Predictors and Outcomes in Patients with Opioid Use Disorder

Treatment Predictors and Outcomes in Patients with Opioid Use Disorder

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Lay Abstract

Numerous countries across the globe are battling with the opioid epidemic which has been greatly impacted by the misuse of prescription opioids. It is important to examine treatment predictors and outcomes of patients with opioids use disorder (OUD) that are currently receiving pharmacotherapy. We conducted two systematic reviews examining 1) the impact of prescription opioids on people with acute low back pain, and 2) the differences between the method of introduction to opioids. We then followed this with 3 clinical papers which examined 1) the differences between the method of introduction to opioids for patients with OUD attending medication assisted treatment (MAT), 2) what are the desired goals of OUD patients attending MAT and 3) what are the differences in outcomes for patients receiving different types of MAT. We found significant differences in these studies and the results should be taken into to consideration when designing and implementing tailored MAT.

Abstract

Background

Opioid use has become a huge public health crisis and opioids are now one of the leading causes of deaths related to drugs worldwide. Identifying differences in predictors and treatment outcomes for people with opioid use disorder (OUD) that were introduced by prescription versus other means is important. It is also vital to understand what the goals are and needs that patients want to achieve out of OUD treatment.

Methods

We used systematic review methodology to first examine any adverse outcomes that may be associated with prescribing opioids for acute low back pain. We also conducted a systematic review and meta-analysis examining what are the differences in patients with OUD that were initially introduced to opioids by prescription in comparison to those introduced by recreational means. We then conducted an observational study using data obtained from the GENetics of Opioid Addiction (GENOA) research collaborative. We examined treatment outcome differences between individuals introduced to opioids through a licit prescription and those introduced through illicit means. We conducted a mixed-methods study asking what the desired goals of patients with OUD from the Pharmacogenetics of Opioid Substitution Treatment (POST) project are. Using data from POST, we also examined the treatment outcome differences between those that were receiving methadone treatment in comparison to those that were on buprenorphine.

Results

The systematic review examining adverse outcomes of prescribing opioids for acute low back pain found that prescribing opioids for ALBP was significantly associated with long-term continued opioid use (1.57, 95% CI 1.06,2.33). The second systematic review found that those who were introduced to opioids through a legitimate prescription were significantly less likely to have illicit opioid use (0.70, 95% CI 0.50, 0.99) while in treatment. Our results from GENOA also showed that those introduced to opioids by prescription were more likely to have chronic pain, an older age of onset of opioid use, less likely to have hepatitis C and use cannabis. When we asked patients what goals they desired out of treatment, we found that the most frequently reported patient important outcomes were to stop treatment (39%) and avoid all drugs (25%). When comparing OUD patients by treatment we discovered that those receiving buprenorphine were less likely to consume illicit opioids and amphetamines but more likely to have used alcohol in comparison to those on methadone.

Conclusion

With this knowledge, we can recognize unique risk factors for each patient and provide more tailored treatment that can incorporate this into clinical practice to address specific concerns in various cohorts of OUD patients. Additionally, the variation in the selection of outcomes demand the need for further research to establish a set of outcomes that considers patients' goals and preferences for OUD treatment.

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List of Abbreviations

MAT - Medication-assisted treatment

OUD – Opioid Use Disorder

ALBP – Acute Low Back Pain

GENOA - Genetics of Opioid Addiction

POST - Pharmacogenetics of Opioid Substitution Treatment

HIV - human immunodeficiency virus

MMT – Methadone Maintenance Treatment

BT – Buprenorphine Treatment

CCSA - Canadian Center of Substance Abuse

RCT – Randomized Controlled Trial

WHO ICTRP - World Health Organization International Clinical Trials Registry Platform

MD – Mean Difference

SMD – Standard Mean Difference

ED – Emergency Department

MEA – Morphine Equivalent Amount

OST – Opioid Substitution Therapy

OUD- Opioid use disorder

RCT- Randomized control trials

NOS- Newcastle- Ottawa scale

PRISMA- Preferred reporting items for systematic reviews and meta-analyses

PRISMA-P Preferred reporting items for systematic reviews and meta-analyses protocols

GRADE- Grading of Recommendations Assessment, Development and Evaluation

CI - Confidence Interval

CDC - Centre for disease and control

DEA – Drug Enforcement Administration

SAMHSA - Substance Abuse and Mental Health Services Administration

NIDA - National Institutes on Drugs Abuse

OR - Odds Ratio

ASI - Addiction severity index

MAP - Maudsley Addiction Profile

NSAIDs - nonsteroidal anti-inflammatory drugs

CATC – Canadian Addiction Treatment Centre

HIREB – Hamilton Research Board of Ethics

DSM-IV - Diagnostic and Statistical Manual of Mental Disorders

SPSS - Statistical Package for the Social Sciences

STROBE - Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)

SD – Standard Deviation

ODSP – Ontario Disability Support Program

Declaration of Academic Achievement

I am the primary author of all studies included in this thesis. I have contributed to all of these studies substantially by taking the lead. I conceived the research questions, writing the protocol, conducted the statistical analyses, interpreting the results and writing the manuscripts. Detailed lists of author contributions are provided at the end of each study.

1 CHAPTER 1

1.1 INTRODUCTION

1.1.1 Opioid Use Disorder

Canada, along with many other nations, is going through an opioid epidemic (1). Opioids are substances that act upon the opioid receptors in the brain including heroin, morphine, hydromorphone, oxycodone, and fentanyl (2). When opioids bind to opioid receptors, it causes the release of dopamine into the brain which leads to intense feelings of euphoria (3,4). This can produce drug-seeking behaviour such as misuse and dependence, which are outcomes notoriously associated with opioid use (3). Repeated and prolonged use of opioids may lead to physiological tolerance in which the opioid receptors in the brain begin to need larger amounts of opioids to achieve a euphoric state and to avoid withdrawal symptoms that may occur otherwise (3,5). Considering its addictive properties, opioid misuse has increased over the past few decades to an alarming concern with a reported 128 people dying daily in the United States from opioid related overdoses (6).

OUD is chronic illness that is characterised by persistent use of opioids, and sustained behavioural changes affecting the individual's life and social functioning (7,8). Currently, there are over 26 million people estimated to have an opioid use disorder (OUD) worldwide (7). While the prevalence of OUD related overdoses presents an important health concern, OUD may also lead to other harmful consequences to individuals and society, including increased susceptibility to infections such as hepatitis and HIV, psychiatric comorbidities, adverse social consequences, and increased mortality

(9–16). Canada is the world's second largest opioid consumer globally (17) and the heightened increase in the number of opioids prescribed has contributed to the current opioid epidemic (18).

1.1.2 Shift in the Demographic Profile

In the past, we have seen that the profile of an individual with OUD was thought to be associated with primarily young, male users with a dependence on heroin (19,20). However, in the last couple of decades, we have seen a novel shift in the demographic characteristics of people with OUD to include a cohort of individuals introduced to opioids via a physician's prescription. The Centre of Disease Control and Prevention (CDC) found that in 2018, over 168 million prescriptions for opioids were written (21) and a national survey on drug use reported that 4.7% Americans stated engaging in nonmedical opioid use (22). This shift in the demographic profile to include prescription opioid users has resulted in an increasing number of women (23,24) and an older population that have developed a dependence on opioids (25–27). With a greater number of women developing OUD, there has been a surge in evidence investigating and identifying sex and gender differences among age, employment status, patterns of substance use and level of education within this vulnerable population (28,29). With identified differences within the OUD population, it is important to consider what treatment options are available and if they are effective for all.

1.1.3 Treatment for Opioid Use Disorder

Medication-assisted treatment (MAT) is currently the gold standard for treatment of OUD and consists of the controlled distribution of opioid agonist and antagonists (5). The two most commonly prescribed MAT in Ontario are Methadone Maintenance Treatment (MMT) and buprenorphine/naloxone treatment (BT). Methadone is a complete opioid agonist with a long half-life, typically given in liquid form (30). On the other hand, buprenorphine/naloxone is a partial opioid agonist which is typically given using a sublingual tablet (31,32). It's been suggested that that BT may be a safer MAT in comparison to MMT as it has less sedation and respiratory depression effects (33,34). However, both MMT and BT are successful in reducing withdrawal symptoms and opioid cravings without the accompanied feelings of euphoria (35,36). This reduction in withdrawal symptoms is a factor that helps prevent opioid relapse (37).

Current evidence examining MAT effectiveness is inconsistent, specifically with respect to the outcomes used to assess treatment effectiveness. More specifically, some studies use treatment retention or completion to determine effectiveness (38,39), while others evaluate treatment programs based on amount of illicit opioid use (40). Studies that use level of illicit opioid use as a measure of effectiveness remain divided on how to define the outcome, with studies reporting illicit use as either the percentage of opioid-negative or positive urine screens over varying timepoints. The variability in these studies is reinforced by the use of different methods to report their findings, with some studies depicting illicit opioid use figures as aggregates for each participant and others pooling the results of each treatment group (40,41). The discrepancies present in the measurement

of treatment effectiveness outcomes sets a limitation on the ability to reach a consensus on the outcome measures most reflective of treatment effectiveness.

The demographic shift in the OUD population and the simultaneous inconsistencies present in the literature assessing treatment effectiveness present a need to explore treatment predictors and outcomes, considering the widespread prevalence of OUD. Concluding statement

1.1.4 Thesis Objectives

The objective of this thesis is to explore the association between treatment predictors and outcomes in patients with opioid use disorder through a succession of five unique studies.

The first study, Chapter 2, is a systematic review and meta-analysis investigating the use of prescription opioids for acute low back pain (ALBP) and resulting adverse outcomes. Meta-analysis of the outcomes of recurrent opioid use and unemployment was completed. This review is published in *Pain Physician.*

The next paper, Chapter 3, is a protocol for a systematic review exploring the association between method of introduction to opioids and treatment outcomes for OUD patients receiving MAT. This protocol is published in *Systematic Reviews.* Chapter 4 is the completed systematic review and meta-analysis using the methods of and examining the aforementioned association in Chapter 3. Meta-analysis of the outcomes for illicit

opioid, cannabis, cocaine, alcohol, benzodiazepine and injection drug use was completed. This paper is published in *Frontiers in Psychiatry.*

Chapter 5 is an observational study looking at socio-demographic, health functioning and treatment outcome differences between those that were introduced to opioids through a legitimate medical prescription in comparison to those introduced through recreational means in patients receiving MMT. This relationship was also explored by sex. This study is published in *Pain Physician.*

Chapter 6 is a mixed-methods study investigating what desired goals OUD patients would like to achieve through MAT. We looked at differences in goals by age, sex, gender, method of introduction to opioids, type of treatment, ethnicity, length of treatment and employment status. This study is published in the *Brazilian Journal of Psychiatry.*

Lastly, Chapter 7, is an observational study examining treatment outcome differences among OUD patients receiving MMT in comparison to BT. This relationship was also explored by sex. This paper is submitted to *Drug and Alcohol Dependence*.

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2 CHAPTER 2

Adverse Outcomes Associated with Prescription Opioids for Acute Low Back Pain: A Systematic Review and Meta-Analysis

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2.1 Abstract

Background: Acute Low Back Pain (ALBP) is a common clinical complaint which can last anywhere from 24 hours to 12 weeks. Though guidelines recommend that in the treatment of ALBP, opioids should be used when other treatments fail, we have seen an increase in opioid prescriptions for ALBP. With the opioid crisis, it is important to examine if there are any adverse outcomes associated with prescribing opioids for ALBP.

Objective: We aim to review the published literature to examine the adverse outcomes associated with opioid use for ALBP.

Study Design: We performed a systematic review with meta-analysis in accordance with our published protocol and PRISMA guidelines. Electronic databases were searched from inception to September 30th, 2017 inclusive. Randomized clinical trials and observational studies on the impact of opioid use in ALBP were included. Eight pairs of independent reviewers performed screening, data extraction and assessment of methodological quality. The identified articles were assessed for risk of bias. Trials with comparative outcomes were reported in a meta-analysis using a fixed effect model.

Results: A total of 13,889 were initially screened for the review and a total of 4 studies were included in the full review, of which 2 studies were meta-analyzed. Our results found that prescribing opioids for ALBP was significantly associated with long-term continued opioid use (1.57, 95% CI 1.06,2.33). There was no significant association found between unemployment duration and prescribing opioids for ALBP (3.54, 95% CI -7.57, 14.66).

Conclusion: Due to the lack of literature examining long-term adverse outcomes associated with prescribing opioids for ALBP, no definitive conclusions can be made. However, with

the literature available, there does seem to be risk associated with prescribing opioids for ALBP so there is a great need to conduct further investigations examining these adverse outcomes for ALBP patients.

PROSPERO Registration: CRD42016033090

Key words: acute low back pain, opioids, prescriptions, low back pain, long term use, opioid use disorder

2.2 Introduction

2.2.1 Rationale

In general, low back pain causes discomfort and pain to a wide number of people each year (1,2) and has become an extremely common clinical complaint (3). Acute Low Back Pain (ALBP) is one of the major causes of disability and is described as pain in the inferior gluteal and costal margin (3–5). This pain typically lasts between 24 hours and 12 weeks (5). Even though a large proportion of ALBP patients recover within 14 days, recurrent pain is continued to be experienced by about 70 percent of ALBP patients within one year of onset (6,7). Additionally, a previous study reported that 85% of all acute back pain is non-specific and hence, it cannot be ascribed to a definite cause (8). However, research has shown that some of the main causes include; trauma, malignancy or bone metastasis, infective cases like an abscess and osteomyelitis, inflammatory conditions like the HLA-B27 arthritis (9–11). ALBP remains a leading cause of disability as well as a major public health problem (12).

The use of non-opioid therapy is the main recommendation for the management of ALBP. The current framework given by the American College of Physicians, as well as the American Pain Society and the European guidelines for managing low back pain in primary care recommend the use and application of non-opioid therapies, like non-steroidal anti-inflammatory drugs, as the initial line of treatment for low back pain(5,10,13).The guidelines further ascertain and propose that opioids need to be used for acute low back pain only in severe cases, particularly when other forms of medications and treatments are deemed ineffective(5,10). Opioid prescriptions for ALBP have greatly increased, though its effectiveness is yet to be evidence supported (14). Moreover, research has indicated that

work loss linked with back pain was more likely for people who have taken opioids compared to those without the use of opioid treatments (15).

Deyo et al. found that over 2 percent of U.S adults reported regular prescription and use of opioids, and more than half of that number have low back pain (16). The research suggests that many of the patients that use prescribed opioids have persistently high levels of low back pain. It has been suggested that despite uncertainties about long-term safety and efficacy for ALBP, the use of prescription opioids for ALBP has risen rapidly in parallel with the opioid crisis (17).

In Canada, opioid misuse through physician prescription is very rampant (18). The Canadian Center of Substance Abuse (CCSA) in 2013 devised a prevention strategy that involved education to the public, patients and physicians (19). It also devised a policy recommendation that was based on evidence to avoid harm of addiction and improve prescription practices. Despite the CCSA efforts, the use of opioids is still high in some parts of Canada. In Ontario, mortality due to prescribed opioid use have increased (20). Opioid use disorder has also led to societal problems like criminality and increased disease infection rates (18,21,22). A recent investigation by Bawor et al. found that more than half of the women as well as a third of the men diagnosed with opioid use disorder were first introduced to opioids through a legitimate prescription (23). There remains a gap in the literature investigating the relationship between the incidence of abuse, misuse or dependence (opioid use disorder) (24) after being prescribed opioids for ALBP.

Evidence for long-term misuse of opioids, as well as other adverse outcomes following prescription of opioids for ALBP, have not been examined systematically. This

lack of research makes it complex for not only clinicians to make informed treatment-related decisions, but also for the patient to make an informed decision regarding their own treatment. This review will make a critical and significant contribution to the practice of prescribing and use of opioids for acute low back pain management – a common debilitating condition experienced by many people.

2.2.2 Objectives

The objective of this review was to conduct a systematic review and meta-analysis on the literature investigating adverse outcomes associated with prescribing opioids for Acute Low Back Pain. Adverse outcomes of interest included prescription abuse, misuse, continued long-term use, development of opioid use disorder, unemployment social adversity, marital discord, criminal activity and mortality.

2.3 Methods

2.3.1 Protocol and Registration

This systematic review was conducted to investigate adverse outcomes associated with prescription opioid use for adult ALBP patients. The Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines were followed (25). The protocol for this systematic review has been published previously and registered with PROSPERO (registration number CRD42016033090) (26).

2.3.2 Eligibility criteria

We included studies reporting on participants 18 years or older of any sex, gender and ethnicity. Patients with a primary diagnosis of ALBP (as defined by reporting low back pain of ≤ 12 weeks without a clear and specific attributable cause) (4), in any setting were included. Inclusion criteria for intervention was studies describing prescription opioids for ALBP and reporting on the duration of use, follow up, incident misuse, social adversity, side effects and mortality. The study designs for inclusion were randomized controlled trials (RCTs), observational studies (included cohort and cross-sectional), pilot or feasibility studies (powered) and other trial designs (e.g. cross-over and cluster RCTs).

2.3.3 Information Sources and Search strategy

The following electronic databases were searched from inception to September 30th, 2017 with no language limitations: PubMed, EMBASE, PsycINFO, CINAHL and Web of Science. In addition, we searched trial databases of the National Institutes for Health Clinical Trials Registry, Cochrane Trials Registry and the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP). We also conducted a manual search of reference lists from identified studies, relevant articles, and systematic reviews, key journals as well as grey literature. Search terms were related to ALBP, prescription opioids and MeSH terms (see Table 2.8.1) for an example of a search strategy). Study authors were contacted where outcome data were insufficient for analysis.

2.3.4 Study Selection

Eight pairs of reviewers performed the initial and subsequent screening with the data extraction of the articles according to the set of inclusion and exclusion criteria independently. Where there was disagreements resolution was reached by either discussion to consensus, or consultation with a third party if it remained unresolved.

2.3.5 Data Collection and Data Items

After identifying relevant studies, the following data were extracted from the full texts of the studies using piloted standardized forms: author, year of study, country, study design, participant demographics (number, age and sex), intervention (type of prescription, dose and duration of treatment), comparators and main outcome measures. In addition, we extracted data on statistical results obtained in each identified study.

2.3.6 Risk of Bias of Individual Studies

Two reviewers conducted independent assessment of the methodological quality of eligible studies, a modified version of Newcastle-Ottawa Scale that has been modified for cross-sectional studies was used to assess the risk of bias for the observational studies (27). Eight items in the Newcastle-Ottawa scale were categorized into criteria based on study selection, comparability, and

appropriateness of outcome measures. For randomized control studies, Cochrane Risk of Bias tool was applied to eligible studies to assess all sources of bias (such as selection bias, attribution bias, reporting bias, etc.) (28). The quality and strength of evidence was assessed

using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria and summarized in Table 2.8.2 (29).

2.3.7 Statistical analyses

We have presented our findings both qualitatively and quantitatively. Where possible we have reported on population characteristics experiencing adverse events as well as intervention characteristics such as prescription patterns, doses and types of opioids, duration of treatment and whether any specific guidelines were followed.

We presented pooled dichotomized data as odds ratio (OR) with 95% confidence intervals and pooled continuous data as mean difference (MD) or standardized mean difference (SMD) with 95% confidence intervals. We quantified data heterogeneity using the I-squared statistics greater than 40% since Cochrane has indicated a value less than 40% may not be a representation of significant heterogeneity (30). To account for confounding, adjusted analyses from observational studies were used. Meta-analysis was conducted using Review Manager 5.2. We were unable to assess publication bias as studies have reported that it is not possible for less than 10 studies (31). We followed the PRISMA reporting guidelines (Figure 2.8.4 flow chart).

2.3.8 Types of Interventions

Experimental

The experimental intervention includes being prescribed any type of opioid for the treatment of acute low back pain. The types of opioids included morphine, diamorphine, fentanyl, alfentanil, remifentanil, methadone, oxycodone, pethidine, tapentadol, tramadol, codeine, dihydrocodeine and meptazinol.

Comparators

The accepted comparators included placebo/not prescribed any opioids, any non-opioid analgesics and any complementary therapies.

2.3.9 Outcome Measures

Continued Opioid Use

We have defined continued opioid use as ongoing opioid use beyond the needed time to treat for acute low back pain. Acute low back pain is a pain condition that does not last more than 12 weeks by definition. Continued opioid use may be measured in a variety of ways such as using a prescription monitoring system to determine if additional prescriptions were prescribed beyond the need to treat ALBP or through urine screens testing for opioids. A full list of outcome measures can be found in Table 2.8.3.

Unemployment

Unemployment is defined as the total time an individual has not worked since being diagnosed with ALBP. This can also be measured in varied ways including disability claims, self-report and government records. A full list of outcomes for unemployment can be found in Table 2.8.3.

Side-Effects

Side-effects are defined as any adverse symptoms experienced by individuals while on any medication that was treating their ALBP. There was much heterogeneity in the side-effects being measured and therefore these results were presented in a narrative summary.

2.4 RESULTS

2.4.1 Study Selection

From the electronic database searches a total of 13,889 relevant abstracts were screened. After removal of 2,554 duplications and exclusion of 11,147 studies that did not meet the inclusion criteria, the full text of the remaining 188 articles were screened and 4 studies were included. The PRISMA flow chart of the selection process is exhibited in Figure 2.8.2. Of the remaining 4 studies, two of the studies were excluded from the meta-analysis due to them not measuring the outcomes of unemployment or continued opioid use (32,33). The final two studies that quantified outcomes of recurrent opioid use and unemployment were subjected to meta-analysis (34,35).

2.4.2 Study Characteristics

The characteristics of the included studies in this review are summarized in Table 2.8.3. Of the 4 studies included in the systematic review, two were retrospective observational studies (34,35) and two were clinical trials (32,33). The two observational studies compared groups that did not receive any opioids when diagnosed with ALBP to groups that did receive opioids for ALBP. The RCTs compared opioid groups (metzapinol and acetaminophen-codeine) to comparator drugs (ketorolac and diflunisal) for ALBP. The

mean age (k=4) across intervention groups was 38.5 years, and mean age across comparator groups (k=4) was 37.5 years. Majority of the sample consisted of male participants (68.8%). Only two studies reported on the outcomes of continued opioid use and disability duration (34,35). Two studies did not report on side effects experienced (34,35) while the other two studies reported on adverse symptoms profile (32,33).

2.4.3 Risk of bias within studies

The quality of the studies included are shown in Table 2.8.2. The Cochrane Risk of Bias and the modified Newcastle-Ottawa Scale (NOS) was used to rate the internal validity of the studies shown in Figure 2.8.2. The Cochrane Risk of Bias tool was used to assess the quality of the RCTs, and NOS was used to assess the quality of the observational studies. Generally, the results of the RCTs included in this review should be interpreted with caution due to the risk of bias shown in Figure 2.8.5. Some of the common issues were surprising. Specifically, one out of the two RCTs did not include any information on random sequence generation, blinding of participants or personnel, blinding of outcome assessment or outcome data. This was especially surprising as blinding in drug studies is not unusual for investigators and participants. Both RCTs did not include any information on allocation concealment. One of the studies should especially be interpreted with caution as it was funded by the company which produces one of the drugs under investigation.

For the two observational studies, both did not provide any information about how any missing data were handled. One of the observational studies did not adjust for confounding variables for unemployment, which places it at high risk of bias. Otherwise,

the two studies were generally well reported on all other characteristics including an appropriate population, sample size, statistical analyses and outcome measurement.

