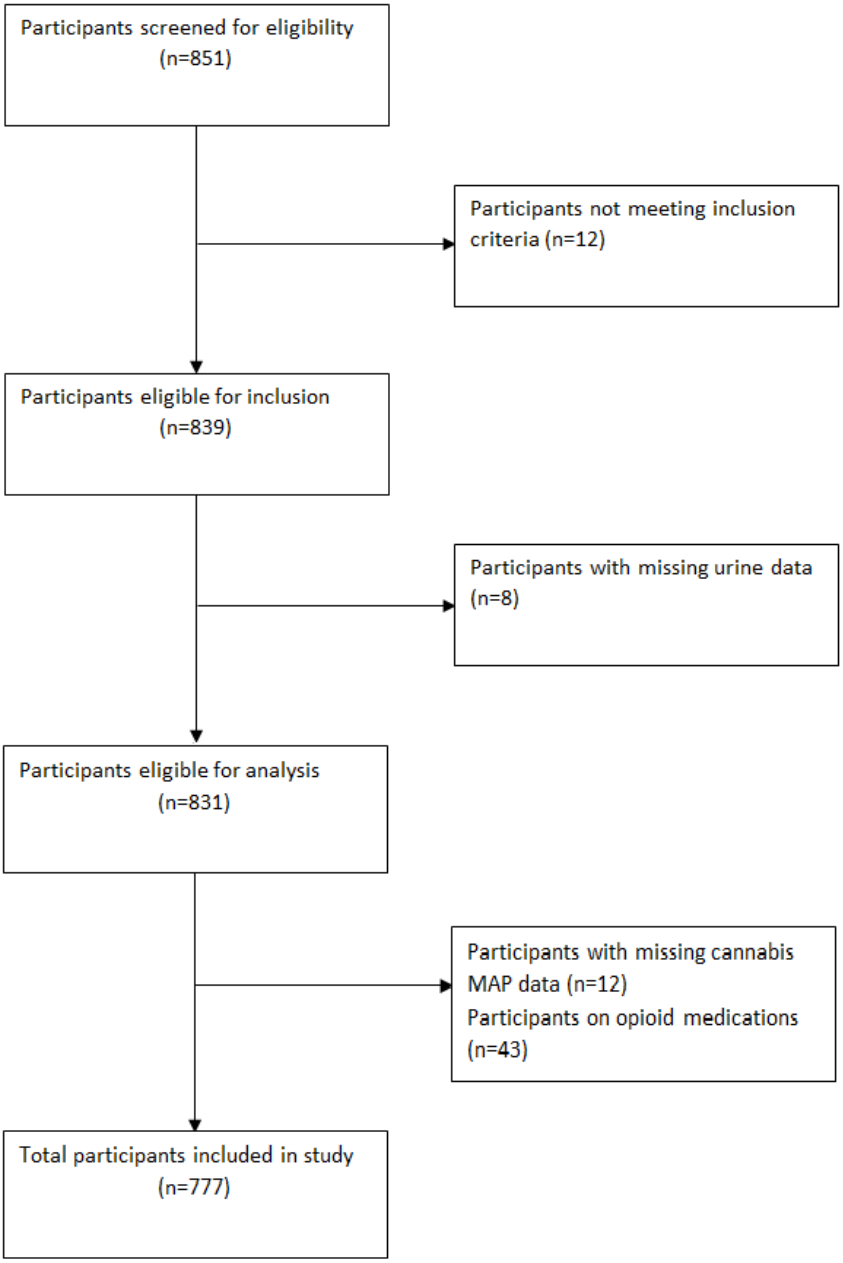

Table 4.7.2 Demographic and clinical characteristics of cannabis users and non-users on MMT