2.4.4 Results of Individual Studies

Recurrent Opioid Use

Our meta-analysis pooled results of two studies comparing the effects of opioid prescription use for ALBP on recurrent use of prescription opioids in the future by measuring the number of prescriptions given utilizing a prescribing database. Please see Figure 2.8.6. The other two identified studies did not report on the outcome of recurrent opioid use (32,33). Opioid prescription in Lee et al., (2016) was defined as receiving and filling a prescription for ALBP within 2 days of the ED visit and it was defined by Webster et al., (2007) as receiving and filling a prescription within 15 days of the ED visit. The total sample size consists of 9,975 participants. In Webster et.al, the range for the prescription opioid dosage was divided into 4 different quartiles that went from 1 to 450+ morphine equivalent amount (MEA). In Lee et al, the mean for MEA was 145. In this analysis, we used the results for the entire population of Lee at al. and the results from the 1-140 MEA group of Webster et al. In our meta-analysis, we used the relative risk ratio to compare the groups that received no opioid prescription to the group that did receive an opioid prescription. The relative risk ratio is defined as the risk of an event, in this case recurrent opioid use, relative to an exposure, prescription for opioids. For recurrent opioid use, we see that those that were prescribed opioids for ALBP were at the 57% (95% CI 1.06,2.33)

more likely to have recurrent opioid use than those that were not given an opioid prescription. However, there is significant heterogeneity (I^2) of 83% present.

Unemployment

Overall, our meta-analysis (Figure 2.8.7) pooled results of two studies comparing the opioid prescription for ALBP and no opioid use, measuring outcomes of unemployment. The other two studies did not report quantitative data on the unemployment outcome. The total sample size consisted of 9,975 participants. Both, Webster et al. and Lee et al. measured unemployment as days filed for worker's disability. Similarly, to the analysis of continued opioid use, we used the results for the 1-140 MEA from Webster at al. and the results of the full sample for Lee et al. In our meta-analysis, we used the standardized mean difference (SMD) to compare the effects of both groups. The SMD is the difference in mean effects between the intervention and comparator groups divided by the pooled standard deviation (SD). In our meta-analysis, an estimated SMD of 3.54 (95% CI -7.57, 14.66) was observed. These results suggest that in terms of unemployment, there is no significant association between those who had opioids prescribed for ALBP versus those that did not have an opioid prescription.

Side Effects

The meta-analysis for Side Effects (Ses) was not possible due to high heterogeneity among the identified studies based on the variability of side effects considered, therefore results have been qualitatively synthesized here. Only two eligible studies reported on SEs experienced. The assessment tools for measurement of Ses together with findings of the two studies are summarized in Table 2.8.2. While the Ses in Innes et al. (1998) study was

recorded at discharge, follow-up and end of the study, Videman et al. (1994) only recorded the side effects at follow-ups for total of three weeks. Furthermore, Innes et al. (1994) used a more structured approach by defining adverse drug events (ADEs) according to severity as well as employing a subjective rating scale at termination of study.

Both studies found similar profile of Ses including mainly gastrointestinal and neurological related symptoms experienced by patients (Table 2.8.2). Videman et al. (1984) in addition found patients reported tiredness, sweating and urinary related symptoms. While both studies reported the number of patients affected by Ses, however only Innes et al. (1998) described the proportion of patients with severe Ses during the study. Nevertheless, both trials reported the number of patients discontinuing treatment due to experiencing Ses during the study. In Innes et al. (1998) study twice as many Ses were reported in one intervention group compared to the other study group while the Videman et al. (1984) found comparable incidence of SEs in both of their study groups. At the study conclusion in one trial (Innes et al., 1998), patient self-reported overall ratings of drug tolerability as 'very good' or 'excellent' was 70% [95% CI, 59 to 81%] and 46% [95% CI, 34 to 58%] in ketorolac and acetaminophen-codeine patient groups, respectively.

Risk of Bias Across Studies

When assessing risk of bias across studies (Figure 2.8.8), we noticed a few trends. First, in the RCTs, both studies did not provide any information on selection bias. One study did not provide any detection bias, or attrition bias. However, both studies were found to have reporting bias. One additional form of bias was an RCT that was being funded by

a company that has developed one of the drugs used. Overall, our results show that the results from the RCTs should be interpreted carefully due to risk of bias.

In the two observational studies, we found that both studies did not report any information on how missing data were handled, and that one study did not adjust for the potential confounders. However, all studies reported the appropriate population, statistical analyses, sample size, and outcome measurement. Overall, our results show that the observational studies were generally well reported but should still be interpreted with caution as they are not without bias.

Additional Analyses

Due to the small number of studies identified for this review, no additional analyses were conducted.

2.5 Summary of Evidence

The main cause of deaths associated with drugs in North America is linked to opioid use with misuse of prescription opioids as the primary contributing factor to the global opioid crisis (36) and economic burden on health care system (37). Currently, after U.S the second largest user of pharmaceutical opioids is Canada (38,39). Despite recommendations from recent guidelines to perform a full risk assessment of ALBP patients before prescribing opioid analgesics (40,41) nevertheless prescription of opioids and misuse of these medications continues (42).

Although the therapeutic efficacy of opioids for management of chronic pain in general is well-established [citations], evidence for prescribing opioids for acute lower back

pain is largely lacking. It is uncertain whether opioid prescribing for patients with ALBP improves recovery rate or return to work and whether adverse side effects are associated with long-term overuse of opioids. To date, there are no systematic reviews on the evidence for long-term use of opioids and other adverse outcomes in patients affected by ALBP. Therefore, given the considerable negative impact of opioids and related-drug misuse outcomes, the evaluation of evidence on long-term functional outcomes associated with opioid overuse in ALBP patients is warranted. To the best of our knowledge this study is the first reported meta-analysis on the synthesis of evidence for long-term opioid overuse and associated adverse outcomes in patients with ALBP. Our findings indicate ALBP patients prescribed opioids are at risk for continuing to have long term opioid prescription use and that opioid therapy for ALBP does not expedite return to work.

2.5.1 Continued opioid use

The meta-analysis of pooled evidence showed that there was a significant difference in recurrent opioid use in patients prescribed opioids versus non-opioid users. This suggests that opioid prescribing for patients affected by ALBP may constitute a risk factor for these patients to continue to use opioids beyond the time required for treatment of the acute condition. Previous studies have also indicated that prescribing opioids for acute pain management poses a high risk for long-term opioid overuse (43,44) Furthermore, patients prescribed opioids for ALBP had double the risk of recurrent opioid use than those that were not given an opioid prescription. In support of our findings, several recent studies have also found higher risks of long-term opioid use and overdose associated with initial opioid exposure (45,46), especially prevalent in opioid-naïve

patients with acute pain(47–49). However, due to the limited number of studies for this meta-analysis and presence of a significant heterogeneity, the results should be interpreted with caution.

Recent systematic reviews have shown that as a result of limited number of trials there is no certainty regarding efficacy and safety of opioids in ALBP individuals (42,50). There is also lack of evidence in support of long-term opioid use at any dose in treatment of acute low back pain. Our systematic review highlights the need for revising current guidelines related to prescribing opioids for ALBP treatment in light of the associated risk factors in prescribing opioids leading to recurrent and prolonged use of opioids.

2.5.2 Disability duration and opioid use

We did not find a significant association between opioid prescription and disability duration for ALBP patients when combining studies results. The findings of Webster et al (2007) revealed longer work disability was linked to prescribing as well as higher doses of opioids despite adjusting for injury severity and demographic factors. This could be due to the negative effect of opioids on physiological well-being or that patients are at greater risk of poor outcomes independent of opioids (42). While, Lee et al (2016) did not find an association between opioid prescribing and disability duration. These studies do not seem to indicate opioids accelerate returning to work or improve functional outcomes. Previous studies showed that prescribing opioids for acute pain to be associated with negative consequences; in a study of primary care patients, patients with acute pain that were prescribed opioids were found to have worsening of pain, function and depression after 6 months than those who did not receive opioids(51). In a

study of acute pain related to work injuries, patients receiving opioids for more than one week were twice as likely to experience long-term disability after one year (52).

2.5.3 Side Effects of Opioid Use for ALBP management

Although there was no quantitative analysis possible for side effects, this review included studies of both observational and non-placebo designs. We found the most commonly reported side effect of opioids in patients with ALBP were gastrointestinal and neurological related symptoms. Other reported side effects included urinary symptoms, tiredness and sweating (33). Other studies have reported similar side effects when administered opioids for acute and chronic pain (53–55). The considerable heterogeneity and side effects variability among the included studies and low number of eligible trials posed a challenge to compare side effects of different opioids. In addition, the two identified trials were both randomized parallel group designs comparing opioids to other types of analgesics with opioids demonstrating significantly higher rate of side effects. The reported overall side effects rates due to opioid medication (65%) were similar in the two randomized trials. Side effects due to long-term use of opioids in patients with ALBP is not clear from the trials included as the follow-up period was for a maximum of 3 weeks. There were also differences in the two included trials in terms of patient clinical demographics such as previous exposure to opioids, severity of pain or dose of opioid medication administered during the trial. These factors may all impact the incidence of side effects and should be taken into account in the design of future trials.

The prevalence of side effects may also depend on methods used for collection of information (56) which varied across the studies. Of note both randomized clinical trials

included mostly healthy young male participants who may recover more rapidly or have higher pain threshold compared to elderly or those with comorbid illness. Other factors that may explain the differences in the reporting of the two randomized clinical trials include differences in duration of pain assessment ranging from a few hours to weekly assessment. Therefore, these findings cannot be generalized to the wider population, and larger scale clinical trials with longer duration of follow up are warranted to determine the influence of gender, age or other demographic factors in reporting side effects.

2.6 Limitations

Despite the strengths of this systematic review (such as adherence to PRISMA guidelines and publication of a protocol) there are potential limitations to consider. For the analysis for unemployment, we were only able to conduct an unpooled analysis. Although we did attempt a meta-analysis, publication bias could not be assessed due to the limited number of studies. There were both statistical and clinical heterogeneity among the included studies due to differences in methodology, study design, risk of selection or performance bias which has been known to potentially affect meta-analysis (57). In addition, most of the studies had an unclear or high risk of bias and poorly defined side effects. Despite such limitations, the rapid rise in prescription related opioid complications including mortality due to overdose, makes this systematic review needed and raises the need for further studies to provide evidence on the efficacy and safety of long-term opioid treatment for patients with ALBP.

There is limited evidence to determine benefits and adverse effects of opioids in various subgroups of patients defined by clinical or demographic characteristics. When facing challenges with randomized clinical trials, well-designed observational studies with control of potential confounding factors are much needed to investigate the efficacy and safety of long-term opioid use in patients with ALBP. Moreover, additional research is needed to compare benefits and safety of various opioids and dosage.

Therefore, definitive conclusions on the effectiveness of opioid long-term therapy for acute back pain are not possible due to the scarcity of clinical evidence. Within limitations of this review, however, significant risks appear to be associated with opioid prescription for acute pain management whereby no improvement is found in employment status and risk of continued are evident.

2.7 Conclusions

This systematic review demonstrates that patients with acute lower back pain prescribed opioids are at a significantly higher risk of continued opioid use. Furthermore, prescribing opioids for ALBP patients is associated with at least one adverse event and delayed recovery. The findings of this systematic review in addition to the widespread opioid-prescribing trend further highlights the urgency to conduct randomized trials to provide evidence on the efficacy and safety of pharmaceutical opioids in treatment of patients with acute low back pain or evidence-based guidelines to avoid prescribing opioids for ALBP.

2.8 Tables and Figures

2.8.1 Example of Search Strategy

MEDLINE=669	1 exp Acute Pain 2 exp Low Back Pain 3 exp Analgesics, Opioid 4 exp Morphine 5 exp Codeine 6 exp Fentanyl 7 exp Tramadol 8 exp Meptazinol 9 exp Pentazocine 10 exp Methadone 11 exp Buprenorphine 12 oxycodone.mp. 13 dipipanone.mp. 14 remifentanil.mp. 15 papaveretum.mp. 16 pethidine.mp. 17 tapentadol.mp. 18 1 or 2 19 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 20 18 and 19 (728) 21 limit 20 to humans (701)

2.8.2 Summary of Findings

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Early Opioid Use**	**No Opioid Use**	**Relative (95% CI)**	**Absolute (95% CI)**		
Unemployment												
2	observational studies	not serious	not serious	not serious	serious [a]	all plausible residual confounding would reduce the demonstrated effect	786	9189	-	MD **3.54 higher** (7.57 lower to 14.66 higher)	⊕⊕◯◯ LOW	IMPORTANT
Late Opioid Use												
2	observational studies	not serious	serious [b]	not serious	not serious	all plausible residual confounding would reduce the demonstrated effect	134/786 (17.0%)	932/9189 (10.1%)	**RR 1.57** (1.06 to 2.33)	**58 more per 1,000** (from 6 more to 135 more)	⊕⊕◯◯ LOW	CRITICAL
Side Effects												
2	randomised trials	not serious	serious [c]	serious [d]	serious [e]	none	One study reported that the group receiving opioids as treatment experienced worse side effects than the group receiving alternative drug whereas another study reported both groups experiencing a similar number of side effects.				⊕◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

Explanations

a. Imprecise as adjusted pooled estimates were not possible to conduct.
b. Inconsistent due to high heterogeneity and large variation across study characteristics, including population, sample size and method of measuring late opioid use.
c. High degree of variability in side effects reported.
d. Often looking at adverse events profile, not specifically exploring established opioid-related side effects.

e. Pooled estimate was not possible as there was large variation between studies as to what side-effects were measured and there was also variation in drugs that were being compared

2.8.3 Summary of Study Characteristics

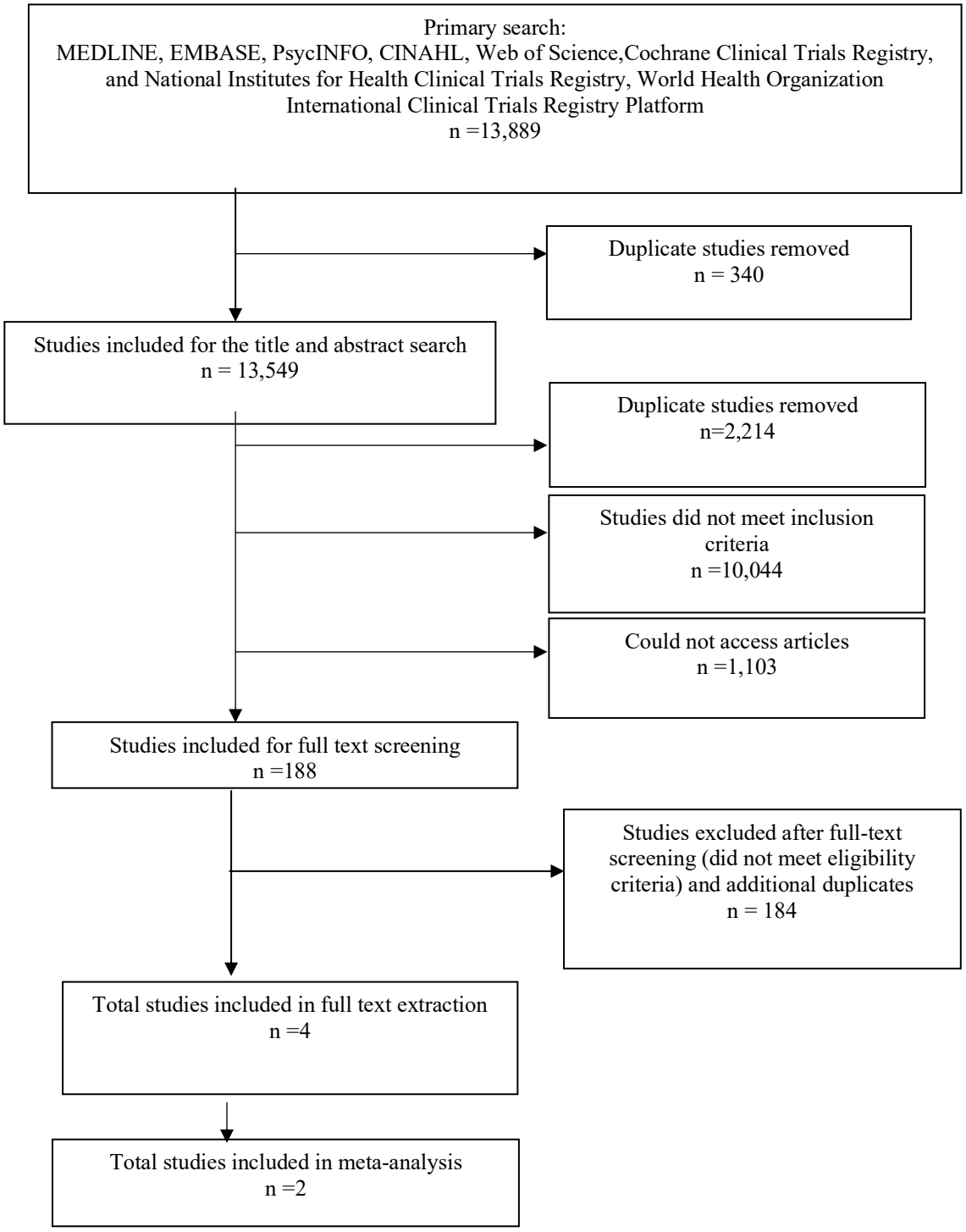
Study Name and Year (Ex. Smith 2001)	Methods (type of study, what is the study comparing, blinds, analysis, sample size)	Participants (age range, sex, exclusion criteria, primary diagnosis)	Interventions (Brief description of the two groups separated by arm)	Outcomes (Tools they use to measure it)
Innes 1998 (32)	Double-blind, randomized clinical trial comparing analgesic efficacy and adverse effects of ketorolac to acetaminophen–codeine in ED patients with acute musculoskeletal low back pain Continuous data analyzed using general linear model ANOVA; ordinal efficacy variables analyzed using Cochran-Mantel-Haenzel (CMH) test adjusted for centre effect and compared between groups using Mann-Whitney U-test; nominal data analyzed by χ^2 or Fisher Exact Probability tests as appropriate; within-group comparisons performed using Student's paired *t*-test for parametric data and Wilcoxon signed-rank paired tests for categorical data	N = 122 Mean age (SD) of ketorolac 33.1 (9.86); mean age of acetaminophen-codeine 36.0 (10.07) Sex: 26 females, 96 males Primary diagnosis: acute musculoskeletal low back pain Exclusion criteria: active peptic ulcer within 6 months; bleeding diathesis or anticoagulant use within 4 weeks; pregnancy or breastfeeding; chronic pain condition or recurring back pain; suspected or known alcohol or drug abuse; received any investigational drug within 4 weeks; co-existing injury or illness contraindicating study medications or interfering with evaluations (e.g. asthma or COPD); allergy, sensitivity, or	Ketorolac tromethamine (KET): 10 mg orally, then 10 mg every 4–6 h as needed (up to 4 doses in 24 h); patients requiring fifth or sixth analgesic dose in any 24-h period given acetaminophen (650 mg per dose) Acetaminophen-codeine (ACOD): 600 mg acetaminophen/60 mg codeine orally, with same dose repeated every 4–6 h as needed (up to 6 doses in 24 h)	Adverse events recorded by research staff at ED discharge, telephone follow-up, and study termination and recorded by patients in their diaries; events occurring more than once for any given patient reported only once under worst recorded severity, outcome, and relation to study drug

	Sample Size: ketorolac 62, acetaminophen-codeine 60	contraindication to acetaminophen, opioids, ASA, or NSAIDs; fracture, dislocation, neurological impairment, or cause of back pain requiring treatment beyond analgesics; receiving medications that might influence pain intensity evaluations (e.g. analgesics, anesthetics, sedating antihistamines, antiemetics, anxiolytics, antidepressants, psychotropic)		
Lee 2016 (35)	Retrospective cohort study examining effects of early opioid prescription for acute occupational low back pain in the emergency department on disability duration, long-term opioid use, total medical costs, and subsequent surgeries Cox proportional hazard analysis to quantify risk of early opioid use on cumulative disability duration; multivariate binomial log regression models to examine relationship between early opioid use and acute disability, chronic disability, and subsequent low back	N = 2887 Mean age (range) of early opioids 40.5 (39.3–41.6); mean age of no early opioids 41.4 (41.0–41.8) Sex: 1106 females, 1781 males Primary diagnosis: acute occupational low back pain Exclusion criteria: zero-cost cases (no payment of medical / indemnity services); medical-only cases (no paid temporary partial / total disability days); cases with WC claims within the year before their injury date; cases with <1 year of tenure; complex cases with	Early opioids: Workers' Compensation claims with an initial ED visit within 3 days post-onset that received early opioid(s) within 2 days of initial ED visit date No early opioids: Workers' Compensation claims with an initial ED visit within 3 days post-onset without any early opioids	Total length of work disability was operationalized as the total number of compensated days lost from work that were covered by indemnity payments (i.e. wage replacement for lost work time) Long-term opioid use was defined as having medical bills for ≥3 opioid

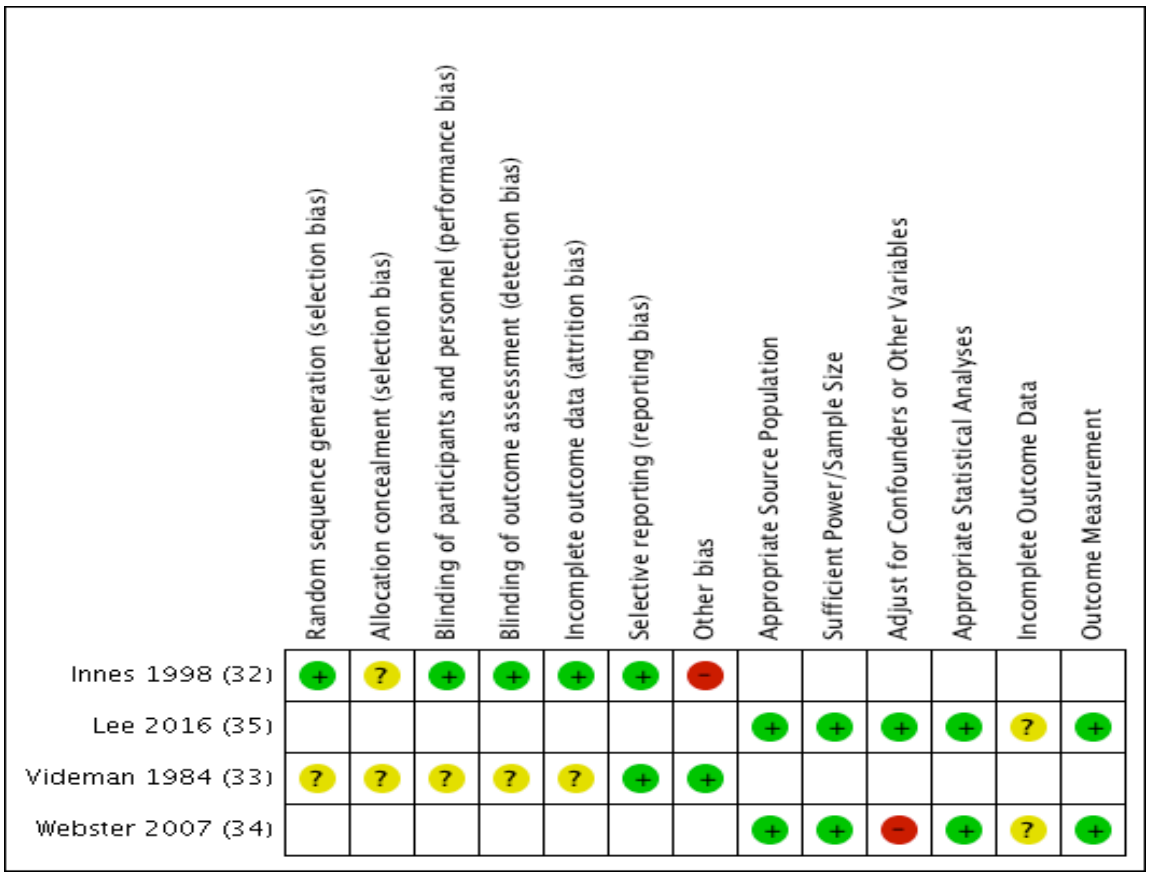
	surgeries; multivariate linear regression models to determine impact of early opioid use on total medical costs Sample Size: early opioids 349, no early opioids 2538	initial hospitalization(s), fractures, or multiple injuries		
Videman 1984 (33)	Double-blind parallel trial comparing clinical efficacy and tolerance of orally administered meptazinol and diflunisal in treatment of lumbago Statistical significance of differences between the two groups evaluated with Student's t-test; differences in duration for which treatments were given in each group evaluated with Kolmogorov-Smirnov's test Sample Size: meptazinol 35, diflunisal 35	N=70 Mean age (SD) of meptazinol 38 (14); mean age of diflunisal 35 (11) Sex: 29 females, 41 males Primary diagnosis: acute low back pain Exclusion criteria: pregnant or breastfeeding; significant haematological, renal, hepatic, respiratory, or circulatory disorders; history of peptic ulceration or GI upset; sensitive to narcotic analgesics and/or benzomorphan derivatives (dependent upon narcotic agents or any other drugs); weight < 45 kg or > 95 kg	Meptazinol: 1 tablet of 200 mg 4 times daily plus placebo resembling diflunisal capsule Diflunisal: 1 capsule of 250 mg 4 times daily plus placebo resembling meptazinol tablet	Details of any side-effects reported were also noted at each visit.
Webster 2007 (34)	Retrospective cohort study examining association	N=8443	No early opioids: no opioid medications received within	Length of disability determined using indemnity

	between early opioid use for acute LBP and several outcomes: disability duration, medical costs, "late opioid" use (5 prescriptions from 30 to 730 days), and surgery in a 2-year period following LBP onset Multivariate linear regression to examine association between receipt of early opioid prescriptions, disability duration, total medical costs; logistic regression to examine association between receipt of early opioid prescriptions and undergoing low back surgery, late use of opioids Sample Size: 0 mg MEA* 6651, 1–140 mg MEA 437, 141–225 mg 494, 226–450 mg 423, 450+ mg 438 *morphine equivalent amount	Mean age (SD) of 0 mg MEA 40.3 (10.4); mean age of 1–140 mg MEA 39.6 (10.3); mean age of 141–225 mg MEA 40.8 (10.7); mean age of 226–450 mg MEA 40.6 (9.5); mean age of 450+ MEA 40.7 (9.7) Sex: 2381 females, 6062 males Primary diagnosis: acute occupational low back pain Exclusion criteria: <1 day of compensated lost time; <1 year of job tenure; any low back pain claims in prior year; lost time began >10 days after low back pain onset; received no paid medical service within 15 days post-onset; received treatment for a fracture or any other concurrent condition within 15 days post-onset	15 days post-onset based on paid medical bills Early opioids: divided into 4 groups based on quartiles of MEA received (1–140 mg, 141–225 mg, 226–450 mg, 450+ mg)	(wage replacement) payments Late opioid prescriptions defined as cases receiving 5 or more opioid prescriptions between 30 and 730 days post-onset

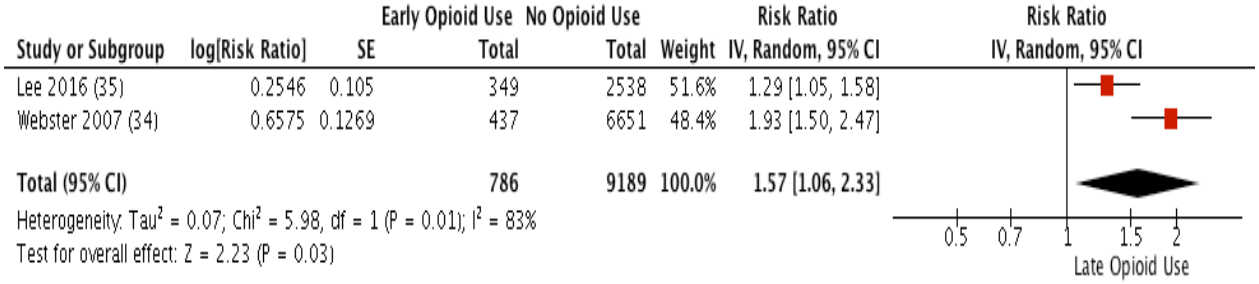
2.8.4 PRISMA Flow Diagram



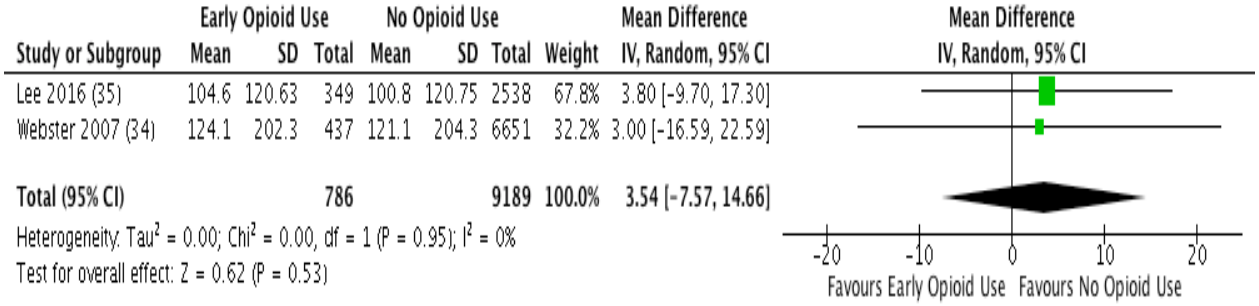
2.8.5 Risk of bias summary



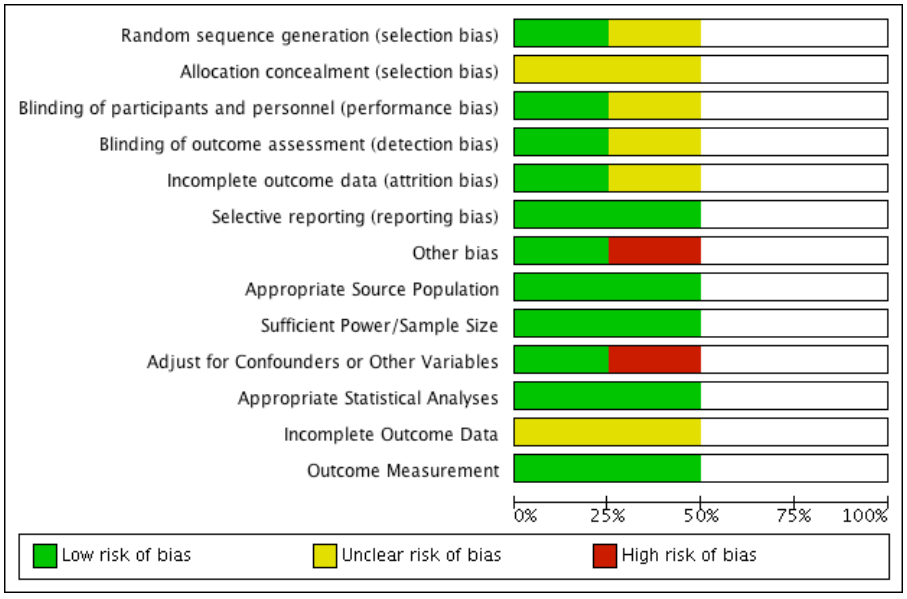
2.8.6 Forrest Plot for Continued opioid use



2.8.7 Forrest Plot for Unemployment



2.8.8 Risk of bias graph



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3 CHAPTER 3

Treatment outcomes in patients with opioid use disorder initiated by prescription: A systematic review protocol

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Sanger N, Bhatt M, Zielinski L, Sanger S, Shahid H, Bantoto B, Samaan MC, de Souza R, Samaan Z. Treatment outcomes in patients with opioid use disorder initiated by prescription: a systematic review protocol. Syst Rev. 2018 Jan 25;7(1):16. doi: 10.1186/s13643-018-0682-0. PMID: 29368662; PMCID: PMC5784712.

3.1 Abstract

Background

In North America, opioid use has become a public health crisis with policy makers declaring it a state of emergency. Opioid substitution therapy (OST) is a harm-reduction method used in treating opioid use disorder. While OST has shown to be successful in improving treatment outcomes, there is still a great degree of variability among patients. This cohort of patients has shifted from young males using heroin to a greater number of older people and women using prescription opioids. The primary objective of this review is to examine the literature on the association between the first exposure to opioids through prescription versus illicit use and OST treatment outcomes.

Method

An electronic search will be conducted on the EMBASE, MEDLINE, PsycINFO, and Cumulative Index to Nursing and Allied Health Literature (CINAHL) databases. Two independent reviewers will conduct the initial title and abstract screenings using predetermined criteria for inclusion and exclusion. Reviewers will then conduct full-text data extraction using a pilot-tested data extraction form in duplicate. A third author will resolve disagreements if consensus cannot be reached. Quality and risk of bias assessment will be conducted along with a sensitivity analysis for all included studies. Qualitative summary of the evidence will be provided and when possible, a meta-analysis will be conducted, along with heterogeneity calculation. The reporting of this protocol follows the PRISMA-P.

Discussion

We expect that this review will help determine whether patients that were initially exposed to opioids through a prescription differ in OST treatment outcomes in comparison to people who used opioids through illicit means. We hope that this review will provide evidence related to prescription opioids exposure and future treatment outcomes, which will aid clinicians in their decisions to prescribe opioids or not for specific populations at risk.

Keywords: Opioid Substitution Therapy, OST, prescription opioids, systematic review, opioid use disorder, protocol

Systematic review registration

PROSEPRO Registration Number: CRD42017058143

3.2 Background

3.2.1 Rationale

The global opioid crisis is marked by a striking 32 to 36 million individuals who used opioids worldwide [1]. Illicit opioid use is associated with an increased risk of infections such as HIV and hepatitis C, dependency, poly-substance use, psychiatric comorbidity, criminal activity and death [2–4]. Opioids are now the primary cause of drug-related deaths in North America, with a 200% increase in the number of opioid-related deaths since 2000 [5]. Regular use of opioids can result in opioid use disorder (OUD), a chronic psychiatric disorder characterized by loss of control over the drug use, behavioural and psychological symptoms related to drug use and impairment in normal function of the affected individuals [2]. Treatment of OUD also takes an economic toll on the healthcare system [6]. The increased misuse of prescription opioids has contributed to these rising numbers of opioid use and its related consequences [5]. Historically, many individuals were first introduced to opioids through recreational drugs such as heroin [7,8]. However recent opioid use patterns have contributed to a demographic shift in which individuals developed OUD after being exposed to opioids by means of prescription drugs such as fentanyl, codeine or oxycodone [9,10]. Today, Canada is the world's second highest consumer of prescription opioids after USA [11].

Currently, opioid substitution therapy (OST) is used to treat OUD. OST is a harm reduction treatment that aims to limit adverse risks and events associated with illicit opioid use [12]. This entails the prescription of longer-acting opioids with less euphoric effects in order to minimize cravings and prevent withdrawal symptoms [12,13]. The most commonly used opioid substitutes are methadone, buprenorphine, naltrexone and suboxone® (a combination of buprenorphine and

naloxone) [12–14]. OST has a positive impact on OUD including a variety of social and health related factors, such as a decline in the use of illicit substances, unemployment, HIV prevalence, criminal activities, and mortality [2,13,15]. OST has also demonstrated improved social functioning and treatment retention [13–15]. However, while OST has demonstrated some success in managing OUD, there is still a great degree of variability in treatment outcomes [4].

This variability in treatment outcomes may be partially explained by a shifting OST population resulting from changes in the way in which an individual is first introduced to opioids. A recent study estimated that 52% of women and 38% of men seeking treatment for OUD having first been exposed to opioids through a prescription [9]. Previous research demonstrates that patients in treatment for OUD were mainly young adult males, around 20 years of age, who injected heroin [8,9,16]. However, the patients receiving OST today are older and have a greater number of women [10,17,18]. This demographic shift warrants new investigation, as past research many no longer apply to this population.

Studies that look at the relationship between patients who initially started misusing opioids through a medical prescription and OST outcomes present conflicting findings. Some studies show that those in buprenorphine treatment that have misused prescriptions only have better treatment retention in comparison to people who have misused heroin[19] while other studies demonstrate that those that have misused prescriptions only do not differ in treatment retention from those misusing illicit opioids such as heroin [20].

The relationship between prescription opioids and OST outcomes may also be affected by physical health status. Opioids have become one of the most commonly used medications for pain in North America due to their analgesic effects [21]. Given the high prevalence of comorbid pain in the OUD population, it has been suggested that the chronic pain population is at risk for an increased likelihood to misuse prescription opioids [21–23].

It remains unclear, however, as to whether an association between initial exposure to opioids through a medical prescription and OST outcomes exists and if confounding variables heavily influence this relationship. Conducting a systematic evaluation of the literature on this topic is essential and can identify factors influencing treatment outcomes that may be overlooked in individual studies. We hypothesize that patients that were exposed to opioids through a prescription will have a different response to OST as defined by illicit opioid use and treatment retention.

3.2.2 Objectives

The aim of this systematic review is to synthesize and appraise the existing literature on the effects of initial exposure to opioids by prescription compared to those introduced through illicit on opioid substitution therapy treatment outcomes in patients diagnosed with opioid use disorder.

Specifically, the study objectives are:

1. Summarize the literature examining the association between exposure to opioids through a medical prescription and OST outcome (primary: illicit opioid use, secondary: treatment

retention and poly-substance use).

2. If possible, combine study findings in a meta-analysis comparing the OST treatment outcomes of those that were initially exposed to opioids through a legitimate prescription and those that were introduced through illicit means.
3. Conduct subgroup analyses based on age, sex, country, and method of OST treatment outcome measurement.

3.3 Methods

3.3.1 Eligibility criteria

This review will consist of published observational cross sectional and cohort studies and randomized control trials (RCTs) examining the association between opioid prescription misuse and OST outcomes. These studies may have been conducted in different settings including hospital, outpatient or community-based. Primary studies will include the main exposure to opioids through a prescription and OST treatment outcomes. The included studies will be comparing those introduced to opioids through a legitimate prescription and those introduced through illicit means. The individuals that began their use through a prescription not prescribed to them will be in the group of those that obtained opioids through other means (i.e. a family member, street or friend) as this can be defined as illicit use. There will be no age, sex, language or type of study population restrictions.

Studies will be excluded if they do not assess at least one of the primary or secondary outcomes

of interest detailed below. Most of the research on OST treatment outcomes study the current type of opioid misuse (i.e. street drugs or prescription) and fail to identify the method of initial exposure to opioids. As such, these studies will be omitted from our analysis, as it will not be possible to make conclusions pertaining to the primary exposure of interest and the association with OST results. In addition, studies investigating patients in OST for other reasons apart from treatment of OUD will also be omitted.

3.3.2 Outcomes and Prioritization

The primary study outcome, illicit opioid use, will be used to determine the effectiveness of the OST, and may be quantified in various ways such as urine toxicology or self-reports as provided in the primary studies. Secondary outcomes will include treatment retention and poly-substance use. Treatment retention may be quantified as ratio of people who are still in treatment at the time the study completion or average period of time in treatment. Poly-substance use may be measured in similar ways to illicit opioid use (i.e. urine toxicology, self-reports).

3.3.3 Information sources

In order to identify the relevant articles that will be used in the review, a health sciences librarian (SS) was consulted to develop a search strategy. The databases to be searched from inception are: EMBASE, MEDLINE, PsycINFO, and Cumulative Index to Nursing and Allied Health Literature (CINAHL). Articles will be identified using search terms related to prescription opioids and opioid use disorder together with their medical subject headings (MeSH) in different combinations (Table 3.5.1). An in-depth search will be carried out comprising of keywords found in the title, and abstract fields. To ensure that unnecessary restrictions on the search findings are

avoided, the study findings will not be included in the search strategy. The searches will be restricted to studies conducted in human research participants. Gray literature will be searched using ProQuest Dissertations as well as Theses Worldwide database. Lastly, a comprehensive hand search of reference lists of the relevant articles will be carried out to identify additional articles that may not have been captured in the original search.

3.3.4 Search strategy

Please see Table 3.5.1.

3.3.5 Study records

3.3.6 Data Management

Articles identified by the search strategy will be uploaded to an online platform known as Google Forms. Google Forms will allow for management of the articles and will also allow the authors to collaborate simultaneously. The review team will be provided training on how to use Google Forms prior to the commencement of the study to ensure calibration of the forms and the data abstraction methods. A pilot of 20 studies will first be carried out to calibrate the study forms and assess level of agreement.

3.3.7 Selection process

Two independent reviewers will carry out the title and abstract screening in duplicate to identify appropriate articles using previously established criteria. Eligible articles will then undergo full-

text review in duplicate. Disagreements will be resolved by discussion and consensus and in cases were no resolution is reached a third author will be consulted. During each stage of screening, a kappa statistic will be used to establish inter-rater agreements. Exceptional agreement between reviewers will be demonstrated as a kappa value of at least 0.75 [24]. In cases were additional clarification is needed, the primary study authors will be contacted to help determine eligibility. The preferred reporting items for systematic reviews and meta-analyses (PRISMA) [25] flow diagram will be used when reporting the full systematic review.

3.3.8 Data collection process

Independent reviewers will retrieve the data using a previously piloted data extraction form in duplicate. To ensure standardization, consistency among reviewers will be addressed by assessing completed pilot data extraction forms.

3.3.9 Data items

The information to be retrieved by the reviewers will consist of: details of the publication such as name of the first author, year of publication, journal, and country of publication, research design that was used, demographics of the research participants, type and method of measuring opioid exposure (i.e. medical prescription or illicit), OST outcome measures, overall findings of the study, and the study statistical results. In the case of missing data for any study, the authors will be contacted.

3.3.10 Risk of bias

The risk of bias will be appraised using the modified Newcastle-Ottawa Scale (NOS) [26,27] to

appraise the likelihood of bias in studies that are mainly observational in nature. This modified scale comprises seven questions that assess bias in four realms: choice bias, performance bias, identification bias, and information bias. Risk of bias is quantified on a scale 0 to 3 where 0 is high risk and 3 is low risk. The modified model has eliminated items concerning the comparability of groups. To assess risk of bias in RCTs, we will use the Cochrane Collaboration tool which will looks at six domains including: selection bias, reporting bias, attrition bias, performance bias, detection bias and other biases [28]. These results will be displayed in a table to facilitate easy comparison between the quality of studies included in this review.

3.3.11 Data synthesis

All included studies will be appraised with a qualitative summary and then if possible, a meta-analysis will be undertaken. Our primary analysis will compare treatment outcomes for patients that initiated opioid use by prescription (and continue to use prescription opioids) to those patients that started using opioids through illicit means. If studies further report that the patients who initially began through prescription have transitioned to using non-prescription opioids (or both), we will conduct a sensitivity analysis by removing these studies to determine whether it has an effect on the outcomes. Studies will be merged in a meta-analysis depending on the similarity between design of the study and the measurements of the outcomes. Depending on the design of the research, direct estimates will be pooled separately as pooling data from observational studies as well as RCTs is not advisable [29].

To account for the anticipated heterogeneity in the included studies, a random effect model for the meta-analysis will be used. This model takes both within-study and between-study variance

into consideration to offer a modest estimate in comparison to a fixed-effect model. The outcomes will be featured on a forest plot. Moreover, a sensitivity analysis might also be carried out to compare the outcomes of the studies with high or low risk of bias.

Heterogeneity will be computed amongst the pooled articles through the use of I^2 statistic. It is recommended that cut-off values are not enforced since the significance of heterogeneity relies on a variety of factors. Although Cochrane has recommended that a value of <40% might not signify a noteworthy amount of heterogeneity [29]. Therefore, likely sources of heterogeneity are going to be evaluated as long as there is an I^2 statistic > 40 %. In this case, subgroup analyses will also be conducted.

Some of the likely sources of heterogeneity includes age, sex, types of opioids and outcomes measurements. These are going to be examined through the use of subgroup analyses. We also plan to conduct a subgroup analysis if possible examining the differences in treatment outcomes for individuals who obtained opioids through different sources (i.e. street, family members, friend).

3.3.12 Meta-bias

An Egger's plot will be created to assess the likelihood of publication bias in the included articles.

3.3.13 Confidence in the cumulative evidence

The grading of recommendations, assessment, development and evaluation (GRADE) framework will be used to assess the quality of the evidence [30]. This scale evaluates evidence based on five realms: risk of bias, publication bias, consistency, directness, and accuracy.

3.3.14 Presenting and reporting of the study results

This systematic review will be reported in compliance with PRISMA reporting guidelines [25]. A flow diagram will be used to demonstrate the selection of studies including reasons for exclusion. The present protocol follows the preferred reporting items for systematic reviews and meta-analyses protocol (PRISMA-P) guidelines which is attached (see Additional file 2) [31].

3.4 Discussion

Using the evidence obtained from this systematic review, we expect to draw conclusions regarding the presence of an association between being exposed to opioids through a medical prescription and opioid substitution therapy outcomes. Examining the current literature in a systematic way will allow us to summarize existing findings on this topic and to critically appraise the risk of bias and methodological quality of these studies. The present literature primarily focused on the cohort of patients that were exposed to opioids through illicit means and little is known about the cohort of patients that starting misusing opioids after using a prescription. This new shift in demographic profile of opioid users and the predominance of prescription opioids use over heroin in different parts of the world including Canada and USA,

the highest opioid consuming countries in the world, warrants a detailed examination of the literature.

Given the rise of prescription opioid use in Canada and USA, it is important that we evaluate factors that may affect the effectiveness of opioid substitution treatment for this cohort of patients.

Abbreviations

OST- Opioid substitution therapy

OUD- Opioid use disorder

RCT- Randomized control trials

NOS- Newcastle- Ottawa scale

PRISMA- Preferred reporting items for systematic reviews and meta-analyses

PRISMA-P Preferred reporting items for systematic reviews and meta-analyses protocols

GRADE- Grading of Recommendations Assessment, Development and Evaluation

Declarations

Acknowledgements

Not applicable

Ethics approval and consent to participate

Not Applicable

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Competing Interests

The authors declare that they have no competing interests.

Authors Contributions

NS: contributed to the conception and design of the study, development of data extraction forms, search strategy, manuscript writing and final review of the manuscript. MB: contributed to the methodological design, critical revision and final review of the manuscript. LZ: contributed to the methodological design, critical revision and final review of the manuscript. SS: contributed to the development of the search strategy and final review of the manuscript. HS: contributed to the critical revision and final review of the manuscript. BB: contributed to the critical revision and final review of the manuscript. CS: contributed to the critical revision and final review of the manuscript. RS: 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 approval of the manuscript. All authors read and approved the final manuscript.

Availability of supporting data

Not applicable

Consent for Publication

All authors consent and approve the manuscript for publication.