Variable	**Cannabis Non-Users** (n=372)	**Cannabis Users** (n=405)
Age in years (SD)	39.78 (11.05)	36.46 (10.94)
Sex (% female)	205 (55.1%)	158 (39.0%)
Ethnicity (% Caucasian)	306 (83.4%)	329 (81.8%)
Marital Status		
Never married	150 (40.3%)	211 (52.1%)
Married/common law/living with partner	126 (33.9%)	112 (27.7%)
Widowed/separated/divorced	96 (25.8%)	82 (20.2%)
Education		
Less than grade 9	67 (18.2%)	89 (22.0%)
Grade 9-12	190 (51.6%)	220 (54.5%)
Trade school, college, university	111 (30.2%)	95 (23.5%)
Employment (% currently working)	132 (35.5%)	141 (34.8%)
Smoking status (% current smoker)	301 (80.9%)	355 (87.7%)
Age of onset of opioid use in years (SD)	26.12 (9.08)	23.86 (7.86)
Methadone dose in mg per day (SD)	78.77 (46.54)	72.36 (45.02)
Current treatment length in months (SD)	51.14 (52.20)	46.18 (46.88)
Physical functioning (SD)	15.06 (7.92)	16.02 (7.38)
Psychological functioning (SD)	12.90 (9.57)	14.27 (8.76)

Notes: *SD*=standard deviation. Maximum score for the MAP physical and psychological functioning is 40, with higher scores indicating worse functioning

Table 4.7.3Multivariable logistic regression analysis on predictors of illicit opioid use

Predictor	***Odds Ratio***	***95% CI***	***P-Value***
Cannabis use	1.16	0.77-1.75	0.485
Sex*Cannabis use	1.52	0.84-2.77	0.169
Age	1.00	0.99-1.02	0.857
Sex	0.83	0.54-1.28	0.399
Methadone dose	1.00*	0.99-1.00	0.023
Duration of treatment	0.99*	0.99-1.00	<0.001

*significant at p < .05

Notes: *OR* = odds ratio. *CI* = confidence interval. Age, methadone dose, and duration of treatment interpreted as a one-point increase.

Table 4.7.4 Multivariable logistic regression analysis on predictors of illicit opioid use by sex

	Men			**Women**		
Predictor	***Odds Ratio***	***95% CI***	***P-Value***	***Odds Ratio***	***95% CI***	***P-Value***
Cannabis use	1.11	0.73-1.69	0.618	1.82*	1.18 – 2.82	0.007
Age	0.99	0.98-1.01	0.588	1.01	0.99 – 1.03	0.356
Methadone dose	0.99*	0.99-1.00	0.010	1.00	0.99 – 1.00	0.634
Duration of treatment	0.99*	0.99-1.00	0.004	0.99*	0.99 – 1.00	<0.001

*significant at $p < 0.025$

Notes: *OR* = odds ratio. *CI* = confidence interval. Age, methadone dose, and duration of treatment interpreted as a one-point increase.

Table 4.7.5 Multivariable logistic regression analysis on predictors of illicit opioid use among cannabis users by sex

	Men			**Women**		
Predictor	***Odds Ratio***	***95% CI***	***P-Value***	***Odds Ratio***	***95% CI***	***P-Value***
Cannabis use heaviness	1.01	1.00-1.01	0.072	1.00	0.99-1.01	0.917
Age	0.99	0.97-1.02	0.476	1.02	0.98-1.05	0.449
Methadone dose	0.99*	0.99-1.00	0.016	1.00	0.99-1.01	0.662
Duration of treatment	0.99	0.99-1.00	0.037	0.99	0.99-1.00	0.035

*significant at $p < 0.025$

Notes: *OR* = odds ratio. *CI* = confidence interval. Cannabis use heaviness, age, methadone dose, and duration of treatment interpreted as a one-point increase.

4.8 Author Contributions and Acknowledgements

LZ was responsible for conception and design of the study, acquisition of data, analysis and interpretation of data, manuscript writing, and critical revision of the manuscript. MB and NS contributed to acquisition of data, manuscript writing, and critical revision of the manuscript. CP, AW, MV, JD, GP, DM, and DD were responsible for data collection, communication with CATC clinics, and critical revision of the manuscript. JM, MS, and SM were responsible for analysis and interpretation of data, and critical revision of the manuscript. LT assisted with statistical analysis and critical revision of the manuscript. ZS contributed to the conception and design of the study, analysis and interpretation of data, and critical revision of the manuscript. All authors read and approved the final manuscript.

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CHAPTER 5

Concluding Remarks

5.1 Overview

Taken together, results of this thesis suggest cannabis use during MMT may be a risk factor for certain treatment outcomes in specific populations of patients. This is not a particularly unexpected finding, given the unique needs of all patients in all areas of medicine. However, novel results of this work led to advances in identifying in what instances cannabis use may contribute to adverse treatment outcomes in patients with opioid use disorder.

The systematic review we conducted summarized and evaluated all the available evidence on the association between cannabis use and several MMT outcomes (illicit opioid use, treatment retention, polydrug use, criminal activity, jail time, injection drug use, needle sharing, and unprotected sex). Results of this study revealed weak quality of evidence and considerable heterogeneity within the literature. Because of the substantial methodological and clinical differences between studies, it was difficult to draw conclusions from the current pool of evidence. We identified gaps and shortcomings in the literature in order to inform our primary study. For example, most studies treated cannabis use as a binary variable and did not adequately adjust for confounding variables.

We conducted a cross-sectional study investigating the association between cannabis use and illicit opioid use within a cohort of MMT patients. To build on past research, we considered sex differences as a potential effect modifier in this association, and defined cannabis use as both a binary and continuous variable. In our analysis, we also controlled for known confounding variables – age, methadone dose, and duration of treatment. Results of this study showed cannabis use was not associated with illicit opioid use in the whole sample, however when stratifying the analysis by sex, we found any cannabis use to be associated with illicit opioid use in women only. This not only highlights the importance of considering sex in health research, but also has implications for clinical practice.

5.2 Clinical Implications and Future Directions

There is an urgent need for OUD treatments, and it is imperative we identify risk factors for poor treatment prognosis to in order to improve its effectiveness. Given the high prevalence of cannabis use among patients with OUD and its documented effects on substance use and psychosocial functioning, it represents a potential risk factor for compromising treatment outcomes.

Results of this thesis suggest certain patients may be more at risk for the adverse effects of cannabis use. In particular, we identified cannabis use to be associated with continued opioid use in women on MMT. Our study also found

women have higher rates of physical and psychological symptoms compared to men, which may be the underlying cause of cannabis use. As such, women may benefit from additional sex-specific treatment programs to manage these comorbid symptoms in addition to treating the physiological symptoms of OUD with methadone.

Future research should build on this association found in women to identify sex-specific risk factors which serve to increase use of both cannabis and opioids, and consider such factors as chronic pain and psychiatric comorbidities. Conducting prospective studies will help elucidate the association between cannabis use and MMT outcomes in a time-dependent manner.

Appendix I

Published Study 1 and Supplementary Material

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Systematic Reviews

PROTOCOL Open Access

Association between cannabis use and treatment outcomes in patients receiving methadone maintenance treatment: a systematic review protocol

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Abstract

Background: With the non-medical use of prescription opioids increasingly becoming a method of abuse in Canada, the number of patients requiring methadone maintenance treatment (MMT) for opioid use disorder has increased dramatically. The rate of cannabis use in this population is disproportionately high (~50 %). Because its use is generally perceived as harmless, cannabis use is often not monitored during MMT. Current literature regarding the effects of cannabis use on MMT is conflicting, and the presence and nature of an association has not been clearly established. The primary objective of this review will be to conduct a systematic review of the literature and, if appropriate, a meta-analysis to determine whether there is an association between cannabis use and MMT outcomes. A secondary objective will be to perform subgroup analyses (by age, sex, method of cannabis measurement, and country) to determine whether cannabis use differentially influences MMT outcomes within these subgroups.

Methods/design: The search will be conducted on the following electronic databases using a predefined search strategy: MEDLINE, EMBASE, PsycINFO, and Cumulative Index to Nursing and Allied Health Literature (CINAHL). Two authors (LZ and MB) will independently screen articles using predetermined inclusion/exclusion criteria and will extract data from included articles using a pilot-tested data extraction form. Disagreements at all stages of the screening process will be settled through discussion, and when consensus cannot be reached, a third author (ZS) will be consulted. An assessment of quality and risk of bias will be conducted on all included articles, and a sensitivity analysis will be used to compare results of studies with high and low risk of bias. We will perform random- and fixed-effects meta-analyses, if appropriate, with heterogeneity calculated using the I^2 statistic and formal evaluation of publication bias.

Discussion: Results of this systematic review will elucidate the association between cannabis use and methadone maintenance treatment outcomes. We will provide evidence that will be useful to clinicians regarding whether monitoring cannabis use during MMT is advantageous for optimizing MMT outcomes.