3.5 Tables and Figures

3.5.1 Search Strategy

MEDLINE=6,250	1 exp Analgesics, Opioid/ 2 (opiate* or opioid* or fentanyl or narcotic* or dilaudid or oxycontin* or oxycod*).ti,ab. 3 1 or 2 4 exp Drug Prescriptions/ 5 (prescript* or prescrib* or pharmaceutical* or legal*).ti,ab. 6 4 or 5 7 3 and 6 8 ((prescript* or prescrib* or pharmaceutical*) adj2 (opioid* or opiate* or dilaudid or fentanyl or codeine or oxyco*)).ti,ab. 9 7 or 8 10 Opioid-Related Disorders/ 11 Heroin Dependence/ 12 Substance-Related Disorders/ 13 Substance Abuse, Intravenous/ 14 ((opiate* or opioid* or heroin* or oxyco* or codeine* or dilaudid or fentanyl or drug* or substance*) adj2 (use* or using or misuse* or abus* or dependence* or dependent* or addict*)).ti,ab. 15 10 or 11 or 12 or 13 or 14 16 9 and 15 17 exp animals/ not (humans/ and exp animals/) 18 16 not 17 19 9 and 15

EMBASE=14,649	1 exp heroin dependence/ 2 opiate/ 3 exp opiate addiction/ 4 substance abuse/ 5 ((opiate* or opioid* or heroin* or oxyco* or codeine* or dilaudid or fentanyl or drug* or substance*) adj2 (use* or using or misuse* or abus* or dependence* or dependent* or addict*)).ti,ab. 6 1 or 2 or 3 or 4 or 5 7 ((prescript* or prescrib* or pharmaceutical*) adj2 (opioid* or opiate* or dilaudid or fentanyl or codeine or oxyco*)).ti,ab. 8 (prescript* or prescrib* or pharmaceutical* or legal*).ti,ab. 9 exp prescription/ 10 exp prescription drug/ 11 (opiate* or opioid* or fentanyl or narcotic* or dilaudid or oxycontin* or oxycod*).ti,ab. 12 exp narcotic analgesic agent/ 13 11 or 12 14 8 or 9 or 10 15 13 and 14 16 7 or 15 17 6 and 16 18 limit 17 to human
PsycINFO=2,898	1 exp Opiates/ 2 (opiate* or opioid* or fentanyl or narcotic* or dilaudid or oxycontin* or oxycod*).ti,ab. 3 exp Prescription Drugs/ 4 1 or 2 5 (prescript* or prescrib* or pharmaceutical* or legal*).ti,ab. 6 3 or 5 7 4 and 6 8 ((prescript* or prescrib* or pharmaceutical*) adj2 (opioid* or opiate* or dilaudid or fentanyl or codeine or oxyco*)).ti,ab. 9 7 or 8

	10 exp Heroin Addiction/ or exp Heroin/ 11 exp Intravenous Drug Usage/ 12 ((opiate* or oxyco* or opioid* or heroin* or codeine* or dilaudid or fentanyl or drug* or substance*) adj2 (use* or using or misuse* or abus* or dependence* or dependent* or addict*)).ti,ab. 13 10 or 11 or 12 14 9 and 13
CINAHL=1,143	1 (MH "Drugs, Non-Prescription") OR (MH "Drugs, Prescription") OR (MH "Prescriptions, Drug") OR (MH "Drugs, Off-Label") 2 (MH "Substance Use Disorders") 3 (MH "Heroin") OR (MH "Substance Dependence") 4 (MH "Substance Abuse, Intravenous") 5 ((opiate* or opioid* or oxyco* or heroin* or codeine* or dilaudid or fentanyl or drug* or substance*) N2 (use* or using or misuse* or abus* or dependence* or dependent* or addict*)) 6 (MH "Analgesics, Opioid") 7 (opiate* or opioid* or fentanyl or narcotic* or dilaudid or oxycontin* or oxycod*) 8 2 OR 3 OR 4 OR 5 9 ((prescript* or prescrib* or pharmaceutical*) n2 (opioid* or opiate* or dilaudid or fentanyl or codeine or oxyco*)) 10 6 OR 7 11 (prescript* or prescrib* or pharmaceutical* or legal*) 12 1 OR 11 13 12 AND 13 14 9 OR 14 15 8 AND 15 (limtiters- human)

3.6 References

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4 CHAPTER 4

Treatment outcomes in patients with opioid use disorder who were first introduced to opioids by prescription: A systematic review and meta-analysis

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This work has been published in Frontiers in Psychiatry. The document has been reformatted from the original version for inclusion in this thesis. The published manuscript is available in Appendix iii. The complete citation is included below.

Sanger N, Bhatt M, Singhal N, Panesar B, D'Elia A, Trottier M, Shahid H, Hillmer A, Baptist-Mohseni N, Roczyki V, Soni D, Brush M, Lovell E, Sanger S, Samaan MC, de Souza RJ, Thabane L, Samaan Z. Treatment Outcomes in Patients With Opioid Use Disorder Who Were First Introduced to Opioids by Prescription: A Systematic Review and Meta-Analysis. Front Psychiatry. 2020 Aug 28;11:812. doi: 10.3389/fpsyt.2020.00812. PMID: 33005151; PMCID: PMC7485127.

4.1 Abstract

Objective: Prescription opioid misuse has led to a new cohort of opioid use disorder (OUD) patients who were introduced to opioids through a legitimate prescription. This change has caused a shift in the demographic profile of OUD patients from predominantly young men to middle age and older people. The management of OUD includes medication-assisted treatment (MAT), which produces varying rates of treatment response. In this study, we will examine whether the source of first opioid use has an effect on treatment outcomes in OUD. Using a systematic review of the literature we will investigate the association between source of first opioid introduction and treatment outcomes defined as continuing illicit opioid use and poly-substance use while in MAT.

Methods: Medline, EMBASE, CINHAL and PsycInfo were searched from inception to December 31st, 2019 inclusive using a comprehensive search strategy. Five pairs of reviewers conducted screening and data extraction independently in duplicate. The review is conducted and reported according to the PRISMA guidelines. A random-effects model was used for meta analyses assuming heterogeneity among the included studies.

Results: The initial search results in 27,345 articles that were screened, and 5 observational studies were included in the qualitative and quantitative analyses. Our results found that those who were introduced to opioids through a legitimate prescription were significantly less likely to have illicit opioid use (0.70, 95% CI 0.50, 0.99) while on MAT. They were also less likely to use cannabis (0.54, 95% CI 0.32, 0.89), alcohol (0.75, 95% CI 0.59, 0.95), cocaine (0.50, 95% CI 0.29, 0.85) and injection drug use (0.25, 95% CI 0.14, 0.43) than those introduced to opioids through recreational means.

Conclusion: This study shows that the first exposure to opioids, whether through a prescription or recreationally, influences prognosis and treatment outcomes of opioid use disorder. Although the increased pattern of prescribing opioids may have led to increased OUD in a new cohort of patients, these patients are less likely to continue to use illicit drugs and have a different prognostic and clinical profile that requires a tailored approach to treatment.
Systematic Review Registration: PROSPERO CRD42017058143.

4.2 Introduction

North America is experiencing an opioid crisis in which the illicit use of opioids is at an all-time high. Opioids are a class of drugs that are often prescribed to relieve pain and can be highly addictive (1). They include licit substances such as oxycodone, Percocet, hydromorphone and street drugs such as heroin. The Center for Disease Control (CDC) reports that in the United States, approximately 115 people die every day from an opioid-related overdose (2). In 2017 alone, more than half the drug-related deaths in the States were due to opioids (2). Opioids are controlled substances and are classified by Drug Enforcement Administration (DEA) into various classes according to their abuse potential and medical utility (3). Opioids such as heroin are a Schedule 1 substance indicating high abuse potential and no medical utility, and fentanyl, oxycodone being Schedule II (3). In response to the opioid crisis, Substance Abuse and Mental Health Services Administration (SAMHSA) conducted a national survey and revealed that over 2.1 million people are suffering from an opioid use disorder (OUD) involving prescriptions opioids alone (4). OUD, previously classified as opioid abuse and dependence, is a disorder that affects the psychological, social and physical aspects of an individual's life (5). Dependence to a substance (i.e. opioids) typically refers to a physical response in the form of withdrawal symptoms when an individual stop using that substance (6). Addiction refers to not being able to resist the urge to use a substance despite there being negative consequence (6). OUD encompass opioid addiction and dependence that signify a problematic use of opioids impacting health and social functioning (5). Withdrawal symptoms experienced due to OUD may include sweating, shakes, anxiety, irritability, and restlessness amongst others (7).

There are several treatments available for OUD which include pharmacological and psychological options. Medication-Assisted Treatment (MAT) includes opioid agonist, antagonists, and partial agonists (8). Some of the more frequently used MATs for OUD are naltrexone, buprenorphine and methadone (8). Methadone, a synthetic opioid agonist, is one of the most common MAT for treating OUD (8,9). While research investigating the effectiveness of methadone maintenance treatment (MMT) has shown that it can reduce opioid cravings as well as other symptoms related to opioid withdrawal (i.e. shakes, sweating) through acting on the opioid receptors (8,10), there is still a high degree of variability for treatment outcomes between individuals such as treatment retention (11–13). Research has suggested that some of this variability may be related to age (14), sex (15), and gender (16) but outcomes are also likely influenced by the increasing prevalence of prescription opioid misuse (17–19).

Current research is suggesting that one reason for the opioid epidemic is the rise of prescription opioid misuse. In 2016 alone, Canada and the United States prescribed over 440 million opioids to patients (20,21). The National Institutes on Drugs Abuse (NIDA) suggest that anywhere from 8 to 12 percent of individuals prescribed opioids are at risk of developing OUD (22). With the rise of prescription opioid misuse, this has led to a shift in the profile of the "typical" illicit opioid user. Twenty years ago, this demographic profile would have consisted of primarily males in their 20s, misusing heroin intravenously (23,24) but now, we are seeing a separate cohort of incoming OUD patients that are female, older in age and misusing prescription opioids (25,26). Prescription medications including opioids are available on the illegal drug market through diversion (27,28). Diversion of prescription medications may occur at any level from the direct pharmaceutical manufacturing site to patients selling the prescriptions

themselves. This has been occurring for many decades for many types of substances (i.e. opioids, benzodiazepines) and with prescription opioids being readily available on the illegal drug market, this has contributed to a demographic shift.

This change in the demographic is substantial because there is evidence that suggests that different types of opioids users have varying experiences while in MAT (29). Previous research suggests that opioid prescription users differ in their treatment outcomes compared to individuals who used heroin (29). Additionally, there is also support for the idea that poly-substance use differs within the OUD population receiving treatment. Poly-substance use has been suggested as a factor that is associated with decreased abstinence from opioids, treatment retention and related to methadone-related mortality (30–33). Recent research found that cocaine, alcohol and other substances were used significantly more by heroin users than prescription users (34). Prescription opioid users attending pharmacological treatment for OUD also had significantly longer treatment retention in comparison to heroin users (35). However, the previous research is inconclusive as other studies suggested that there is no significant difference in treatment outcomes between prescription introduced and recreational opioid users (36). The magnitude to which this demographic shift has impacted treatment outcomes in specific MAT patient groups has yet to be investigated in a systematic way, and there are conflicting findings in the current literature.

Additionally, there are new, synthetic opioids (i.e designer fentanyl and its' analogs) that are available on the street and have been found to be mixed in other illicit substances such as cocaine, methamphetamines and heroin (37). There has been an 88% increase in synthetic opioid-related deaths from 2013 to 2016 whereas the number deaths due to heroin alone use seem

to remain consistent (38–40). Prescription opioids are also readily available on the illegal drug market through methods such as prescription resales and theft of prescriptions/prescription pads (28). In recent years, various governments have come up with legislative changes to control access and prescribing patterns for opioids (41–43). With there being new types of synthetic opioids and prescription opioids readily available on the street, it is important to examine if method of introduction to opioids impacts OUD treatment outcomes.

The purpose of this review is to examine differences in patients with OUD on MAT by those introduced to opioids through prescription versus by recreational means on outcomes of continued opioid use, poly-substance use and treatment retention.

This review will fill this knowledge gap and aims to have an important impact in how treatments are designed and tailored to various subgroups within the OUD population. Tailored treatments to address specific concerns in this population may improve MAT outcomes.

4.2.1 Objectives

The aim of this systematic review is to examine if opioid use disorder patients introduced to opioids through legitimate prescription differ in methadone maintenance treatment outcomes in comparison to those that were introduced to opioids through recreational means.

Specifically, we wanted to examine if these two cohorts differed in:

1. Continued opioid use while in MAT
2. Poly-substance use while in MAT
3. Treatment retention while in MAT

4.3 Methods

4.3.1 Protocol and Registration

This systematic review was conducted to investigate OUD treatment outcomes by comparing those introduced to opioids through legitimate prescriptions and those introduced through recreational means. The Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines were followed (44). The protocol for this systematic review has been peer reviewed, published previously (45), and registered with PROSPERO CRD42017058143.

4.3.2 Eligibility Criteria

This review investigates the association between method of introduction to opioids and MAT outcomes in different settings (i.e. hospital, outpatient, community based) by examining published observational cross-sectional and cohort studies, as well as randomized control trials (RCTs). Included studies compared legitimate prescription opioid introduction to recreational opioid introduction, which can be defined as the use of opioids obtained through means outside of a prescription (i.e. family member, street, using another's prescription)

Studies that failed to measure the initial method of introduction to opioids were not included. Studies that did not assess at least one of the primary or secondary outcomes of illicit opioid use, poly-substance use and treatment retention were excluded. There were no restrictions on age, sex, or language.

4.3.3 Information Sources and Search Strategy

A search strategy was developed by a health science librarian (SS) to search for studies in the EMBASE, MEDLINE, PsycINFO, and Cumulative Index to Nursing and Allied Health

Literature (CINAHL) databases. These databases were searched from inception until December 31, 2019. Search terms were related to prescription opioids and opioid use disorder together with their medical subject headings (MeSH) in different combinations. We also did a manual search of the references of relevant articles to identify any studies that may have been missed. The search strategy has been published in the protocol (45). We have also included the search strategy in the Appendix.

4.3.4 Study Selection

Previously established selection criteria were used by five pairs of reviewers in order to independently complete the title and abstract screening and subsequent full-text review of the eligible articles. Both stages of screening were carried out in duplicate. Upon the occurrence of a disagreement on the status of an article eligibility, resolution was reached through discussion to consensus between the pair, or with the consultation of a third party. Inter-rater agreements were established using a kappa statistic, where a kappa value of at least 0.75 is indicative of exceptional agreement between reviewers (46). The mean kappa value between pairs was 0.88.

4.3.5 Data Collection and Data Items

A piloted data extraction form was used by reviewers to retrieve data in duplicate. These forms extracted information relating to the author, year of publication, journal, and country of publication. Details of the study's methodology and results were also retrieved. More specifically, information on research design used, demographics of the research participants, type and method of measuring initial type of opioid introduction (i.e. medical prescription or recreational), MMT outcome measures, overall findings of the study, and the study's statistical

results was included. If data pertaining to the aforementioned items was missing, the authors were contacted.

4.3.6 Risk of Bias of Individual Studies

The risk of bias was independently assessed by 2 reviewers who reviewed the methodological quality of the eligible studies using the Newcastle-Ottawa Scale (NOS), used mainly for observational studies to assess choice bias, performance bias, identification bias, and information bias (47). A modified model was used that has eliminated items concerning the comparability of groups (48). It consists of 7 questions and is quantified on a scale of 0 to 3, where 0 is high risk of bias and 3 is low risk of bias. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria was utilized to assess the quality and strength of the evidence (49). This is provided in Table 4.7.1.

4.3.7 Statistical analyses

All included studies were qualitatively summarized. A meta-analysis was conducted on the primary outcome of illicit opioid use and the outcome of poly-substance use. Review Manager 5.2 was used to conduct the meta-analyses. The substances included in this were cannabis, alcohol, injection drug use, cocaine, and benzodiazepines. These were the substances that were examined in the included studies. Two of the included studies investigated treatment retention but were unable to be meta-analyzed as they were reported in different ways. The outcomes are presented in a forest plot. The meta-analyses reflect the associations found between the outcomes and method of introduction to opioids (legitimate prescription and recreational). Due to the limited number of studies, we were not able to conduct any subgroup analyses for age, sex, country, and type of MAT treatment.

We have shown our pooled dichotomized data as odds ratio (OR) with 95% confidence intervals. The I2 statistic was used to compute heterogeneity. Cochrane suggests that a value of <40% might not signify a noteworthy heterogeneity (50). A random effect model, which considers both within study and between study variance in comparison to the fixed-effect model, was used to account for expected heterogeneity in the included studies. We were not able to conduct an adjusted analysis as covariates were not controlled for. We were unable to examine publication bias as we have less than 10 included papers. Previous studies have reported that it is not possible to assess publication bias with less than 10 studies (51). PRISMA reporting guidelines were followed throughout this process (44).

4.3.8 Types of Interventions

Experimental

The experimental intervention includes those participants that were introduced to opioids through recreational use and are now in MAT for OUD.

Comparator

The accepted comparators include those that were introduced to opioids through a legitimate physician's prescription and are now in MAT for OUD.

4.3.9 Outcome Measures

Continued Opioid Use

We have defined continued opioid use to be the use of any opioids while the patient is in methadone maintenance treatment.

Poly-Substance Use

We defined poly-substance use as the use of any of the previously defined substances before or during MMT.

Treatment Retention

We defined treatment retention as the length of time a patient stayed in their MAT without dropping out.

4.4 Results

4.4.1 Study Selection

From the databases searched, a total of 27,345 articles went through the title and abstract screening process. After removing 3,264 duplicates and 24,076 studies that did not meet the inclusion criteria, a total of five studies were included. Figure 4.7.3 is the PRISMA flow diagram of the screening process. All five studies were included in the meta-analyses of the outcomes. Three out of five studies were subjected to the meta- analysis of the primary outcome of illicit opioid use (52–54).

4.4.2 Study Characteristics

The characteristics of the included studies are summarized in Table 4.7.2. Five papers were included in this systematic review, all of which were observational studies looking at patients in MAT for opioid use disorder. Two studies looked at patients receiving buprenorphine or methadone treatment (52,55). One study included patients undergoing methadone treatment (54). One study only looked at buprenorphine treated patients (56) while the final study looked at buprenorphine-naloxone patients (53). All five of these studies compared individuals initially

introduced to opioids for prescription use with individuals introduced to opioids via recreational use. The majority of the sample consisted of male participants (60.4%).

Three out of five studies looked at the primary outcome of illicit opioid use (36,53,54). Two studies examined injection drug use (52,56), three studies examined cannabis use , two studies examined alcohol use (54,56), two studies examined benzodiazepine use (54,55), and three studies examined cocaine use (54–56). Additionally, two studies examined treatment retention (30,32).

4.4.3 Risk of bias within studies

The quality of the studies included are shown in Figure 4.7.4. Justifications for assessments are presented in Appendix I with the risk of bias tables. The modified Newcastle-Ottawa Scale (NOS) was used to rate the internal validity of the studies shown in Figure 4.7.4 and assess the quality of these observational studies (47,48). Generally, most of the studies included have relatively low to moderate risk of bias, except for one (55). Specifically, this study shows a high risk of bias when adjusting for confounders or other variables as the researchers did not adjust for confounders, instead opting to perform student t-tests. Another study also shows an unclear risk of bias when adjusting for confounders or other variables since the information they provide is unclear (53). Two of the studies included show an unclear risk of bias in terms of incomplete outcome data, simply because they do not provide any information about this (53,55). Aside from these biases, all five of the observational studies were generally well reported on all other characteristics, including appropriate source population, sufficient power and sample size,

appropriate statistical analysis, valid outcome measurement, and objective assessment of the outcome of interest.

4.4.4 Results of Individual Studies

Illicit Opioid Use

Our meta-analysis pooled results from three studies comparing the continuation of opioid use among individuals first introduced to opioids by a legitimate prescription vs. a recreational source. Cooper et al., (2018) collected self-reported data on past month and lifetime opioid use. We used the data provided on the past month opioid use. Dreifuss et al., (2013) collected data on the continued use of opioids using weekly substance use reports and urine drug screens. Sanger et al., (2018) used urine drug screens to investigate illicit opioid use. The remaining two studies did not report on the outcome of continued opioid use (55,56). Canfield et al., (2010) examined progression of opioid use over time, but not as an outcome of the means of opioid use introduction. Tsui et al., (2010) reported on the different patterns in type of opioids the groups would use (i.e. prescription, street drugs or both) but did not provide information pertaining to the exact number of patients that were currently using opioids between licit and illicit method of introduction groups.

The studies included in our meta-analysis comprise a total sample size of 1400 participants. Cooper et al., (2018) reported that those introduced through a prescription were associated with a lower prevalence of lifetime heroin use, but no difference in past-month illicit opioid use. Dreifuss et al., (2013) found that those introduced to opioids by means of a prescription were associated with discontinued opioid use in the final weeks of treatment, whereas those introduced

through illicit means were associated with continued opioid use in treatment. In Sanger et al., (2018) there was no significant association between the source of opioid introduction and continued opioid use. We conducted an unadjusted analysis using odds ratios to compared continued opioid use during treatment among those who were first introduced to opioids through a prescription versus an illicit source. We found that individuals who were introduced to opioids through prescription means were significantly 30% less likely to have continued to use opioids while in MAT (OR 0.70, 95% CI 0.50, 0.99, p-value 0.04). Please see Figure 4.7.5.

Injection Drug Use

Our meta-analysis pooled results from two studies comparing injection drug use among participants first introduced to opioids through a prescription versus an illicit source. Cooper et al., (2018) collected self-reported data on injection drug use history. Tsui et al., (2010) used the Addiction Severity Index (ASI) to collect self-reported data on current and past use of prescription opioids and heroin, including the route(s) of administration. The remaining three studies did not report on the outcome of injection drug use(53–55). Canfield et al., (2010) reported a combination of intranasal and intravenous routes of administration and intravenous drug use could not be extrapolated. Dreifuss et al., (2013) and Sanger et al., 2018 did not report any data on intravenous drug use.

The studies included in our meta-analysis comprise a total sample size of 248 participants. In Cooper et al., (2018) those introduced to opioids through a prescription have a lower prevalence of any injection drug use. Tsui et al., (2010) reported that those introduced to opioids by a physician were less likely to have any injection drug use. We conducted an unadjusted analysis

using odds ratios to compare any injection drug use among those who were introduced to opioids through a prescription vs. an illicit source. We found that individuals who were introduced to opioids through a prescription source were significantly less likely to engage in injection drug use in comparison to those introduced through recreational means (OR 0.25, 95% CI 0.14, 0.43, p-value <0.001). Please see Figure 4.7.6.

Cannabis Use

Our meta-analysis pooled results from three studies comparing cannabis use in the initiation source of opioid use, by means of prescription vs. an illicit source. Canfield et al., (2010) collected self-reported data on cannabis use history. Sanger et al., (2018) used the Maudsley Addiction Profile (MAP) to acquire self-reported data on cannabis use in the past 30 days. Tsui et al., (2010) acquired self-reported data on regular use of cannabis. The remaining two studies did not report on the outcome of cannabis use (52,53).