Systematic review registration: PROSPERO CRD42015029372

Keywords: Methadone maintenance treatment, MMT, Cannabis, Marijuana, Systematic review, Protocol

Abbreviations: MMT, Methadone maintenance treatment; MOOSE, Meta-analysis of observational studies in epidemiology; NOS, Newcastle-Ottawa Scale; PRISMA, Preferred reporting items for systematic reviews and meta-analyses; PRISMA-P, Preferred reporting items for systematic review and meta-analysis protocols; RCT, Randomized controlled trial

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Background

There are an estimated 33 million opioid users globally [1], which is markedly contributing to the global burden of disease [2]. Illicit opioid use is associated with significant personal health risks, such as accidental injury, dependency, infectious disease [3], and potential for fatal overdose, in addition to its effects on the social concerns of healthcare costs, criminal activity, and employment [2]. Although the prevalence of heroin use has remained constant in Canada, a dramatic rise in the use of prescription opioids has resulted in a surge in opioid detoxification admissions from 2000 to 2004 [4]. In both the USA and Canada, illicit use of prescription opioids has become a significant contributor to emergency room visits and mortality [5]. This changing landscape and steady increase in problematic opioid use in North America signals an urgent need for evidence-based treatment practices.

Canada has witnessed a fivefold increase in patients on methadone maintenance treatment (MMT) since the mid-1990s [6]. MMT is an opioid substitution therapy and is the most widely researched pharmacological treatment for opioid use disorder [7]. Methadone is a long-acting synthetic opioid intended to reduce cravings and withdrawal symptoms without producing the euphoric effects associated with illicit opioids [8]. Studies have shown this treatment to be effective in decreasing illicit opioid use, reducing criminal activity, and reducing mortality rates among patients [7]. Although an overall efficacious treatment for reducing illicit opioid use, MMT is limiting in that it has high attrition rates [9] because it often requires patients to be on the treatment for life [10].

Polydrug use is common among MMT patients [11, 12], with cannabis consistently being the most commonly used illicit drug in this population [13–15]. This may be due to the fact that cannabis is generally perceived as harmless [16]. While it may be the case that mortality directly resulting from cannabis use is unlikely [2], associations with other adverse health outcomes have been found. In particular, regular cannabis use increases the risk of motor vehicle accidents and respiratory problems and poses a risk for dependency [17]. Long-term use is also associated with lower school performance and decreased life satisfaction [16]. Furthermore, cannabis use is associated with adverse mental health outcomes. The strongest evidence comes from studies on psychotic disorders, with a systematic review showing a strong, positive relationship between incidence of psychosis and cannabis use, which increases as frequency of cannabis use increases [18]. Studies have also found associations with other psychiatric illnesses including mood disorders (unipolar and bipolar) [19–21] and anxiety (particularly panic disorder and social anxiety) [22, 23]; however, evidence for a directional association with these disorders is inconclusive. Nonetheless, it remains a possibility that cannabis use during the treatment of opioid addiction could influence its outcome.

Studies on the association between cannabis use and MMT outcomes have produced conflicting results, with some demonstrating beneficial effects on outcomes [14] and others showing an association with adverse treatment outcomes. For example, Wasserman et al. [24] found that cannabis use at baseline and throughout the study period was significantly associated with subsequent heroin use during treatment, whereas Scavone et al. [14] found that patients using cannabis during the study reported significantly less daily expenditure on acquiring opioids. Most studies, however, have failed to produce a statistically significant association between cannabis use and MMT retention or illicit opioid use [13, 25–28]. Epstein and Preston [26] found that cannabis use increased other outcomes such as jail time and family conflict, suggesting that its use during MMT may act indirectly via social and lifestyle risk factors. The relationship between cannabis use and MMT outcomes may also include complex interactions with health behaviors. For instance, depressive symptoms and illicit substance use during MMT is significantly associated with a lack of HIV medication adherence [20], which may in turn affect MMT outcomes and overall health status among patients.

It remains unclear whether there is a true association between cannabis use and MMT outcomes and to what degree this association may be mediated by other confounding variables. A systematic investigation and evaluation of the studies is necessary, as well as the identification of any gaps in the literature. We hypothesize that the use of cannabis in patients with opioid use disorder treated with methadone is associated with poor response to MMT as defined by illicit opioid use and length of treatment retention. Evidence indicates that treatment retention is a critical factor in MMT success, with research suggesting that those in treatment for less than 90 days resemble those receiving no treatment at all [29]. Indeed, MMT dropout is significantly associated with drug use relapse and other high-risk health behaviors [11] and is a useful indicator of treatment response. We will also consider secondary outcomes to evaluate risky health and social behaviors including criminal activity, jail time, polydrug use, injection drug use, needle sharing, and unprotected sex. Isolating each outcome and controlling for potential confounders will help to clarify the association between cannabis use and MMT outcomes.