The studies included in our meta-analysis comprise a total sample size of 1191 participants. In Canfield et al., (2010) participants who were first introduced to opioids by means of a prescription were less likely to have ever used cannabis. Sanger et al., (2018) reported that those first introduced to opioids by a prescription were less likely to have used cannabis in the past 30 days than those first introduced to opioids by a recreational source. In Tsui et al., (2010) participants who were introduced to opioids by a physician were less likely to report prior use of cannabis. We conducted an unadjusted analysis using odds ratios to compare cannabis use among those who were introduced to opioids by a prescription versus an illicit source. We found that

those who initiated the use of opioid(s) through a prescription source were significantly less likely to use cannabis (OR 0.54, 95% CI 0.32, 0.89, p-value 0.02). Please see Figure 4.7.7.

Alcohol Use

Our meta-analysis pooled results of two studies comparing the effect of opioid introduction on alcohol use. Sanger et al., (2018) used the Maudsley Addiction Profile (MAP) to acquire self-report data on alcohol use within the past 30 days. Tsui et al., (2010) collected self-report data on regular use of alcohol by asking participants the question "prior to starting opiates, did you ever have daily or regular use of alcohol?". The remaining three studies did not report on the outcome of alcohol use (52,53,55). Cooper et al., (2018) asked participants about injection use of alcohol and reported their results as a measure of injection history of any drug. Dreifuss et al., (2013) examined alcohol use as a predictor of treatment success but not as an outcome of initial exposure to opioids. Canfield et al., (2010) did not report any data on alcohol use.

The studies included in our meta-analysis comprise a total sample size of 1116 participants. In Sanger et al., (2018) there was no significant association between source of opioid initiation and alcohol use. In Tsui et al., (2010) there was no significant difference in regular use of alcohol prior to opioids between those who were introduced to opioids by a physician versus those who were not. For this meta-analysis, we used the results for the entire population from both Sanger et al., (2018) and Tsui et al., (2010). We conducted an unadjusted analysis using odds ratios to compare alcohol use among those who first initiated opioids through a prescription versus an illicit source. We found that individuals who were introduced to opioids through a legitimate

prescription were significantly less likely to have used alcohol (0.75, 95% CI 0.59, 0.95) (OR 0.75, 95% CI 0.59, 0.95, p-value 0.02). Please see Figure 4.7.8.

Cocaine Use

Our meta-analysis pooled results of three studies investigating cocaine use. Canfield et al., (2010) collected self-reported data on any previous cocaine use. Sanger et al, (2018) used the MAP to acquire self-report data on cocaine use within the past 30 days. Tsui et al., (2010) collected self-report data on regular use of cocaine by asking participants the question "prior to starting opiates, did you ever have daily or regular use of cocaine?". The remaining two studies did not report on the outcome of cocaine use (52,53). Cooper et al., (2018) collected data on the use of cocaine only in the context of injection drug use and reported their results as a measure of injection history of any drug. Dreifuss et al., (2013) examined cocaine use as a predictor of treatment success but not as an outcome of initial exposure to opioids.

The studies included in our meta-analysis comprise a total sample size of 1191 participants. In Canfield et al., (2010) there was no significant difference in use of cocaine between those who reported obtaining their first opioid through a prescription versus an illicit source. In Sanger et al., (2018) there was no significant association between source of opioid initiation and cocaine use. In Tsui et al., (2010) participants who were first introduced to opioids by an illicit source were significantly more likely to report prior use of cocaine. For this meta-analysis we conducted an unadjusted analysis using odds ratios to compare cocaine use among those who first initiated opioids through a prescription versus an illicit source. We found that individuals who were

introduced to opioids through prescription were significantly less likely to use cocaine (OR 0.50, 95% CI 0.29, 0.85, p-value 0.01). Please see Figure 4.7.9.

Benzodiazepine Use

Our meta-analysis pooled results of two studies comparing benzodiazepine use among participants first introduced to opioids through a prescription versus an illicit source. Canfield et al., (2010) collected self-report data on any previous benzodiazepine use. Sanger et al, (2018) used the MAP to acquire self-report data on benzodiazepine use in the past 30 days. The remaining three studies did not report on the outcome of benzodiazepine use (52,53,56). Cooper et al., (2018) collected data on previous injection use of benzodiazepines and reported their results as a measure of injection history of any drug. Dreifuss et al., (2013) examined the use of sedatives as a predictor of treatment success but did not specifically assess benzodiazepine use as an outcome of initial exposure to opioids. Tsui et al., (2010) did not collect any data on benzodiazepine use.

The studies included in our meta-analysis comprise a total sample size of 1051 participants. In Canfield et al., (2010) there was no significant difference in benzodiazepine use among those who reported obtaining their first opioid through a prescription vs. an illicit source. In Sanger et al., (2018) there was no significant association between source of opioid initiation and benzodiazepine use. We conducted an unadjusted meta-analysis using odds ratios to compare benzodiazepine use among those who first initiated opioids through a prescription vs. a recreational source. We found that there was no significant association between individuals who

were introduced to opioids through prescription and those that were introduced through recreational means (OR 0.82, 95% CI 0.54, 1.26, p-value 0.37). Please see Figure 4.7.10.

Treatment Retention

Two studies examined treatment retention (52,54) however we were unable to combine study results to conduct a meta-analysis. Sanger et al., (2018) examined the mean length in treatment and found that there was no significant association between the prescription introduction and recreational introduction groups (54). Cooper et al., (2018) reported the length of treatment in median years. They reported no significant association between those introduced to opioids through a prescription in comparison to those introduced by recreational means for length of current treatment in median years (52).

4.4.5 Risk of Bias Across Studies

When assessing risk of bias across studies (Figure 4.7.11), we noticed a few trends. First, two of the studies show an unclear or high risk of detection bias, which indicates that the studies either did not adjust for confounders and other variables or did not properly report that they did so (53,55). Secondly, two of the studies also show an unclear risk of detection bias as they fail to provide outcome data, or the data provided is unclear (53,55). Overall, our findings show that the results from these two observational studies should be interpreted carefully due to risk of bias. Further, our results show that the other three observational studies were generally well reported and bias free (52,54,56). Please see Figure 4.7.11.

4.4.6 Additional Analysis

As there were a small number of studies included in this review, it was not possible to conduct any additional analyses.

4.5 Discussion

4.5.1 Summary of Evidence

Opioid use disorder is a serious illness that affects approximately 26 to 36 million people across the globe (2). Not only does this illness affect the individual in multiple aspects of their lives, it places a great economic burden on healthcare systems (57). We have recently seen a dramatic increase in the number of people misusing opioids, a significant proportion of whom misuse prescription opioids specifically. While this crisis has global impacts, North America has experienced the majority of the burden of illness. The United States alone consumes 80% of the global supply of prescription opioids, and it is estimated that their use has increased by 300% since 1991 (58). Research has suggested that those prescribed an opioid prescription for chronic pain have a risk of up to 60% of misusing prescriptions (59). It is critically important to investigate the emerging cohort of patients who were introduced to opioids by legitimate prescriptions to see whether they fare differently in MAT compared to those who were introduced to opioids recreationally. To our knowledge, this is the first systematic review to synthesize the literature examining this question.

Our meta-analysis found that those that were introduced to opioids through a legitimate prescription were less likely to use illicit opioids while in treatment than those that were introduced to opioids through recreational means (OR 0.70, 95% CI 0.50, 0.99, p-value 0.04).

Our findings also revealed that the prescription introduction to opioids cohort were less likely to have used cocaine (OR 0.50, 95% CI 0.29, 0.85, p-value 0.01), alcohol (OR 0.75, 95% CI 0.59, 0.95, p-value 0.02), cannabis (OR 0.54, 95% CI 0.32, 0.89, p-value 0.02), and injection drugs (OR 0.25, 95% CI 0.14, 0.43, p-value <0.001). There was no association found between the source of introduction to opioids and benzodiazepine use (OR 0.82, 95% CI 0.54, 1.26, p-value 0.37).

Those introduced to opioids through prescriptions were found to be less likely to continue using opioids during treatment than those whose first introduction was through recreation. This suggests that first introduction to opioids through illegal means predicts continued use during treatment, and that the first introduction may explain trends in subsequent opioid use. Brands et al. demonstrated that patients in MMT who used only prescription opioids had significantly less experience with sharing opioid injection equipment in comparison to those patients who used heroin only or initially (60). While this study did not ask patients about their first introduction to prescription opioids, most patients using prescription opioids only (86%) or initially (61.9%) indicated that their initial reason for using opioids was to manage pain. They conclude that those who were likely introduced to opioids through prescription as a means of treating pain tend to engage in less risk-taking behavior and are less likely to continue using opioids during treatment in comparison to those not using opioid drugs to manage pain (60). Further, in another study of patients in treatment for OUD, those using only prescription opioids had a higher treatment retention, fewer opioid-positive urine samples, and were more likely to complete treatment than those patients using a combination of heroin and prescription opioids or those using heroin

exclusively (35). Taken together, first introduction and reason for use, perhaps mediated by risk-taking behaviours, may predict future opioid use and explain our finding that those who were not first introduced to opioids through a prescription have an increased likelihood of continued use in treatment. People whose opioid use was first initiated through prescription also tend to be demonstrate lower risk-taking behaviour, further supporting the observation that those who initiate opioid use from a prescription tend to be less likely to continue use during treatment.

Prescription-introduced opioid users are more likely to be female, generally have an older age of opioid use onset, and are more like to have completed a post-secondary education (54). These factors likely influence the level of continued use of illicit opioids in treatment as women in general are less likely to use opioids (61)and are shown to engage in fewer risks than men in terms of both everyday risk-taking behaviours (62) as well as in financial, recreational, ethical and recreational domains (63).Risk-taking attitudes are found to be reduced with age (63), and older adults are also less likely to partake in risk-taking behaviour and illegal opioid use while in treatment. A study of treatment outcomes for opioid use found that 61% of older adults had no positive urine screens for opioids, compared to 35% in younger adults after initiating treatment (64).

Our finding that those introduced to opioids through recreational means are more likely to engage in using other substances such as alcohol, marijuana, and cocaine, is also congruent with the literature. Studies have found that the nonmedical use of opioids was significantly associated with the use of other illicit substances (57). Specifically, there is research that suggests that there are differences in polysubstance use between prescription users and recreational users, and that

this poly-substance use in recreational opioid users may be associated with risk-taking behaviors. A study investigating HIV risk-taking behaviour found that men who are recreational, poly-substance drug users were more likely to engage in risky behaviours such as the sharing of needles and sex without protection (65). Morely et al. took a closer look at recreational drug users and found that different mental disorders and behaviour patterns are predictive of the type and degree of polysubstance use a recreational user engages in (66). Depression and anxiety disorders were found to be predictive of medication and cannabis use, whereas violent and risky behaviour suggested the use of illicit or all drugs. In contrast, participants in the non-polysubstance class were more likely to be female, have a lower desire to use drugs, and were less likely to have a diagnosis of anxiety or depression, or engage in violent risk-taking behaviours. Thus, risk-taking behaviour and the presence of mental illness may be predictive of polysubstance use in recreational drug users, which would explain our finding that recreational drug users have a higher likelihood of misusing more than one illicit substance. A study reported that respondents who had experienced at least one major depressive episode in the past year were more likely to engage in non-medical use of prescription pain relievers (67). Providing support and resources for comorbid mental health concerns within this population may be an area that clinicians and policy makers should consider implementing within OUD treatment plans.

With the increased availability of prescription opioids contributing to the opioid epidemic, countries across the globe have taken initiatives to control access and prescribing patters of opioids. Some of these initiatives include legislative changes through guideline recommendations in opioid prescribing for chronic, non-cancer pain, acute pain conditions and prescription monitoring programs (42,68). Research examining these changes have suggested that there is a

decrease in opioid prescribing with these measures in place such as using the recommendation of nonsteroidal anti-inflammatory drugs (NSAIDs) over opioids for acute pain (68–72). These findings in combination with the ever-changing synthetic opioids drug market would suggest that is important to continue to tailor recommendations to fit the ever-changing opioid user.

These findings are important as they can help develop tailored MAT programs for patients. It may be important to consider comorbid medical conditions such as pain that may have led to being introduced to opioid by prescription or concurrent substance use when creating a treatment plan. This systematic review has highlighted that those introduced to opioids by prescription means are less likely to use other substances including opioids. This cohort of individual are most likely people that did not intend to engage in risk-taking behavior. They ended up dependent to opioids because of the associated addictive properties. They may benefit from being treated in different settings and with the use of different approaches to addiction philosophy. Addiction specialists should consider addressing harm reduction strategies such as hepatitis C treatment awareness and provision of clean needles to those still engaging is IV drug use while in treatment. Pain specialists and pharmacists may want to consider including a brief educational component and treatment plan to mitigate problematic use potential surrounding opioids when prescribing opioids to a patient is necessary. Additionally, those who were introduced through recreational means likely have a different set of problems to address than those whose use began with prescriptions. Perhaps there should be additional support provided for patients that desire to stop using additional substances alongside illicit opioids. The current lack of data present on poly-drug use, the associated risks and individual goals is limited and should be expanded on in

order to develop personalized support for poly-drug users. Some research has predicted that the increased strictness of prescribing opioids will not have a huge impact on the number of opioid overdoses and deaths (73). Targeting illicit opioid use in treatment is where focus should also be.

Policy makers may want to provide different treatment settings for OUD patients and, by identifying patients with high risk behaviour patterns who were introduced to opioids recreationally, can take advantage of opportunities for interventions to reduce patients' hazardous use of other substances. It is also important to address the lack of information on the emergence of novel opioid substances and their apparent popularity with illicit opioid users as it limits the level of insight current literature can provide to drug addiction services and clinicians. Due to the lack of information on current opioid related changes future directions may include updating this paper to possibly highlight novel data on poly-drug use and opioid derivatives. Furthermore, due to the extended focus on North American and Australian data present in this paper future studies could explore ethnic and socioeconomic differences present in method of introduction to opioids.

4.5.2 Strengths and Limitations

This systematic review has some clear strengths, with the most notable being the methodological strengths. Firstly, this is the first systematic review to our knowledge that compares the method of introduction to opioids and treatment outcomes in OUD patients while in MAT. We were able to conduct six different meta-analyses on illicit opioid use, cocaine use, alcohol use, cannabis use, benzodiazepine use, and injection drug use. We employed rigorous screening methods to ensure all possible studies were included. Additionally, we presented our findings in a qualitative

and quantitative method. Despite having a small number of studies included, the heterogeneity of the meta-analyses was less than 40%.

As with most systematic reviews, ours is not without limitations. The first limitation is that we were not able to conduct adjusted analyses. Unfortunately, not all the studies adjusted for confounding variables, which necessitates a more cautious interpretation of the findings. It is also important to mention that the included studies are before 2018, which may limit the impact of findings on the current opioid climate. Also, the analysis conducted was focused on North American or Australian data (the most available data), which minimizes the generalizability of the findings. We were also unable to conduct any analysis to detect publication bias due to a paucity of included studies. There is a lack of research on examining treatment outcome differences by the method of introduction to opioids as well as limited data on novel opioids and fentanyl derivatives. There is a need to not only to continue to examine this association through additional primary studies, but to also to investigate whether the type of opioids initially prescribed has ramifications on the risk of subsequently developing OUD. Additionally, standard urine screens may not be able to detect novel opioid. However, regardless of being able to detect novel opioids, our results did find a significant association for illicit opioid use and method of introduction to opioids. This finding may be a moderate estimation of the association and the actual association may be greater.

4.6 Conclusion

This review highlights the differences found in illicit opioid use, cocaine use, alcohol use, injection drug use and cannabis use in found in the cohort of patients that were introduced to

opioids through a legitimate prescription and those introduced to opioids by recreational means. These differences are important for health policy makers and can help shape the success of these patients through further investigation.

Conflict of Interest

The authors declare that they have no competing interests.

Author Contributions

NS: contributed to the conception and design of the study, search strategy, screening and data extraction, analysis of results manuscript writing and final review of the manuscript. MB contributed to the conception and design of the study, screening and data extraction, analysis of results and critical revision and final review. NS, BP, AD, MT, HS, AH, NB, VR, DS, MB, EL: contributed to the methodological design, manuscript writing, critical revision and final review of the manuscript. RD, MCS, LT: contributed to the methodological design, critical revision and final review of the manuscript. SS: contributed to the development of the search strategy and final review of the manuscript. ZS: contributed to the conception and design of the study, critical revision and final approval of the manuscript. All authors read and approved the final manuscript.

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None.

Data Availability Statement

The datasets analyzed for this study can be available upon request.

4.7 Tables and Figures

4.7.1 Summary of Findings

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Prescription opioid**	**Illicit opioid introduction**	**Relative (95% CI)**	**Absolute (95% CI)**		
Illicit opioid use												
3	observational studies	not serious	not serious	not serious	serious [a]	strong association	339/691 (49.1%)	309/709 (43.6%)	OR 1.42 (1.01 to 2.00)	**87 more per 1,000** (from 2 more to 171 more)	⊕⊕◯◯ LOW	CRITICAL
Marijuana use												
3	observational studies	not serious	not serious	not serious	serious [a]	strong association	399/651 (61.3%)	258/540 (47.8%)	OR 1.87 (1.12 to 3.12)	**153 more per 1,000** (from 28 more to 263 more)	⊕⊕◯◯ LOW	IMPORTANT
Cocaine use												
3	observational studies	not serious	not serious	not serious	serious [a]	strong association	175/651 (26.9%)	91/540 (16.9%)	OR 2.01 (1.17 to 3.46)	**121 more per 1,000** (from 23 more to 244 more)	⊕⊕◯◯ LOW	IMPORTANT
Any injection drug use												
2	observational studies	not serious	not serious	not serious	serious [a]	very strong association	122/167 (73.1%)	32/81 (39.5%)	OR 4.07 (2.31 to 7.15)	**332 more per 1,000** (from 206 more to 429 more)	⊕⊕⊕◯ MODERATE	IMPORTANT
Alcohol Use												
2	observational	not ser	not serious	not serio	serious [a]	none	259/607	185/509 (36.3%)	OR 1.34 (1.05 to	**70 more per 1,000**	⊕◯◯◯ VERY LOW	IMPORTANT

	studies	ious		us			(42.7 %)		1.71)	(from 11 more to 131 more)		
Benzodiazepine Use												
2	observational studies	not serious	not serious	not serious	serious [a]	none	73/551 (13.2 %)	53/500 (10.6%)	OR 1.21 (0.79 to 1.86)	**19 more per 1,000** (from 20 fewer to 75 more)	⊕◯◯◯ VERY LOW	IMPORTANT

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

Explanations

a. Imprecise as adjusted pooled estimates were not possible to conduct.

4.7.2 Summary of Characteristics

Study	Country	Study Design and type of opioid substitution treatment	Participants (sample size in each group, age range, sex, inclusion/exclusion criteria, primary diagnosis)	Physicians prescription and recreational use Definitions	Outcomes (definition and how they were measured)	Statistical Analysis	Results
Canfield, 2010	United States	Cross-sectional Type of OST: N/A (patients	N = 75 (physician prescription: n = 31, Illicit opioid: n = 44)	Physician prescription: participants who reported that	Collected self-report data related to participant demographics, socio-economic	Fisher exact test for between group comparisons	First-time licit users were about 5 years older; more likely to have a college degree; more likely to have health insurance; less likely to have ever used marijuana [27/31 (87%)

		recruited from inpatient detoxification unit)	Mean age (range): 31.5 (18–70) Sex: 49 male (65%), 26 female (35%) Inclusion criteria: met DSM-IV criteria for opiate dependence, wished to become abstinent from opioids, at least 18 years old, able to understand spoken English, able to provide informed consent, had urine toxicology positive for opiates on day of admission Exclusion criteria: none (other than patient refusal)	their addiction began with opioids that were prescribed for them (i.e., licit use) Recreational use: participants who traced the onset of their addiction to either diverted prescription medications or from "street drugs" (i.e., illicit drug use)	characteristics, age of first opioid use, types of opioids preferred, routes of administration, how participants first began using opioids, and how their use progressed over time	of categorical variables; Student t-test for between group comparisons of continuous variables	vs. 44/44 (100%) p=0.026]; less likely to have used drugs via an intranasal or intravenous route; less likely to have past legal problems, prior arrests, misdemeanor convictions, and felony convictions; and less likely to report heroin as their current drug of choice [9/31 (29%) vs. 28/44 (64%) p=0.005]
Cooper, 2018	Australia	Prospective cohort Type of OST: not reported	N = 108 (physician prescription: n = 41, illicit opioid: n = 67) Mean age: 41 (range not reported) Sex: 52 male (48%), 56 female (52%)	Participants were classified as having 'iatrogenic dependence' if their first opioids of concern were prescribed	Collected self-report data on participants' current physical health, opioid use history (including past month medical and illicit opioid use as well as lifetime use of heroin), injection	χ^2 tests, independent *t*-tests, and Mann-Whitney *U* tests used to examine baseline differences between those who	No significant difference between iatrogenic dependence vs. non-iatrogenic dependence in unsanctioned opioid use in the past month [19.5% vs. 25.4%, odds ratio 0.71, 95% CI (0.28,1.84)] Iatrogenic dependence associated with a lower prevalence of lifetime heroin use [40% vs. 67.2%, odds ratio 0.31, 95% CI (0.14,0.70)] and

			Inclusion criteria: had entered treatment for pharmaceutical opioid dependence, were competent in English Exclusion criteria: not reported	by a doctor for a legitimate medical reason	drug use history (including heroin, non-medicinal / non-prescribed opioids, methamphetamine, cocaine, ecstasy, cannabis, alcohol, tobacco, non-medicinal / non-prescribed benzodiazepines, hallucinogens, and other), and mental health	initiated opioid use for iatrogenic and non-iatrogenic reasons	injection of any drug [41.5% vs. 68.7%, odds ratio 0.32, 95% CI (0.14, 0.73)]
Dreifuss, 2013	United States	Cross-sectional Type of OST: sublingual buprenorphine / naloxone	N = 360 (physician prescription: n = 199, illicit opioid: n = 117) Mean age: 32.5 (range not reported) Sex: 209 male (58%), 151 female (42%) Inclusion criteria: met DSM-IV criteria for current opioid dependence; were at least 18 years old; unsuccessful in Phase 1 of POATS study (returned to opioid use) and	Physician prescription: first obtained opioids via a legitimate prescription Recreational use: given their first opioids by a family member or friend, or initially bought them from a drug dealer	Pain and Opiate Analgesic Use History administered at baseline to assess opioid use history Substance Use Report (corroborated by weekly urine drug screens) administered weekly during treatment and every two weeks during follow-up as primary measure to determine "successful outcome" in Phase	Bivariate analyses compared patients who were successful at end of treatment with those who were not; continuous variables assessed with independent t-tests, dichotomous variables with chi-square tests; multivariate logistic	Having a legitimate prescription as the first source of opioids was associated with successful treatment whereas obtaining opioids from a drug dealer or another non-medical source was associated with unsuccessful outcome

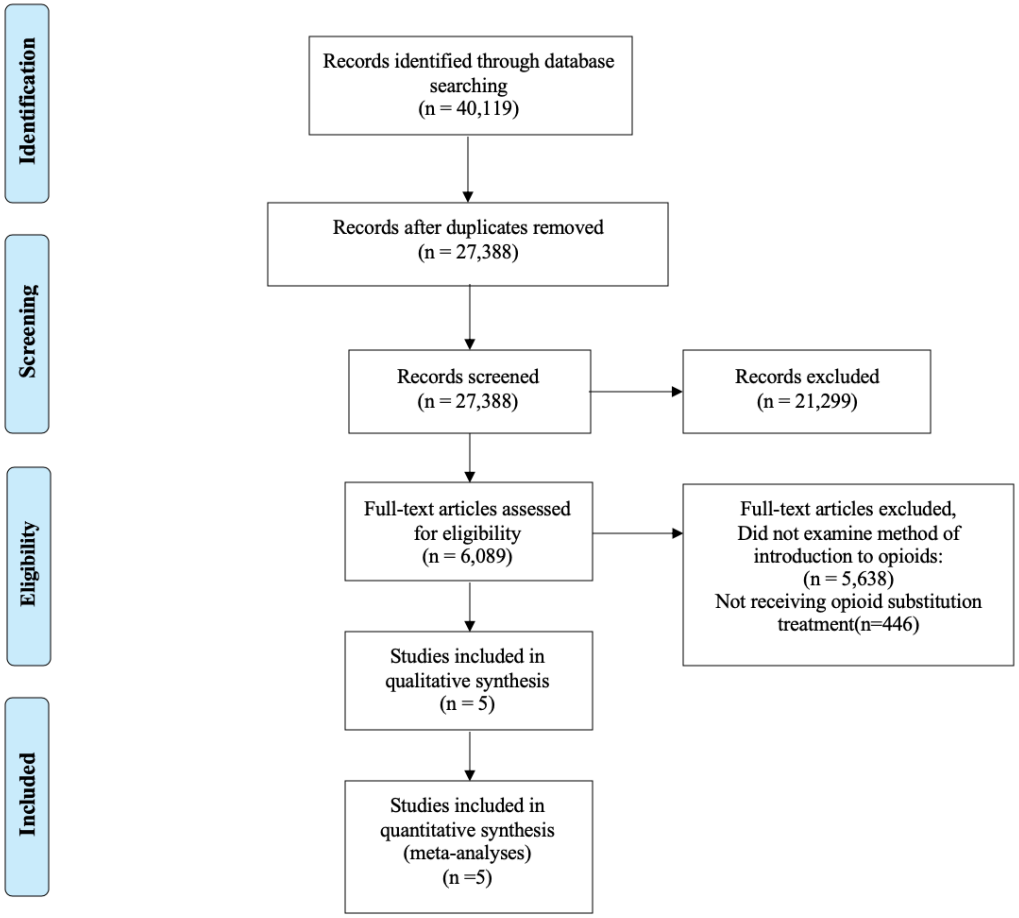
			subsequently enrolled in Phase 2 Exclusion criteria: heroin use on ≥ 4 days in past month; lifetime diagnosis of opioid dependence due to heroin alone; history of ever injecting heroin; concurrent formal ongoing substance abuse treatment		2 (abstinence from opioids during final week of treatment and ≥2 of 3 weeks prior)	regression models assessed relative contribution of baseline predictors when examined in combination with other variables	
Sanger, 2018	Canada	Prospective Cohort Type of OST: methadone maintenance treatment	N = 976 (physician prescription: n = 469, illicit opioid: n = 507) Mean age: 40.8 in physician prescription group, 36.9 in illicit opioid group (ranges not reported) Sex: 535 male (54.8%), 441 female (45.2%) Inclusion criteria: over 18 years of age; met DSM-IV criteria for opioid dependence (modified in DSM-	Physician prescription: initial exposure to opioids through a medical prescription Recreational use: initial exposure to opioids through other means including at home, family member, street, school, or friend	Maudsley Addiction Profile (MAP) administered to measure health and social functioning, including specific details of self-reported drug use (e.g. number of times drug was used within past 30 days, typical dose, route of administration) Illicit opioid use measured by regular urine drug screens at baseline and 6-month	Multivariable logistic regression used to examine relationship between socio-demographic factors, health functioning, and illicit drug use in relation to source of initial opioid use	Women were more likely to be initiated to opioids via prescription (OR = 1.385, 95% CI 1.027-1.866, P = .033) Those initiated via prescription were more likely to have post-secondary education, older age of onset of opioid use, less likely to have hepatitis C, and less likely to have used cannabis Chronic pain significantly associated with initiation to opioids through prescription (OR = 2.720, 95% CI 1.998-3.722, P < .0001) Men initiated by prescription were less likely to have liver disease and less likely to use cannabis, while women initiated by prescription had a higher methadone dose

			5 to opioid use disorder); on methadone maintenance treatment; able to provide informed, written consent, undergo urine drug screens, and provide information on source of initiation to opioids Exclusion criteria: receiving an alternate opioid substitution therapy; currently taking prescription opioids; currently on suboxone; unable to provide a urine sample		follow-up		
Tsui, 2010	United States	Cross-sectional Type of OST: buprenorphine	N = 140 (physician prescription: n = 40, illicit opioid: n = 100) Mean age: 38 (range not reported) Sex: 106 male (76%), 34 female (24%) Inclusion criteria: age 18–65; DSM-	Participants' responses to the question: "Who introduced you to opiates?" (possible responses included physician, sexual partner, friend,	Collected self-report data on current (last 30 days) and past use of prescription opioids and heroin (including route of administration) using Addiction Severity Index (ASI) Collected self-report data on	Descriptive analyses comparing individuals who reported physician introduction to opioids to those who did not report physician introduction; examined differences in	No significant differences in gender, age, race, marital status, employment, or insurance status among individuals who did and did not report being introduced to opioids by a physician Participants introduced by physician were more likely to be currently using prescription opioids only, less likely to have injected drugs (38% vs. 76%, $p<0.01$), half as likely to currently inject drugs (28% vs. 57%, $p<0.01$), and

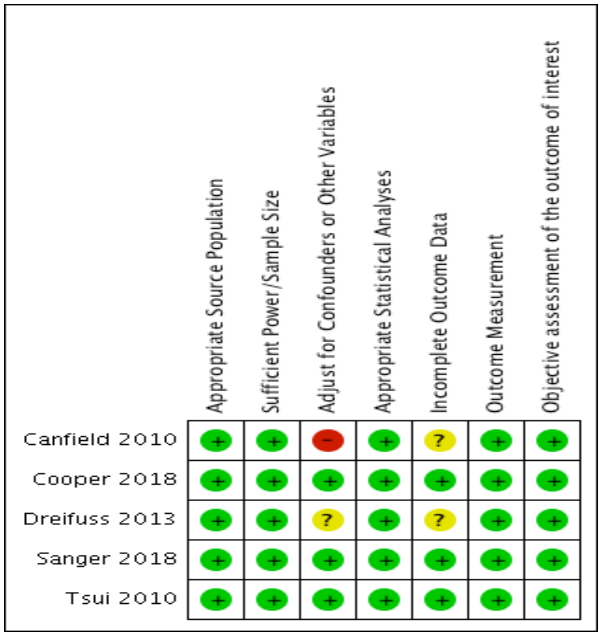
			IV diagnosis of opioid dependence; Hamilton Depression Revised Scale (MHDRS) score > 14; absence of significant suicidal ideation; willingness and ability to complete 3-month treatment with buprenorphine; no history of severe mental illness (bipolar disorder, schizophrenia, schizoaffective, or paranoid disorder); no currently prescribed medications for depression (participants not specifically excluded if taking tricyclic anti-depressant only for pain); ability to complete the study assessment in English Exclusion criteria: NR	family member, stranger, and no one)	regular use of alcohol, marijuana and cocaine by asking, "Prior to starting opiates, did you ever have daily or regular use of (drug)?"	demographic, clinical, and substance use-related variables between participants using Student t-tests and Pearson chi-square tests	significantly less likely to report prior use of marijuana (53% vs. 72%, p=0.03) and cocaine (23% vs. 45%, p=0.01) Regular use of alcohol prior to starting opioids was equally reported among those who were and were not introduced by a physician to opioids

4.7.3 PRISMA flow diagram

Figure 1. Prisma Flow Diagram



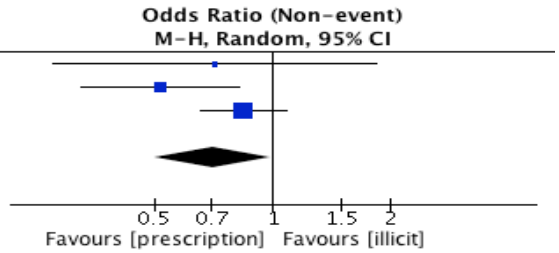
4.7.4 Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



4.7.5 Forest Plot for Illicit Opioid Use

Study or Subgroup	Illicit opioids Events	Total	Prescription opioids Events	Total	Weight	Odds Ratio (Non-event) M-H, Random, 95% CI
Cooper 2018	17	67	8	41	11.2%	0.71 [0.28, 1.84]
Dreifuss 2013	72	117	90	199	32.4%	0.52 [0.32, 0.82]
Sanger 2018	250	507	211	469	56.4%	0.84 [0.65, 1.08]
Total (95% CI)		**691**		**709**	**100.0%**	**0.70 [0.50, 0.99]**
Total events	339		309			

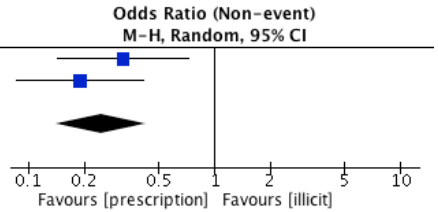
Heterogeneity: Tau² = 0.04; Chi² = 3.28, df = 2 (P = 0.19); I² = 39%
Test for overall effect: Z = 2.01 (P = 0.04)



4.7.6 Forest Plot for Any Injection Drug Use

Study or Subgroup	Illicit opioids Events	Total	Prescription opioids Events	Total	Weight	Odds Ratio (Non-event) M-H, Random, 95% CI
Cooper 2018	46	67	17	41	48.7%	0.32 [0.14, 0.73]
Tsui 2010	76	100	15	40	51.3%	0.19 [0.09, 0.42]
Total (95% CI)		**167**		**81**	**100.0%**	**0.25 [0.14, 0.43]**
Total events	122		32			

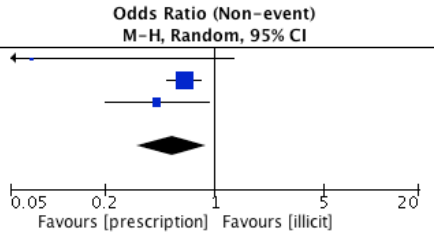
Heterogeneity: Tau² = 0.00; Chi² = 0.86, df = 1 (P = 0.35); I² = 0%
Test for overall effect: Z = 4.88 (P < 0.00001)



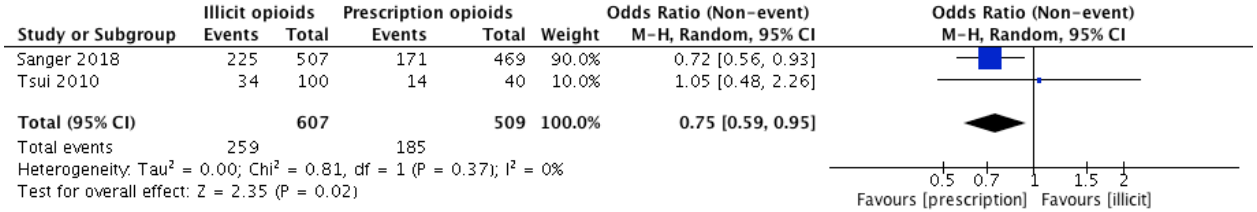
4.7.7 Forest Plot for Cannabis Use

Study or Subgroup	Illicit opioids Events	Total	Prescription opioids Events	Total	Weight	Odds Ratio (Non-event) M-H, Random, 95% CI
Canfield 2010	44	44	27	31	2.9%	0.07 [0.00, 1.33]
Sanger 2018	283	507	210	469	67.9%	0.64 [0.50, 0.83]
Tsui 2010	72	100	21	40	29.2%	0.43 [0.20, 0.92]
Total (95% CI)		**651**		**540**	**100.0%**	**0.54 [0.32, 0.89]**
Total events	399		258			

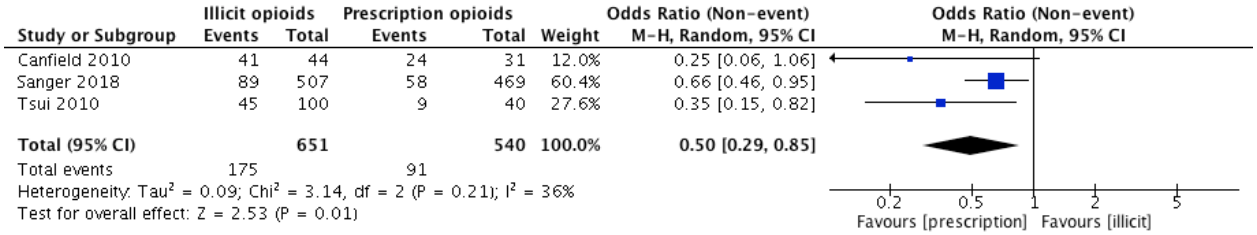
Heterogeneity: Tau² = 0.08; Chi² = 3.07, df = 2 (P = 0.22); I² = 35%
Test for overall effect: Z = 2.39 (P = 0.02)



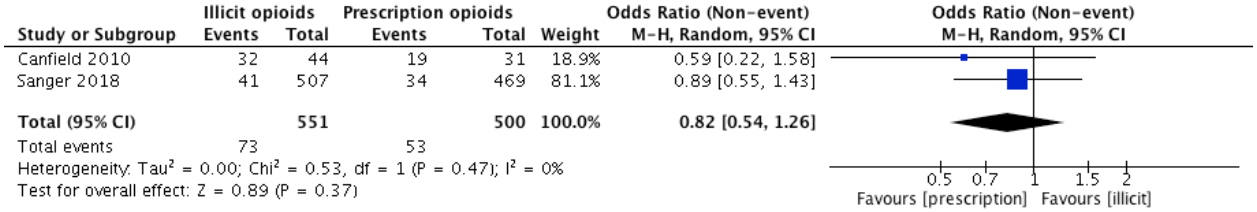
4.7.8 Forest Plot for Alcohol Use



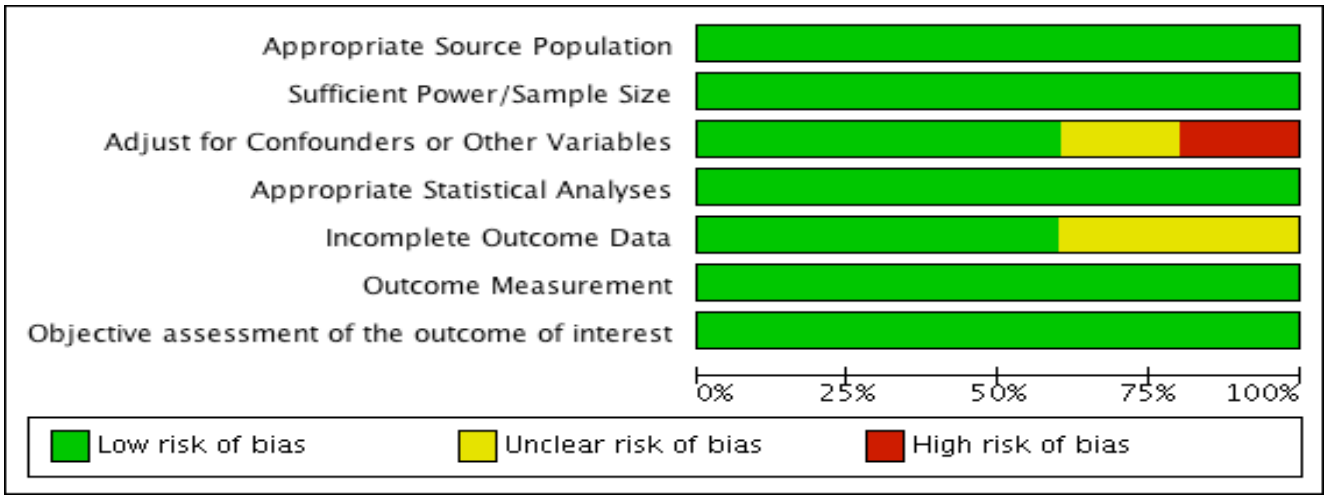
4.7.9 Forest Plot for Cocaine Use



4.7.10 Forest Plot for Benzodiazepine Use



4.7.11 Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



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5 CHAPTER 5

Association between Socio-Demographic and Health Functioning Variables among Patients with Opioid Use Disorder Introduced by Prescription: A Prospective Cohort Study

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5.1 Abstract

Background: Prescription opioid misuse in Canada has become a serious public health concern and has contributed to Canada's opioid crisis. There are thousands of Canadians that are currently receiving treatment for opioid use disorder, which is a chronic relapsing disorder with enormous impact on individuals and society.

Objectives: The aim of this study was to compare the clinical and demographic differences between cohort of patients that were introduced to opioids through a prescription and those introduced through non-medical purposes.

Study Design: This was an observational, prospective cohort study.

Setting: The study took place in 19 Canadian Addiction Treatment Centres across Ontario.

Methods: We included a total of 976 participants that were diagnosed with Opioid Use Disorder and currently receiving methadone maintenance treatment. We excluded participants that were on any other type of prescription opioid or were missing their 6-month follow up urine screens. We measured the participants initial source of introduction to opioids along with other variables using the Maudsley Addiction Profile. We also measured illicit opioid use using urine screens at baseline and at 6-months follow-up.

Results: Almost half the sample(n=469) were initiated to opioids via prescription. Females were more likely to be initiated to opioids via a prescription (OR = 1.385, 95% CI 1.027, 1.866, p = 0.033). Initiated via prescription were also more likely to have a post-secondary education,

have an older age of onset of opioid use, less likely to have hepatitis C and use cannabis. Chronic pain was significantly associated with initiation to opioids through prescription (OR = 2.720, 95% CI 1.998, 3.722, $p < 0.0001$). Analyses by sex revealed that males initiated by prescription were less likely to have liver disease and less likely to use cannabis while females initiated by prescription had a higher methadone dose.

Limitations: This project was limited by its study design being observational in nature, no causal relationships can be inferred. Also, the data could not determine to what degree the prescribed opioids played in developing opioid use disorder.

Conclusions: Our results have revealed that almost half of this MMT population has been introduced to opioids through a prescription. Given that the increasing prescribing rates of opioids has an impact on this at-risk population, alternative treatments for pain should be considered to help decrease this opioid epidemic in Canada.

Keywords: opioid use disorder, chronic pain relief, methadone maintenance treatment, prescriptions, male, female

5.2 Introduction

In 2015, a report conducted by the United Nations Office of Drugs and Crime reported that approximately 32 to 36 million people worldwide abuse opioids (1). Opioids are the leading cause of drug-linked death worldwide and are an even bigger concern for North America (2,3). Recent research has shown that this surge in illicit use is associated with the availability of opioids through medical prescriptions (4). Opioid use disorder (OUD) is a chronic, relapsing disorder that is categorized by serious psychological, social, and physical adversities (5). Negative consequences that may result from OUD include increased risk of infection and death, poly-substance use, psychiatric comorbidity, as well as criminal activity (5–7). OUD also creates an economic toll on the healthcare system, specifically due to the high costs linked to managing the disorder (8). In 2015, it was estimated that treatment for OUD in methadone clinics in Ontario alone cost $156 million (8,9).

Ontario has experienced an unprecedented increase in the number of patients undergoing methadone maintenance treatment (MMT) for OUD in the last 10 years, with over 50,000 individuals reported to be in MMT programs in 2016(6,8). While MMT may be successful in treating OUD in some patients (10–12), treatment outcomes are highly variable, with several patients exhibiting poor health and social functioning, and continuing use of illicit substances (7). The majority of the research conducted in the MMT population has been focused on heroin and street users and fails to compare them to cohort of patients that were initiated to opioids via prescription. Differentiating between patients with prescription influenced OUD and non-medically influenced OUD is important for establishing a socio-demographic profile and unique risk factors for treatment failure in this population. Few studies have looked at the MMT population and dichotomized the study population by source of initiation to opioids. With recent

research also finding that there is now an increase in females misusing opioids with 52% of women and 38% of men seeking treatment having first been exposed to opioids through a prescription (13), an investigation into sex differences is also warranted.

The objective of this study was to investigate clinical and socio-demographic differences of patients with OUD who were introduced to opioids via prescription compared to those who obtained opioids by other means (i.e. family, friends, street). We also aimed to examine sex differences between the two groups, which to our knowledge has not been done before.

5.3 Participants and Study Design

The data for this study was obtained from a larger project called the Genetics of Opioid Addiction (GENOA) study program, which is an ongoing multicentre cohort in collaboration with the Populations Genomics Program at McMaster University and Canadian Addiction Treatment Centres (CATC)(14). Participants were recruited from nineteen different CATC clinics across Ontario through May 2013 and November 2016. This project was approved by the Hamilton Integrated Research Ethics Board (HIREB; Study ID 11-056).

To be eligible for GENOA, patients had to meet the following inclusion criteria: be over 18 years of age, meet the criteria for opioid dependence using the DSM-IV criteria (modified in DSM-5 to opioid use disorder), on methadone maintenance treatment, were able to provide informed, written consent, and urine drug screens. In addition, for this study participants also had to provided information on source of initiation to opioids. Subjects that were receiving an alternate opioid substitution therapy, currently taking prescription opioids, currently on suboxone® or unable to provide a urine sample were excluded from this study (Fig 5.7.1).

Eligible participants provided informed consent and conducted a structured face-to-face interview at baseline, during which they were asked to provide basic demographic information and were asked questions on health and social functioning. Specifically, the data collected consisted of information on socio-demographics, family background, psychiatric background, and details on drug use. Details of illicit opioid use were collected through regular urine drug screens. Details of illicit opioid use collected at baseline and followed up at 6-months.

5.3.1 Measures

All study participants were asked about the initial source of through which they were introduced to opioids (i.e. physician prescription, family, street) and this information was recorded on case report forms. For this study, this variable was dichotomized into prescribed opioids (initial exposure to opioids through a medical prescription) and illicit opioids (initial exposure to opioids was through other means including at home, family member, street, school or friend). Demographic information including age of onset of opioid use, methadone dose, treatment duration, education and employment status were also collected.

The Maudsley Addiction Profile (MAP) was administered to measure health and social functioning (15). Within the MAP, specific details of self-reported drug use were collected that looked at the number of times the drug was used within the past 30 days, typical dose and the route(s) of administration. The illicit drugs included heroin, cocaine, illicit methadone, benzodiazepines, amphetamines and cannabis. The same information about alcohol use was also collected. The MAP also collected medical history, which asked if the patient has been diagnosed with the following physical health conditions: HIV, hepatitis, chronic pain, liver disease, diabetes and epilepsy.

Illicit opioid use was measured by regular urine drug screens and reported as the percentage of positive opioid screens (positive opioid screens divided by total urine screens). Illicit opioid use was measured at baseline and at 6-months follow-up.

5.3.2 Statistical Analysis

To summarize the demographic data of the study population, descriptive statistics were used. The continuous variables are demonstrated as means and standard deviations, while dichotomous variables are depicted as percentages.

The primary analysis studied the relationship between socio-demographic factors, health functioning and illicit drug use in relation to source of initial opioid use conducted using a multivariable logistic regression. Covariates included age, sex, methadone dose and treatment duration. The variables of ethnicity, marital status, education, and drug use (heroin, cocaine, illicit methadone, alcohol, benzodiazepines and amphetamines) were transformed into dichotomous variables. Ethnicity was categorized as Caucasian and other. Education was categorized as high school or less and post-secondary education (trade school/college/university/postgraduate). Marital Status was grouped into currently with a partner (currently married/common-law) or no current partner (never married/separated/divorced/widowed). Drug use was categorized as any drug use within the past 30 days or no drug use. A secondary analysis which looked at sex differences was conducted using the same model, variables and covariates.