Objectives

The objective of this systematic review is to summarize the existing literature examining the effects of cannabis use on treatment outcomes during methadone maintenance treatment in patients with opioid use disorder by identifying and evaluating the current evidence.

Specifically, our aims are as follows:

1. Summarize primary research to examine the relationship between cannabis use and primary methadone maintenance treatment outcomes (treatment retention and illicit opioid use) and secondary outcomes (criminal activity, jail time, polydrug use, injection drug use, needle sharing, and unprotected sex).
2. Combine statistical outcomes of the primary studies in a meta-analysis, when appropriate.
3. Conduct subgroup analyses based on sex, method of cannabis measurement, and geographical region of study to explore potential confounders in the relationship.
4. Critically appraise the existing literature and identify areas requiring further research.

Methods and design

Search strategy

An experienced health sciences librarian (NB) will be consulted when creating and implementing the search strategy. The following databases will be searched from their inception to present: MEDLINE/PubMed, EMBASE, PsycINFO, and Cumulative Index to Nursing and Allied Health Literature (CINAHL). Relevant articles will be identified from the comprehensive search strategy using all relevant search terms related to methadone maintenance treatment and cannabis, and their medical subject heading (MeSH) equivalents in varying combinations (Table 1). A wide search will be conducted to include titles, abstracts, and keyword fields. Outcome variables will not be included in the search strategy so as not to impose unnecessary limitations on search results. The searches will all be limited to human studies. Gray literature will also be searched using ProQuest Dissertations and Theses Global database. Finally, we will conduct a thorough hand search of past reviews and reference lists of included studies to identify potentially relevant articles that the initial search strategy may not have captured.

Table 1 Search strategy

Database	Search strategy
MEDLINE (*n* = 420)	1. exp Opiate substitution therapy/ 2. Methadone/ 3. Methadone.mp. 4. MMT.mp. 5. Cannabis/ 6. Marijuana Abuse/ 7. Marijuana Smoking/ 8. Medical Marijuana/ 9. Cannabis.mp. or marijuana*.mp. 10. THC.mp. or hash*.mp. or ganja.mp. or hemp.mp. or bhang*.mp. 11. 1 or 2 or 3 or 4 12. 5 or 6 or 7 or 8 or 9 or 10 13. 11 an 12 14. Limit 13 to humans
EMBASE (*n* = 1761)	1. exp opiate substitution treatment/ 2. exp methadone treatment/ 3. exp methadone/ 4. Methadone.mp. 5. MMT.mp. 6. exp cannabis/ 7. exp "cannabis use"/ 8. exp cannabis addiction/ 9. exp cannabis smoking/ 10. exp medical cannabis/ 11. Cannabis.mp. or marijuana*.mp. 12. THC.mp. or hash*.mp. or ganja.mp. or hemp.mp. or bhang*.mp. 13. 1 or 2 or 3 or 4 or 5 14. 6 or 7 or 8 or 9 or 10 or 11 or 12 15. 13 and 14 16. Limit 15 to humans
PsycINFO (*n* = 194)	1. exp methadone maintenance/ 2. methadone.mp. 3. MMT.mp. 4. exp cannabis/ 5. exp marijuana usage/ 6. cannabis.mp. or marijuana*.mp. 7. THC.mp. or hash*.mp. or ganja.mp. or hemp.mp. or bhang*.mp. 8. 1 or 2 or 3 9. 4 or 5 or 6 or 7 10. 8 and 9 11. Limit 10 to humans
CINAHL (*n* = 50)	1. (MH "Methadone") 2. "Methadone" 3. "MMT" 4. (MH "Cannabis") 5. (MH "Medical Marijuana") 6. "marijuana" or "cannabis" 7. "THC" or "hash*" or "ganja" or "hemp*" or "bhang*" 8. 1 or 2 or 3 9. 4 or 5 or 6 10. 7 and 8 (limiters – human)

Inclusion/exclusion criteria

This review will include published observational studies or randomized controlled trials (RCTs) of the relationship between cannabis use and methadone maintenance treatment outcomes in any setting (hospital, outpatient, or community-based). Included studies will measure cannabis use at baseline for cross-sectional studies and during treatment for cohort studies and RCTs, which may be measured using objective measures (i.e., urine or hair analyses) or self-reports.

Studies will be excluded if they do not measure at least one of the primary or secondary outcomes of interest. If cannabis use is measured as an outcome rather than a predictor variable, it will be excluded. Many studies in this domain report frequency of cannabis use as part of the demographics of the sample, and as such, these will be excluded as we cannot make any conclusions regarding its direct association with MMT outcomes. Studies including patients on opioid substitution therapy (i.e., buprenorphine or buprenorphine/naloxone) other than methadone will be excluded. Furthermore, studies looking at patients

on methadone for anything other than treatment of opioid use disorder (i.e., illicit methadone use or chronic pain treatment) will be excluded. No age restrictions will be applied, as opioid addiction affects people of all age groups. There will be no other demographic limitations or language restrictions.

Outcome measures

Two primary outcomes variables will be measured which evaluate the success of methadone maintenance treatment. These include illicit opioid use which may be measured in any way (self-reports, urine toxicology, hair analysis), as well as treatment retention. Treatment retention may be measured as either proportion of individuals remaining in treatment at the end of study or average length of time in treatment. In addition to the MMT outcomes, secondary outcomes will be considered which reflect the patients' social and personal functioning and other drug use behaviors. These include criminal activity, jail time, polydrug use, injection drug use, needle sharing, and unprotected sex.

Data management

All articles retrieved during the initial search will be uploaded to Covidence, an online software system used to manage systematic reviews and promotes collaboration among authors. Training will be provided to all members using the Covidence software. The review team will define a set of inclusion and exclusion criteria, and pilot test the title/abstract screening with the first 100 articles. Upon completion of title and abstract screening, full-text articles will be uploaded to the Covidence system for purposes of the full-text review.

Selection of studies

Two independent reviewers (LZ and MB) will complete the initial title and abstract screening to identify eligible articles using a predetermined criteria. Articles deemed eligible will be retrieved for a full-text review. Any disagreements during the screening process that cannot be settled through discussion will be resolved by a third party (ZS). Authors of the studies will be contacted if any clarification or additional data is needed during the full-text review to determine eligibility. For each phase of screening, a kappa statistic will be calculated to determine inter-rater agreements. A kappa value of 0.75 or greater reflects excellent agreement [30]. Studies determined to be ineligible will be excluded from the review. Reasons for ineligibility and exclusion will be reported using the preferred reporting items for systematic reviews and meta-analyses (PRISMA) [31] or meta-analysis of observational studies in epidemiology (MOOSE) [32] flow diagrams.

Data extraction

The two reviewers (LZ and MB) will independently extract data from the included studies using a pilot-tested data extraction form (see Additional file 1). To maximize consistency, a calibration exercise will be performed using articles not included in the review with the two reviewers prior to starting the data extraction phase. The authors will extract the following information from each study: publication details (name, author, year, journal, and country), study design (type of study, participant information, inclusion criteria, and length of study), demographics (mean age, ethnicity, and sex), measurement of cannabis (self-report, urinalysis, or hair analysis), outcome measures, the main findings, and statistical results (effect measures, p values, confidence intervals, etc.). If multiple outcomes are reported, all of them will be recorded so we can combine the studies with similar outcome measurements. Authors will be contacted in the case of missing or incomplete data.

Assessment of quality

Risk of bias in will be assessed by two independent raters (LZ and MB) using the Newcastle-Ottawa Scale (NOS) [33]. An adapted version of a modified NOS was developed by Bawor et al. to be used to assess risk of bias in observational studies [34]. This version includes seven questions evaluating bias in four domains of biases: selection bias, performance bias, detection bias, and information bias. Risk of bias is measured on a scale of 0 (high risk) to 3 (low risk). The adapted version has removed items regarding the comparability of groups and suitable follow-up for cohort and case-control studies, as these items are not relevant for our topic of interest. The Cochrane Collaboration tool will be used for randomized controlled trials which assess risk of bias using six domains: selection bias, performance bias, detection bias, attrition bias, reporting bias, and other biases [35].