The data analysis was conducted using IBM SPSS Version 23(16). The results reported a 95% confidence interval, adjusted odds ratio and the alpha level of significance was set to a= 0.05 for the primary analysis. For the secondary analysis looking at sex differences within men and

women, an alpha of a=0.025 was set. Collinearity was considered by looking at the variance inflation factor (VIF) and none of the variables had a VIF of 10 or greater. This study adheres to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)(17). Sample size was calculated by using the logistic regression rule of having at least 10 events per predictor variable (18). This rule was satisfied, as we included 976 participants in the primary regression with 23 predictors. In the secondary analysis, we included 441 females and 535 males with 22 predictors each.

5.4 Results

A total of 1390 participants were potentially eligible for this study. A total of 82 participants were excluded, as they were on suboxone®, and 57 participants were excluded, as they were taking additional prescribed opioids. Additionally, 21 participants were excluded for missing data on initial opioid exposure and 254 participants were missing data on their 6 months' urine screens. A final number of 976 participants were included in the analysis (Fig. 5.7.1).

Demographics

Our sample included a comparable number of prescription initiated to opioids (n = 469) to illicit opioids (n = 507). Approximately half of all prescribed opioid participants were females (51.0%), which was considerably higher in comparison to the illicit opioids group (39.8%). The prescribed opioids group's average age of onset of opioid was 27.4 (SD=8.87), which was greater than the illicit opioids group mean age of 23.1 (SD=8.04). The average daily methadone dose for prescribed opioid-users was 78.2 mg (SD = 41.8), which was marginally greater than the average dose of 74.1 mg (SD = 46.0) for the illicit opioids group. The prescribed opioids

group also had approximately twice as many participants experiencing chronic pain (51.8%) in comparison to the illicit opioids group (25.6%). We had a total of 0.9% of participants with HIV in the prescription initiated and 0.2% in the illicit means group. With these numbers being very small, we had to remove from the primary and secondary analyses. A complete summary of demographic and clinical characteristics comparing prescribed opioid-users and illicit opioid-users are reported in Table 5.7.2.

5.4.1 Primary Analysis

The results of the multivariable logistic regression for the association between source of opioid initiation and other socio-demographic and health functioning variables are provided in Table 5.7.2. There was a significant association between being female and being initiated to opioids via prescription, after adjusting for current age, methadone dose, and treatment duration (OR = 1.385, 95% CI 1.027,1.866,p = 0.033). Education was found to be significantly associated with being initially prescribed opioids, suggesting that participants in the prescribed group were more likely to have a post-secondary education in comparison to the illicit opioids group (OR = 1.71, 95% CI 1.23, 2.38, p = 0.002). Participants that were initiated to opioids via prescription were almost 3 times as likely to have been diagnosed with chronic pain (OR = 2.72, 95% CI 1.97, 3.75, p <0.001). Age of onset of opioid use was significantly higher in those introduced to opioids through a prescription (OR = 1.05, 95% CI 1.03, 1.08, p < 0.001). Participants that had been introduced to opioids through medical means were less like to have prevalent hepatitis (OR = 0.64, 95% CI 0.44, 0.94, p = 0.022), and were less likely to have used cannabis in the 30 days prior to enrolling in the study.(OR = 0.66, 95% CI 0.49, 0.90, p = 0.008).

5.4.2 Secondary Analysis

Our secondary analyses by sex looked at the relationship between source of opioid and a variety of variables (Tables 5.7.4 & 5.7.5). Similar to the primary analyses, chronic pain, education, and age of onset of opioid use had an association with initiation to opioids via prescription for both males and females. Males had an association between illicit opioid use and liver disease (OR = 0.32, 95% CI = 2.03, 4.81, p = 0.017). There was no significant association for continued illicit opioid use at 6-months for either males or females.

5.5 Interpretation

This prospective cohort study compared individuals in MMT that were initiated to opioids via medical prescription versus introduced through illicit means of opioids on social-demographic characteristics, health functioning and continued illicit substance use. Almost half of the sample was introduced through a medical prescription (n=469) and were more likely to, have an older age of onset of opioid use, have a post-secondary education, be female and were less likely to use cannabis. We also found that the prescription-initiated group was less likely to have hepatitis C and more likely to have chronic pain. When we explored these differences by sex, we found that the male prescription group had a lower prevalence of liver disease and cannabis use. Females initiated through a prescription were less likely to have hepatitis and more likely to have a higher methadone dose.

Our findings highlight important distinguishing characteristics for the prescription-initiated group, consistent with the literature. The literature has suggested that increased physician-prescribing of opioids, there has been a rise in older age patients misusing opioids (19–21). Opioids are most commonly prescribed for chronic, non-cancer pain conditions (19,21)

typically prevalent among older adults, such as low back pain, arthritis and fibromyalgia (22,23). Some studies have suggested up to 60% of chronic pain patients are at a high risk for prescription misuse (24). The prescription-initiated group was more likely to have a post-secondary education. There may be many factors influencing this but a significant one may be that the recreationally initiated group was younger at age of onset of opioid use and that the early start to recreational drug use may have influenced further education. Research has found that youth that begin to use heroin at a young age have significantly higher high school drop-out rates in comparison to the prescription-using group (25). Additionally, females are more susceptible to chronic pain for a variety of factors, including greater amounts of estrogen in comparison to males. Estrogen has been shown to increase pain sensitivity and the risk of developing inflammation-related diseases (23,26,27). Recent research shows that females are more likely to be prescribed painkillers such as Percocet®, OxyContin, and Vicodin with higher dosages in emergency settings (28). We found that females initiated by prescription were likely to have a higher methadone dose which has been shown to help with chronic pain as methadone is a synthetic opioid (29). There is stereotyping towards men which assumes that males are more likely to misuse substances (30) yet this may not hold true in the OUD population. There seems to be a selection bias with females who are older, more educated and have chronic pain that are likely to be prescribed an opioid yet have a likelihood of being diagnosed with OUD.

We found that those initiated to opioids through a prescription were less likely to have hepatitis C and less likely to use cannabis (31,32). In our analysis by sex, we also found that males initiated to opioids through a prescription were less likely to have liver disease. Injection drug use increases the likelihood of contracting hepatitis through the sharing of needles which significantly has a significant impact on the liver and as can using multiple substances (33–35).

Males introduced to opioids through a legitimate prescription were also less likely to use cannabis. Though we cannot infer any causal relationship from our results due to the cross-sectional nature of the study, this finding suggests that those who began opioid use through illicit means may require additional care to manage ongoing use of cannabis. Previous research has shown that it is important to manage cannabis use, as it is associated with ongoing opioid use during MMT among a subset of the population (36).

5.6 Limitations

This study is limited by the observational design, such that we cannot make any causal inferences about the association between the source of opioid use and health functioning. We also could not determine the extent of prescription opioids in developing opioid use disorder from our collected data. However, the concept of identifying the initial source of introduction to opioids is novel and to our knowledge no other study looking at a large MMT population has examined this. The information collected on illicit drug use was mainly reliant on self-report, thus susceptible to social desirability bias. In attempt to reduce this bias, all research assistants were trained to build rapport with the study participants and administer the questionnaire in a standardized manner.

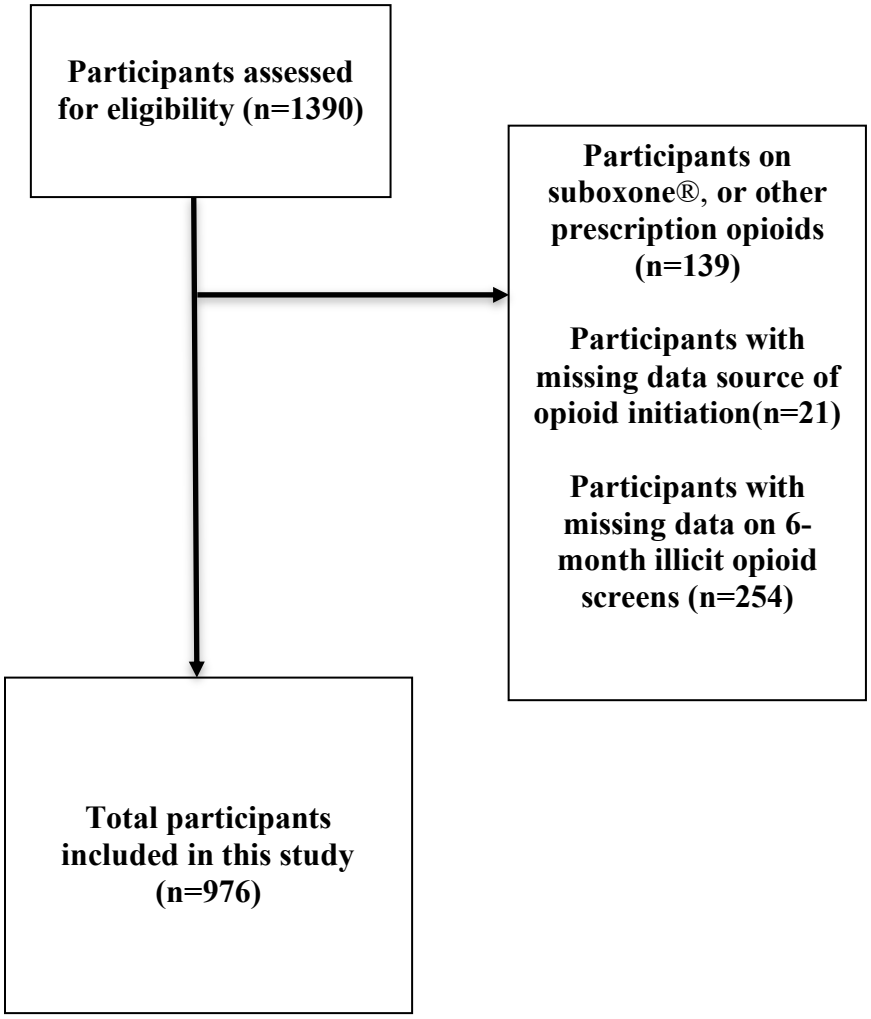
5.6.1 Conclusion

Few studies have compared functioning and treatment outcomes for MMT patients that were exposed to opioids by medical prescription versus recreational use. Our study shows important

differences exist between these groups of patients, including significantly greater comorbid chronic pain in the prescription opioid group, which has implications in developing specific treatment plans for these groups of patients. Given that approximately half of the MMT sample was initiated to opioids by a physician prescription, it is important to note the differences between this group of patients and those who obtained opioids by other means. Differences in education level, comorbid medical issues and concurrent substance use may be important to consider when developing treatment programs as well as specific goals of care for MMT patients. Many recent investigations, including our study, have shown the heterogeneity among the MMT patient population indicating a need for personalized care for these patients. The source of initial opioid use may be useful in clinical practice to promote discussion about specific concerns, such as hepatitis C treatment, concurrent substance use and chronic pain, and recommend appropriate harm reduction strategies to patients.

5.7 Tables and Figures

5.7.1 Flow diagram for eligibility and inclusion of participants



5.7.2 Demographic characteristics of study sample

Variables (n=976)	Prescribed Opioids	Illicit opioids
Total number of patients	469	507
Age (SD)	40.8(10.4)	36.9(11.2)
Sex, % female	51.0	39.8
Currently employed, n (%)	158 (33.7)	183 (36.1)
Marital status		
Never married (%)	177 (37.7)	270 (53.3)
Currently married/Common-law (%)	150 (32.0)	156 (30.8)
Separated/Divorced/Widowed(%)	142 (30.2)	81 (16)
Ethnicity		
Caucasian (%)	418 (89.1)	438 (86.4)
Native North American (%)	28 (6.0)	34 (6.7)
Other (%)	23 (4.9)	35 (6.6)
Level of Education		
None/Elementary School (%)	96 (20.5)	115 (22.7)
High school (%)	208 (44.3)	278 (54.8)
Trade school (%)	21 (4.5)	11 (2.2)
College/university (%)	140 (29.9)	98 (19.3)
Postgraduate (%)	2 (0.4)	2 (0.4)
Details of Opioid Use		
Age of onset of opioid use in years (SD)	27.4(8.87)	23.1(8.04)
Methadone treatment duration in months (SD)	51.3(49.2)	48.1(48.7)
Methadone dose in mg/day (SD)	78.2(41.8)	74.1(46.0)
Baseline Illicit Opioid Use, % positive screens	17.0	18.8
Medical history, %		
HIV	0.9	0.2
Hepatitis	21.7	28.8
Diabetes	6.2	4.9
Liver disease	4.1	6.1
Chronic pain	51.8	25.6
Epilepsy	2.1	2.0
Other*	52.9	40.2
Self-reported drug use at least once in past 30 days, %		
Heroin	5.8	12.8
Illicit methadone	1.3	1.2
Illicit benzodiazepine	7.3	8.0
Cocaine	12.4	17.5
Cannabis	44.7	55.8
Amphetamine	3.0	3.1
Alcohol	36.4	44.4

*The "other" category consisted of any other responses including the most common being hypertension, acid reflux, asthma, cancer, celiac disease, Crohn's disease, migraines, colitis, degenerative disc disease, hyperthyroidism, hypothyroidism, gout, heart murmur and ulcers.

5.7.3 Multivariable logistic regression analysis on factors associated with source of opioid initiation (N =976)

	OR	95% CI	P-VALUE
Age	1.008	0.988-1.027	0.443
Sex	1.385	1.027-1.866	0.033*
Currently Working	0.847	0.612-1.172	0.316
Methadone Dose (mg/day)	1.000	0.997-1.004	0.802
Treatment Duration	1.000	0.996-1.003	0.842
Currently Married/Common-law	1.108	0.746-1.389	0.909
Ethnicity	0.810	0.522-1.255	0.345
Education	1.765	1.278-2.437	0.001*
Age of opioid use onset	1.049	1.028-1.072	<0.001*
Epilepsy	1.252	0.471-3.326	0.653
Hepatitis	0.616	0.424-0.893	0.011*
Liver Disease	0.480	0.232-0.994	0.048
Chronic Pain	2.720	1.998-3.722	<0.001*
Diabetes	0.872	0.455-1.672	0.680
Other	1.213	0.902-1.632	0.201
Heroin	0.605	0.343-1.066	0.082
Illicit Methadone	1.251	0.483-3.242	0.605
Alcohol	0.838	0.622-1.128	0.244

Cannabis	0.671	0.501-0.900	0.008*
Benzodiazepine	1.106	0.671-1.821	0.694
Amphetamine	1.112	0.553-2.236	0.766
Cocaine	0.865	0.587-1.295	0.481
Illicit Opioid Use at 6 months (% positive screens)	1.112	0.510-2.427	0.789

Heroin, Illicit Methadone, Alcohol, Cannabis, Benzodiazepines, Amphetamine, Cocaine interpreted as a categorical variable consisting of two levels: no days drug used and used drug at least once in 30 days.
Ethnicity Interpreted as a categorical variable: Caucasian and Other
Marital Status interpreted as a categorical variable: Currently with a partner and currently not with a partner
*Significant at $p < 0.05$
OR odds ratio, *CI* confidence interval

5.7.4 Multivariable logistic regression analysis on factors associated with source of opioid initiation in females (n=441)

Females

	OR	**95% CI**	**P-VALUE**
Age	1.015	0.984-1.047	0.357
Currently Working	0.901	0.536-1.514	0.694
Age of opioid use onset	1.065	1.029-1.102	<0.0001
Methadone Dose (mg/day)	1.006	1.001-1.012	0.031
Treatment Duration	0.998	0.993-1.003	0.417
Epilepsy	1.545	0.408-5.855	0.533
Hepatitis	0.551	0.308-0.986	0.045
Liver Disease	1.149	0.346-3.817	0.821
Chronic Pain	2.267	1.381-3.719	0.001

Diabetes	0.477	0.184-1.236	0.128
Other	1.259	0.794-1.995	0.328
Ethnicity	0.959	0.508-1.809	0.897
Marital Status	1.035	0.641-1.673	0.888
Education	1.683	1.044-2.712	0.033
Alcohol	0.810	0.504-1.301	0.383
Heroin	0.401	0.135-1.187	0.099
Illicit Methadone	1.216	0.267-5.536	0.801
Benzodiazepine	1.271	0.561-2.879	0.565
Cocaine	0.677	0.364-1.259	0.218
Amphetamine	1.614	0.432-6.030	0.477
Cannabis	0.677	0.430-1.064	0.091
Illicit Opioid Use at 6 months (% positive screens)	0.375	0.099-1.416	0.148

Heroin, Illicit Methadone Alcohol, Cannabis, Benzodiazepines, Amphetamine, Cocaine interpreted as a categorical variable consisting of two levels: no days drug used and used drug at least once in 30 days.
Ethnicity Interpreted as a categorical variable: Caucasian and Other
Marital Status interpreted as a categorical variable: Currently with a partner and currently not with a partner
*Significant at $p < 0.025$
OR odds ratio, *CI* confidence interval

5.7.5 Multivariable logistic regression analysis on factors associated with source of opioid initiation in males (n =535)

Males

	OR	95% CI	P-VALUE

Age	1.003	0.977-1.030	0.829
Currently Working	0.751	0.505-1.208	0.267
Age of opioid use onset	1.045	1.016-1.074	0.002
Methadone Dose (mg/day)	0.997	0.992-1.002	0.197
Treatment Duration	1.002	0.997-1.006	0.463
Epilepsy	0.934	0.208-4.318	0.930
Hepatitis	0.721	0.431-1.206	0.212
Liver Disease	0.278	0.104-0.742	0.011
Chronic Pain	3.146	2.062-4.798	<0.0001
Diabetes	1.251	0.500-3.130	0.633
Other	1.196	0.798-1.796	0.386
Ethnicity	0.596	0.310-1.144	0.120
Marital Status	1.024	0.667-1.571	0.915
Education	1.941	1.221-3.085	<0.0001
Alcohol	0.875	0.586-1.305	0.512
Heroin	0.732	0.359-1.494	0.392
Illicit Methadone	1.097	0.280-4.298	0.894
Benzodiazepine	1.012	0.521-1.965	0.973
Cocaine	0.999	0.569-1.754	0.998
Amphetamine	0.817	0.344-1.943	0.648
Cannabis	0.646	0.428-0.974	0.037
Illicit Opioid Use at 6 months (% positive screens)	2.292	0.825-6.370	0.112

Heroin, Illicit Methadone Alcohol, Cannabis, Benzodiazepines, Amphetamine, Cocaine interpreted as a categorical variable consisting of two levels: no days drug used and used drug at least once in 30 days.
Ethnicity Interpreted as a categorical variable: Caucasian and Other

Marital Status interpreted as a categorical variable: Currently with a partner and currently not with a partner
*Significant at $p < 0.025$
OR odds ratio, *CI* confidence interval

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6 CHAPTER 6

The future of precision medicine in opioid use disorder: the inclusion of patient important outcomes in clinical trials

Running title: Patients' important outcomes in opioid addiction treatment

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6.1 Abstract

Opioid use has reached an epidemic proportion in Canada and the USA that is mostly attributed to excess availability of prescribed opioids for pain. This excess in opioid use led to an increase in the prevalence of opioid use disorder (OUD) that require treatment. The most common treatment recommendations include medication assisted treatment (MAT) combined with psychosocial interventions. Clinical trials investigating the effectiveness of MAT, however, have a limited focus on effectiveness measures that overlook patient important outcomes. Despite MAT, patients with OUD continue to suffer negative consequences of opioid use. There is a lack of inclusion of patients' goals and personalized medicine in clinical trials and guidelines thus missing an opportunity to improve prognosis of OUD by considering precision medicine in addiction trials. Patients with OUD receiving MAT (n= 2031, mean age 39.1 years (SD 10.7), 44% female) were interviewed to identify patients' goals for MAT. The results show the most frequently reported patient important outcomes were to stop treatment (39%) and avoid all drugs (25%). These results are inconsistent with treatment recommendations and trials' outcome measures. We discuss theses inconsistencies and make recommendations to incorporate these outcomes to achieve patient-centered and personalized treatment strategies.

Key words: opioid, outcomes, clinical trials, patient important

6.2 Introduction

Substance use disorder is a chronic and complex behaviour with multifaceted health and social consequences. Prescription opioid misuse has reached a public health crisis in the USA and Canada, with its reach spreading to other societies at a global level[1–3]. The root and progression of the opioid crisis in North America has been covered in all types of media as the opioid crisis has touched the lives of many; and its detrimental effects are seen daily in the form of increased mortality and healthcare utilization. In a recent outlook on the rationale for the opioid over-prescription patterns that started in the 1980s and have continued since, managing pain was the catalyst for the wide distribution of opioids, based on weak evidence contained in a letter to the editor published in the New England Journal of Medicine[4,5]. Nonetheless the rate of opioid prescribing and use continues to rise leading to an increased incidence of opioid use disorder (OUD). A report conducted by Substance Abuse and Mental Health Services Administration (SAMHSA) found that over 2.1 million people in the United States are suffering from an OUD related to prescription opioids[6].

OUD is a chronic, relapsing disorder that effects all aspects of an individual's life, ranging from physical, social and psychological aspects[7]. A central feature of OUD are the withdrawal symptoms that are experienced when opioids are abruptly stopped, or the dose is reduced. Examples of these symptoms are sweating, agitation, shakes and muscle pains[7]. Research has also suggested that the severity of withdrawal symptoms experienced may be associated with why patients who are receiving treatment for OUD relapse[8].

There are various treatment options available for OUD patients which are usually a combination of psychological and pharmacological interventions. The pharmacological intervention includes Medication Assisted Treatment (MAT) which can include opioid agonists, partial agonists and antagonists[9,10]. One of the most common types of MAT is methadone maintenance treatment (MMT). Methadone is a synthetic opioid that can have long-lasting effects for up to 24 hours[9] and helps to alleviate withdrawal symptoms usually without the euphoric effects associated with opioids[9]. While studies have shown that MMT is effective, there is still great variability in treatment response[11,12] and inconsistent outcome measures to assess the effectiveness of methadone[13].

As OUD can affect people in multiple ways including physical and mental health, social impact, economic burden, quality of life and life expectancy, it is therefore difficult to identify which of these aspects clinical trialists, healthcare services and providers should focus on when developing treatment programs. There are many challenges to consider when deciding on selecting an outcome measure for a chronic disorder with multifaceted impact such as OUD. There is also a need to consider what patients wanted as a successful and desirable treatment outcome for them to ensure better prognosis and personalized medicine approach. More specifically, the challenges that need to be addressed include how a personalized medicine approach impacts MAT clinical trials and guidelines recommendations. Important questions to consider in regard to this challenge include: what is an outcome of treatment success, and who selects the desired outcome? How should treatment programs be evaluated? What is the best use of limited healthcare and social services resources in managing OUD? How do personal characteristics affect

treatment outcomes? And finally, how might addressing these challenges may support precision medicine practice in addiction clinical trials?

Guidelines for the management of OUD make recommendations for treatment based on findings from clinical trials, experts' opinions and literature review. Guidelines strongly recommend the use of MAT to reduce opioid use and/or retain patients in treatment[14]. These strong recommendations and the selected outcomes do not consider patient important goals or different socio-demographic profiles of patients. Thus, these guidelines present a notion that the same treatment is recommended for every patient. Although these recommendations and treatment outcomes are important and reduce harm for many patients with OUD, there remains an important aspect of patients' relevant treatment goals, such as the focus on personalized treatment, that is not being considered in current evidence-based practice.