Quality of the literature will be measured using the grading of recommendations, assessment, development, and evaluation (GRADE) framework, which scores articles based on five domains—risk of bias, publication bias, consistency, directness, and precision [36]. These findings will be summarized in a table, allowing for an assessment of the confidence of the estimates. A summary of the findings will be provided in a table to easily compare the quality of studies included in this review and allow for confidence of estimates.

Statistical analyses

All included studies will first be reviewed in a qualitative summary, followed by a meta-analysis if possible. Studies will be combined in a meta-analysis based on similarities in study design and outcome measurements. Direct estimates will be pooled separately based on study design,

as pooling data from observational studies and RCTs is cautioned against due to the inherent susceptibility of observational studies to selection biases [37]. A random-effects model for meta-analysis will be used to account for the expected heterogeneity in the literature, which assumes both within-study and between-study variability to provide a more conservative estimate compared to a fixed-effects model. These results will be presented in a forest plot. In the case of missing data, we will attempt to contact authors to obtain the relevant data. If the missing data cannot be obtained, we will employ an imputation method. We may also conduct a sensitivity analysis to assess the impact of missing data on the overall treatment effects. A sensitivity analysis will also be conducted to compare the overall results of studies with high or low risk of bias.

Heterogeneity will be calculated among pooled studies using the I^2 statistic. It is advised not to impose cut-off values because the importance of heterogeneity depends on a multitude of factors. However, Cochrane suggests that a value <40 % may not represent a notable amount of heterogeneity [37]. Thus, possible sources of clinical heterogeneity will be examined given an I^2 statistic > 40 %, and subgroup analyses will be performed. Possible sources of heterogeneity include age, sex, method of cannabis measurement, and country, and these will be investigated using subgroup analyses.

Subgroup analyses

Subgroups are identified a priori so we can make stronger inferences about the effects of the subgroups [38]. Subgroup analyses will be conducted on the following variables: age, sex, method of cannabis measurement, and country. Drug addiction is a disorder that afflicts people of all ages, and thus no age restrictions will be placed on the articles in this review. However, there are differences in the biological and social mechanisms involved with youth and adults, so cannabis may differentially influence treatment outcomes in the two populations. Because a consistent age range is not used to define youth in MMT studies [28, 39, 40], MMT studies will be included in the subgroup analysis if the authors specify that they are investigating youths or adolescents.

Methadone maintenance treatment has been found to differentially affect men and women [34], and prevalence of cannabis use tends to be higher in males [41]. However, females display a stronger dose-dependent effect from cannabis compared to males, with significantly lower mental quality of life as dosage increases [42]. Furthermore, women demonstrate a faster trajectory towards the development of cannabis use disorder [43]. Thus, particularly among heavy cannabis users, we expect treatment outcomes in women to be more negatively impacted by cannabis use. Stratifying these populations using a subgroup analysis may reveal differences in the way cannabis use affects MMT outcomes for males and females.

We will also compare results of studies that use subjective or objective measures of drug use. Studies have shown that a large number of patients in treatment for addiction underreport drug use [44], whether intentionally or not, and thus objective measures of drug use, such as urine or hair analysis, may provide a more accurate estimate of cannabis use in the population. Therefore, we expect to find a stronger association between objective measures of cannabis and MMT outcomes compared to studies using subjective measures.

Finally, any potential differences found between studies from different regions of the world or different decades will be qualitatively commented on and compared to current literature on drug use patterns considering the varied pattern of drug use across the world [2]. Specifically, North America has the highest proportion of cannabis use and high rates of opioid use, largely due to the surge in non-medical use of prescription opioids [1]. Illicit drug use is considerably less in Europe, with lower rates of cannabis use compared to North America, as well as significantly less opioid use [1]. On the other hand, more than half of the world's opioid-using population lives in Asia, although cannabis rates are below the global average [1]. These different patterns of illicit drug use around the world signify that different societal mechanisms are at play, which may impact treatment outcomes for drug addiction.

Presenting and reporting of results

This systematic review will be reported in accordance with the PRISMA guidelines [31]. Additionally, we expect to include many observational studies, in which case these will be reported following the MOOSE guidelines [32]. A flow chart will be used to display the selection of articles with reasons for exclusion. Study characteristics and measured outcomes will be compiled into summary tables. An Egger's plot will be included to examine potential publication bias in the selected studies. If a meta-analysis is possible, results will be presented in a forest plot. The current protocol follows the preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) statement (see Additional file 2 for checklist) [45].

Discussion

Using evidence from this systematic review, we expect to make conclusions regarding the presence of an association between cannabis use and methadone maintenance treatment outcomes. Systematically reviewing the literature will contribute to our understanding of the mechanisms involved in treatment retention and drug relapse in patients with opioid use disorder. We will also be investigating cannabis use and its association with other

outcomes related to overall social and physical well-being in MMT patients.

To our knowledge, this will be the first systematic review conducted on this topic. Given the current trend of cannabis being approved in many US states and the move towards a more liberal use in Canada, it is imperative that these policy decisions are evidence-based. The findings of this systematic review will also be of value to clinicians administering methadone maintenance treatment to patients with opioid use disorder, as it will provide evidence regarding whether monitoring cannabis use during MMT is necessary, and how it may predict a patient's treatment outcomes.

Additional files

Additional file 1: Data extraction form. (PDF 7 kb)
Additional file 2: PRISMA-P Checklist. (PDF 279 kb)

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Availability of supporting data
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Authors' contributions
LZ contributed to the conception and design of the study, development of the data extraction forms and search strategy, manuscript writing, critical revision, and final review of the manuscript. MB contributed to the conception and design of the study, development of the search strategy, critical revision, and final review of the manuscript. RE contributed to the methodological design, critical revision, and final review of the manuscript. SP contributed to the methodological design, critical revision, and final review of the manuscript. NB contributed to the consultation for search strategy and quality assessment and final review of the manuscript. JM contributed to the critical revision and final review of the manuscript. MS contributed to the critical revision and final review of the manuscript. SM contributed to the critical revision and final review of the manuscript. LT contributed to the critical revision and final review of the manuscript. ZS contributed to the conception and design of the study, critical revision, and final review of the manuscript. All authors read and approved the final manuscript.

Authors' information
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Competing interests
The authors declare that they have no competing interests.

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Ethics approval and consent to participate
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Data Extraction Form

Study ID: _____ Reviewer Initials: _____

Publication Details

Author (last name, first initial): _____ Year: _____
Title: _____
Journal: _____ Country: _____

Methods

Study design: _____ Study setting: _____
Length of study: _____
Description of sample:
_____
Exposure: _____ Intervention (if applicable): _____

Demographics

Number of participants: Total: _____ Men: _____ Women: _____ Per group: _____
Mean age (SD): Total: _____ Men: _____ Women: _____
Per group: _____
Ethnicity:
_____

Exposure measurements (cannabis). Circle one.

Self-report Urinalysis Hair analysis Other _____
Comments:
_____

Outcome measurements:

Illicit opioid use: _____
Treatment retention: _____
Criminal activity: _____
Jail time: _____
Polydrug use: _____
Injecting behaviours: _____
Comments:
_____

Results

Statistical methods: _____ Adjusted for: _____
Coefficient: _____95% CI: _____ p-value: _____
Findings: _____
Limitations: _____

Inclusion Criteria

Patients on methadone maintenance treatment

RCT or observational study design

Cannabis measured as a predictor variable

Exclusion Criteria

Patients on any other opioid substitution therapy

Methadone being used for purposes other than maintenance treatment (i.e. recreational or detoxification)

Cannabis measured as an outcome variable

Study does not measure a primary (illicit opioid use, treatment retention) or secondary (criminal activity, jail time, polydrug use, and injecting behaviours) outcome variables

Additional Comments:

_____
_____
_____
_____
_____

PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☐	☐	3
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☐	N/A
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☐	☐	70
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☐	☐	5-41
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☐	☐	323-332
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☐	☐	N/A
Support					
Sources	5a	Indicate sources of financial or other support for the review	☐	☐	334-335
Sponsor	5b	Provide name for the review funder and/or sponsor	☐	☐	N/A
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☐	☐	335-336
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☐	☐	74-134
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☐	☐	136-147

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☐	☐	163-178
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☐	☐	150-161
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☐	☐	451 (Table 1)
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☐	☐	189-194
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☐	☐	196-206
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☐	☐	208-218
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☐	☐	211-216
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☐	☐	180-187
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☐	☐	220-235
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☐	☐	237
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☐	☐	238-256
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☐	☐	258-289
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☐	☐	N/A

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☐	☐	N/A
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☐	☐	230-235