The overwhelming variation in the selection of MAT outcomes in trials, as well as the lack of inclusion of patient important outcomes in current guidelines, demand further research to establish a set of treatment outcomes that considers patients' goals and preferences. This will allow future trials to measure the effectiveness of MAT and tailor treatment recommendations based on personalized profiles to improve OUD prognosis and move towards precision medicine in MAT clinical trials.

6.2.1 Objectives

The objectives of this study were to:

1. Identify treatment goals of patients with OUD receiving MAT
2. Investigate if there are differences in patient reported treatment goals by age, sex,

gender, ethnicity, employment, treatment duration and type of treatment received

Our ultimate purpose of the study is to provide suggestions for the inclusion of patients' goals (patient important outcomes) in clinical trials to promote the use of precision medicine in managing OUD.

6.3 Methods

This is a mixed methods study using qualitative and quantitative data collection and analyses.

6.3.1 Eligibility Criteria

Participants were eligible for this study if they were 16 years of age or older, if they fulfilled the DSM-5 criteria for OUD, were receiving MAT for OUD at the time of recruitment and provided written informed consent.

6.3.2 Data Collection

Data were part of a large research program, investigating factors associated with OUD. The current study is a primary study that was planned *a priori* within a large program of OUD related research. Participants were recruited from and interviewed at community-based addiction treatment centres in Canada. Participants were interviewed face-to-face by research personnel and data related to MAT treatment and urine drug screens were obtained for 3 months. Data collection for this study occurred between May 2018 and August 2019. Data collected included socio-demographic details, current and past

substance use, and psychological and physical health symptoms using structured questionnaires. Demographic information included age, gender (social construct), sex (biological construct), ethnicity, marital status, employment, education and MAT. Urine drug screen results for the past 3 months were collected at the time of study enrollment. Study participants were also asked an open-ended question: "What are your goals of treatment?". Answers related to this question were written by research personnel at the time of the interview in a free text format without any restriction to the text length or content.

6.3.3 Quantitative Statistical Methods

The participants' demographic information was summarized using descriptive summary measures expressed as mean (standard deviation) or median (minimum-maximum) for continuous variables and number (percent) for categorical variables.

Patient important outcomes were defined based on the participants' goals and were compared based on 6 variables: age, sex, gender, ethnicity, employment, and type of current MAT. Age was trichotomized into three age groups, as defined by Statistics Canada[15]. The groups were defined as "youth" from 16-24 years old, "adults" from 25-64 years old, and "senior" 65+. Sex was coded as male, female, and intersex. Gender was coded as cisgender male, cisgender female, and other. Other consisted of transgender male, transgender female, two-spirit, non-binary, genderfluid, genderqueer, and agender as reported by participants in response to the question "what gender do you most identify

with?". Ethnicity was self-reported by participants and was coded as European, East Asian (Chinese, Japanese, Malaysian, Korea, Papua New Guinea, Thailand, Philippines, Indonesia, Vietnam, Cambodia, Laos, Myanmar/Burma, Bhutan, Singapore), Persian and Arab, African, South Asian (Indian, Sri Lanka, Pakistan, Nepal, Bangladesh), Indigenous (Native North American, Native South or Latin American, Australian Aborgine), and other/mixed. Employment was coded as currently working, or not working. Type of treatment was defined as methadone, buprenorphine/naloxone (suboxone), or other.

6.3.4 Qualitative Data Analyses Methods

QSR International's Nvivo 12 Qualitative Data analysis software, was used to perform a deep level analysis on the participants' treatment goal response data[16]. The data management and analyses plans are described in steps 1-3.

Step 1: Cleaning and Importing the Data

In order to conduct the qualitative analysis, the data were cleaned using Microsoft Excel to minimize typographical errors present in the free-text responses to the question asking participants about their treatment goals. The data were imported onto Nvivo, and the text pertaining to participant goals was imported as an open-ended question, while attribute assigning data such as age and sex were imported as close-ended questions. Close-ended questions are not codable questions in Nvivo and were not analyzed using this software.

Step 2: Word Frequency Query and Text Search Queries

The free-text data were run through a word frequency query to logically arrange the information and determine the most common four-letter words. The words that occurred most frequently were considered to be representative of the participants' perspectives, as it is assumed that important and significant words are used more often[17.] The word count query helped identify the initial patterns in the data, and there is evidence that this function improves analytic accuracy when compared to manual qualitative word frequency analyses[17]. In order to avoid decontextualization of the free-text answers, the minimum number of letters permissible in the word frequency query was four. Any word with a frequency weighting of greater than 0.5% was coded as a node. A node is a collection of references found in the free-text data that corresponds to a particular theme or word[18]. Words with a word frequency percentage above 0.5% that were related to a similar theme were grouped in the same node. Words with word frequency percentages above 0.20% were scanned and included in existing nodes with which they shared similarities.

The text search query allows words and their stemmed variants to be identified as references found in the free-text data responses. Text search queries were conducted for words identified in the word frequency queries to identify the related stemmed words. Results from the text search query were then coded into the appropriate nodes. Patterns and coding strategies emerged as a result of grouping similar words into nodes. These nodes were then labelled as themes.

Step 3: Matrix Coding Queries

Matrix coding queries help compare participant responses across and between different demographic categories[18]. Before comparing demographic categories, this query was run between coded references (text that had already been coded at a node) and participant responses, to identify any responses which had not been coded at a node. If a participant had a free-text response but was missing a corresponding coded reference at any of the different nodes, the free-text response was reviewed, and a reference was added to the appropriate node. This process brought forth new words and themes that were eventually combined with existing nodes. Any new words that were identified were also put through a text search query to ensure all the stemmed words were identified and coded into a node. The process of conducting a matrix query to identify any missing references and new/stemmed words, was completed iteratively until all participant responses had a coded reference(s).

Another matrix coding query was run between different demographic categories and the nodes to identify the attributes associated with each node. The demographic categories included were age, sex, gender, employment, ethnicity, and type of treatment. The output of a matrix coding query is a chart that displays the number of references coded at each node and the corresponding demographic attributes for each participant.

6.3.5 Quantitative Data Analyses Methods

Univariate exploratory analyses were conducted to identify statistical differences among the groups in their desired treatment outcomes. The themes used in these analyses were derived from the completed Nvivo analysis of the free text goals. A chi-squared $\chi 2$

analysis was completed for each Nvivo identified treatment outcome (stop MAT, avoid illicit drugs, live a "normal" life, pain management, prevent OUD symptoms, taper off MAT, no changes in treatment) with age, sex, gender, ethnicity, employment, type of treatment and source of first exposure to opioids (licit vs. illicit). Alpha of 0.05 was used to establish significance. All analyses had a degree of freedom of one and created a 2x2 output. The associated phi value (φ) was reported for these analyses. Age had a degree of freedom of 2. For these analyses the Cramer's V value was reported.

6.4 Results

6.4.1 The Study Participants' Characteristics

A total of 2032 participants were recruited for this study. One participant had treatment goal data missing, which resulted in a sample of 2031 participants (1135 males, 896 females and 1 intersex) whose treatment goals were qualitatively analyzed. The mean age was 39.1 years, 71.3% were of European ethnicity and 66.2% were not currently working. Demographic details are presented in Table 6.8.1. Most participants had at least one positive urine drug screen for illicit opioid while they are on MAT (68.2%), and 44.1% was first exposed to opioids through licit means (they were prescribed opioids for medical reasons).

6.4.2 Objective 1: Qualitative Patient Important Outcome Data Results

Seven major themes were identified using Nvivo analysis in order of frequency:

1. Stop MAT (includes stop methadone or buprenorphine/naloxone treatment completely, or to not be dependent on MAT)
2. Avoid illicit drugs (includes wanting to get clean, stay clean, abstinence, or sobriety from a variety of drugs not just opioids)
3. Live a "normal" life (includes wanting a stable life, normal life, education, job or work, good mental health, or wanting to support their family or stay alive)
4. Pain management (includes chronic pain, or pain management)
5. Prevent OUD symptoms (includes withdrawal and craving)
6. Taper off MAT (includes wanting to taper off, wean off, or reduce dose)
7. No changes in treatment (includes keep everything as is, stabilize the dose, or nothing to add)

Participants were free to provide multiple desired treatment outcomes and therefore the total number of responses exceeds the number of participants. Participants who had goals corresponding to both the stop MAT treatment and taper off MAT treatment themes, were grouped under the stop MAT treatment theme and removed from the taper off MAT treatment theme. These themes were separated as one implies getting off the program entirely (stop MAT), while the other theme implies, they may stay on the program but at a lower dose. This resulted in the total number of responses to decrease from 3310 to 3020. Figure 6.8.2 shows the percentage of the seven different outcomes. The most desired goal was to stop MAT (39% of responses), followed by avoiding illicit drugs (25%) whereas the lowest percentage was for the goal to have no changes in treatment (4% of responses).

6.4.3 Objective 2: Patient Important Outcomes by Pre-Defined Groups Results

Patient responses were analyzed in comparison with age, sex, gender, ethnicity, employment, and treatment duration and type. Results are shown below.

Age

There was a total of 203 youth responses, 2780 adult responses, 37 seniors' responses (Figure 6.8.3). The most common goal for all three age groups was to stop treatment (youth 39.9%, adults 38.6%, seniors 32.4%). The least common goal for the youth group was pain management (1.5%).

Sex

The most common goal for both female and male participants was to stop treatment (females 39.6%, males 37.8%) (Figure 6.8.4). To live a normal life was the one response for intersex (intersex 100%).

Gender

There were a total of 1351 cisgender female responses, 1646 cisgender male responses, and 23 other responses. The most common goal for both cisgender female and cisgender male participants was to stop treatment (cisgender females 39.7%, cisgender males 37.7%). The most frequent goal identified by participants grouped under the "other" category was to stop treatment (39.1%).

Ethnicity

The majority of participants were European (n= 2154) followed by "other" (n=437) and Indigenous n=367. The most common goal for all ethnicities was to stop treatment.

Employment

The highest reported outcome by both unemployed and employed participants was to stop treatment (unemployed 36.6%, employed 42.7%). (Figure 6.8.5). The greatest difference in response by employment was seen in the pain management theme (unemployed 9.47%, employed 4.78%).

Type of Treatment

There were a total of 2399 responses corresponding to the methadone treatment, and 616 responses relating to the buprenorphine/naloxone treatment and 4 responses for other forms of treatment (Figure 6.8.6). The most common goal for both methadone and buprenorphine/naloxone treatment were to stop treatment (methadone 38.2%, buprenorphine/naloxone 40.1%).

Length of treatment

The most common goal in all lengths of treatment was to stop treatment (1 year or less 34.2%, 1-5 years 40.5 %, 5-10 years 42.6 %, 10-15 years 36.0%, 15+ years 41.4%).

First exposure to opioids: legitimately prescribed (licit) versus recreational exposure (illicit)

The most common goal in participants regardless of the source of first exposure to opioids was to stop treatment (licit 37.9%, illicit 39.1%). Participants who were first exposed to opioids through licit means had more responses listing pain management as their goal compared to those who were first exposed to opioids through illicit means (licit 12.4%, illicit 4.3%).

6.4.4 Correlation analyses results

Univariate exploratory analyses to identify statistical differences among the groups in their important outcomes showed that all groups were wanted to stop MAT and avoid illicit drugs as the most chosen treatment goals while some differences among groups were also observed. Specifically, the following associations were found to be significant: pain management and age ($p = <0.001$), stop MAT and sex ($p = 0.047$), stop MAT and ethnicity ($p = 0.001$), taper off MAT and ethnicity ($p = 0.007$), pain management and employment ($p = <0.001$), stop MAT and employment ($p = 0.013$), taper off MAT and employment ($p = 0.008$), live a "normal" life and type of treatment ($p = 0.030$), pain management and type of treatment ($p = 0.005$), pain management and source of first exposure to opioids ($p = <0.001$), and live a "normal" life and source of first exposure to opioids ($p = 0.021$).

6.5 Discussion

In this large study of 2031 patients with OUD, we identified that 39% of patients wanted to stop MAT and 25% wanted to stop all drugs not just opioids. Yet the current MAT programs are focused on treatment retention and stopping or reducing illicit opioid use. This suggests that 64% of this cohort are not meeting treatment goals for the traditional MAT programs. This may be an important consideration when assessing MAT effectiveness measures as well as considering individual patient preferences based on sociodemographic factors and personalized medicine.

Patients of all ages wanted to stop MAT and avoid illicit drugs. While older adults had pain management as their second most frequent goal, except for pain management as a treatment goal for older patients, the majority of patients regardless of their sociodemographic variables wanted stop or taper off MAT.

Current OUD management guidelines recommend the use of MAT to manage OUD however these guidelines do not include patients related goals and do not specify the length of time that MAT should be considered for[19]. In this study, patients' most frequently reported goal of OUD treatment is stopping MAT (39%). Yet in the absence of recommendations based on evidence from clinical trials on the duration of MAT and the desire of patients to stop MAT, the treatment adherence and the prognosis of OUD are unlikely to be favourable.

The guidelines also strongly recommended "against a treatment strategy involving withdrawal management alone without plans for transition to long-term evidence-based addiction treatment (e.g., opioid agonist treatment such as buprenorphine/naloxone (OAT))[19], since this approach has been associated with nearly universal relapse and, subsequently, elevated risk of unsafe drug use and/or overdose in comparison to no treatment provision", while patient important goals identified in our study stated that only 8% of responses were related to OUD symptoms management. Most participants in this study had at least one positive urine drug screen for opioid while they are on MAT (68.2%) during the past three months despite being on MAT for an average of 4.5 years. The risk of relapse and overdose are real challenges in OUD, but many trials use short term and narrow focus outcome measures such as urine drug screens to determine

treatment effectiveness. If efficacy of MAT is based on opioid negative urine drug screens, then MAT is ineffective in 68% of patients in this study. The use of urine drugs screen to measure the effectiveness of MAT in these trials fails to capture important outcomes associated with the chronicity of OUD, which limits the scope of patients' treatment.

A frequently mentioned treatment goal (25%) was to avoid all illicit drugs, and not just opioids. We previously reported that comorbid substance use in this population is common, with 42% having a comorbid substance use disorder[20]. Despite this high co-substance use and patients' goals of stopping all drugs clinical trials of MAT for OUD exclude patients with co-substance use [14]. This exclusion is leaving a significant proportion of patients with OUD with unmet needs and unmeasured treatment outcomes.

Another factor we explored that may influence patient's treatment goals is the type of MAT prescribed. In this study we reported patients' treatment goals by the type of MAT they are receiving. There is a stigma associated with methadone maintenance treatment[21] and therefore the patients' desire to be off treatment may be explained by the stigma attached to methadone, however the results of this study showed that patients on other MAT also wanted to be off treatment. Therefore, stigma alone may not explain why the most frequent patients' important outcome is to stop treatment.

The results also suggest that patients who were first exposed to opioids through licit vs. illicit means may have different desires to achieve out of MAT. We found that those who were exposed to opioid through licit means were significantly more likely to have pain management as a goal. This may be because it is likely that their first exposure

to opioid was for pain management as opioids are commonly prescribed for pain. In addition MAT including methadone, are used for pain management and therefore it is expected that patients with chronic pain conditions may wish to continue using MAT to relieve pain. Additionally, those that were introduced to opioids through illicit means were likely to list "live a normal life" as a goal. Previous research that has looked into the sources of introduction to opioids has found that there are differences in substance use and demographic characteristics in those introduced by prescription versus other means[33,34]. This suggests that participants who were introduced to opioids through illicit means may have substance use disorder vulnerability factors such as novelty seeking and risk taking behavior compared to people with pain who were prescribed opioids and would be more likely to have treatment goals pertaining to stability/living a normal life[34].

Although the reasons for why patients wanted to be off MAT cannot be explained in this study, a treatment plan that includes patient important goals and evidence-based informed precision medicine is needed to improve treatment outcomes in OUD. While it may seem challenging to have a consensus on what constitutes a good treatment outcome between patients and treatment programs, previous studies showed that it is possible to have such an agreement[22]. Despite such a possibility, there is a lack of important and patient identified sets of outcomes in clinical research and practice[23]. No previous work on patients' important outcomes in OUD to inform clinical trials has been completed, despite the ongoing opioid crisis.

Comparing treatment plans and goals varies greatly between clinical care settings, patients' expectations and services delivered[24]. For example, the duration of treatment

may have an impact on patient's engagement in services with patients perceiving these services more helpful than short term treatment[25]. Furthermore, patients' suggestions on their treatment goals often differ from their clinicians' opinions. A study found that patients with addiction saw physical health as their goal more often than their clinicians[26]. Thus, patient and clinician communication about the goals and expectations of treatment may be beneficial to translate patients' opinion and choice of what is a relevant outcome for them into the course of treatment. Communication may also help patients' positive opinions on long-term goals become a part of their service plan, potentially leading to achievable goals. This concept was summarized by stating that limiting discrepancies between patients' and clinicians' goals of addiction service might lead to convergence, which is likely necessary for positive treatment goals and better service for patients with addiction[26].

Discrepancies are often related to the concept that existing treatments and clinical trials in OUD have used convenience outcomes that are objectively measurable such as urine drug screen, without consideration for patients' important outcomes, sociodemographic differences, and patients' goals or group differences. Additionally, guidelines also indicate that there is little consistent evidence to evaluate the effectiveness of OUD treatment[27]. Reviews evaluating OUD treatment effectiveness have found great variability in the selected goals between studies[28–30], leading to difficulty in establishing a real treatment effect. Each study measures a different set of goals that define success in arbitrary or accessible terms, limiting comparison between such studies. This is an important limitation in addiction research that must be overcome in order to have a

consensus on what works for OUD management and how to assign a treatment goal.

6.6 Limitations

Despite being the largest study to date and including unrestricted responses from patients receiving active treatment, there are certain study limitations that should be considered. The participants in the study may not represent all patients with OUD as there is an expected self-selection bias in voluntary participation in research compared to those who do not participate. The study findings may not be generalizable to the entire Canadian population as our study sample has been recruited from community clinics in the province of Ontario. It is important to note that our mean age and sex distribution resembles data collected by Public Health Ontario in 2018 where the patients' age groups and sex distribution were similar to the study participants [31].

Other limitations to consider are other variables that may play a role in determining the patients' goals that are not measured in this study such as personality type. Previous research suggests that there may be a relationship between specific traits and chronic substance use[32]. There is also the possibility that patients who no longer attend treatment programs and achieved sustainable recovery may have different outlook on treatment goals compared to patients with an active phase of the disorder. Despite these limitations, the responses provided by 2031 patients in active treatment are important findings that at least will apply to a similar population in the active phase of the disorder.

6.7 Conclusions

In this mixed-methods study we analyzed the answers to an open-ended question to let the participants express their opinions without any constraints on the type, length or direction of the answer, for what they wanted out of treatment for OUD. We identified patients' important outcomes for OUD that may inform future trials to include patient-centred outcome when investigating MAT for OUD. Opioid use has not seen adequate control despite many measures in place and therefore identifying effective ways to manage OUD remains both urgent and timely. Treatment guidelines and programs rely on well conducted clinical trials, when including patients important outcomes, the results of which may lead to a paradigm shift in what treatments outcomes should be considered, what medications are truly effective, for what goal, to what patient these results apply and how treatment programs will be evaluated when it comes to resource allocations and policy making. Thus, we need a shift in how these treatments are tested for effectiveness to incorporate patient important outcomes and provide precision medicine approach to managing the OUD epidemic.

Acknowledgment

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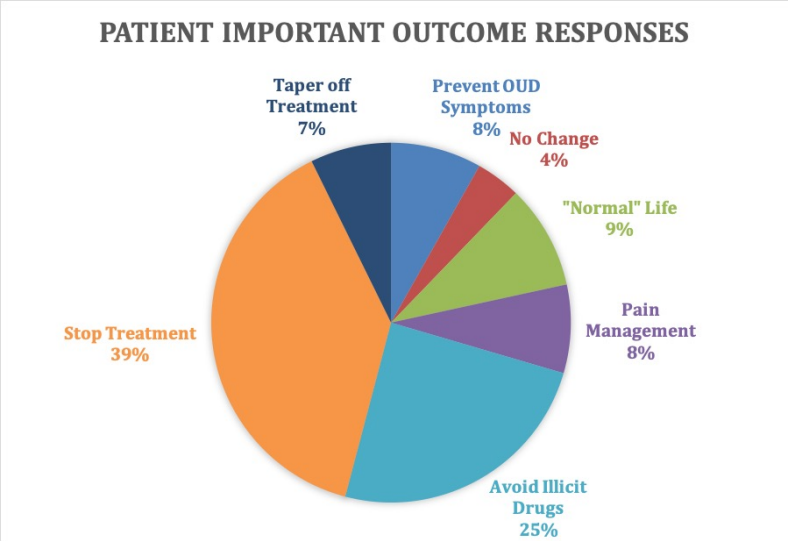
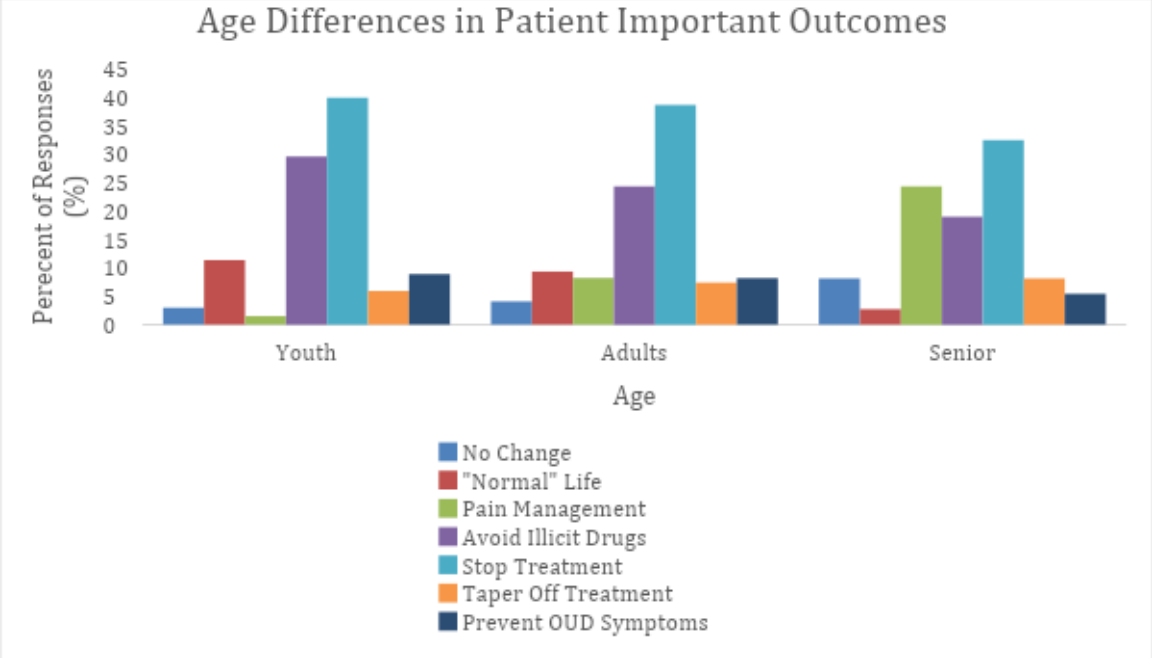
6.8 Tables and Figures

6.8.1 Demographic Characteristics

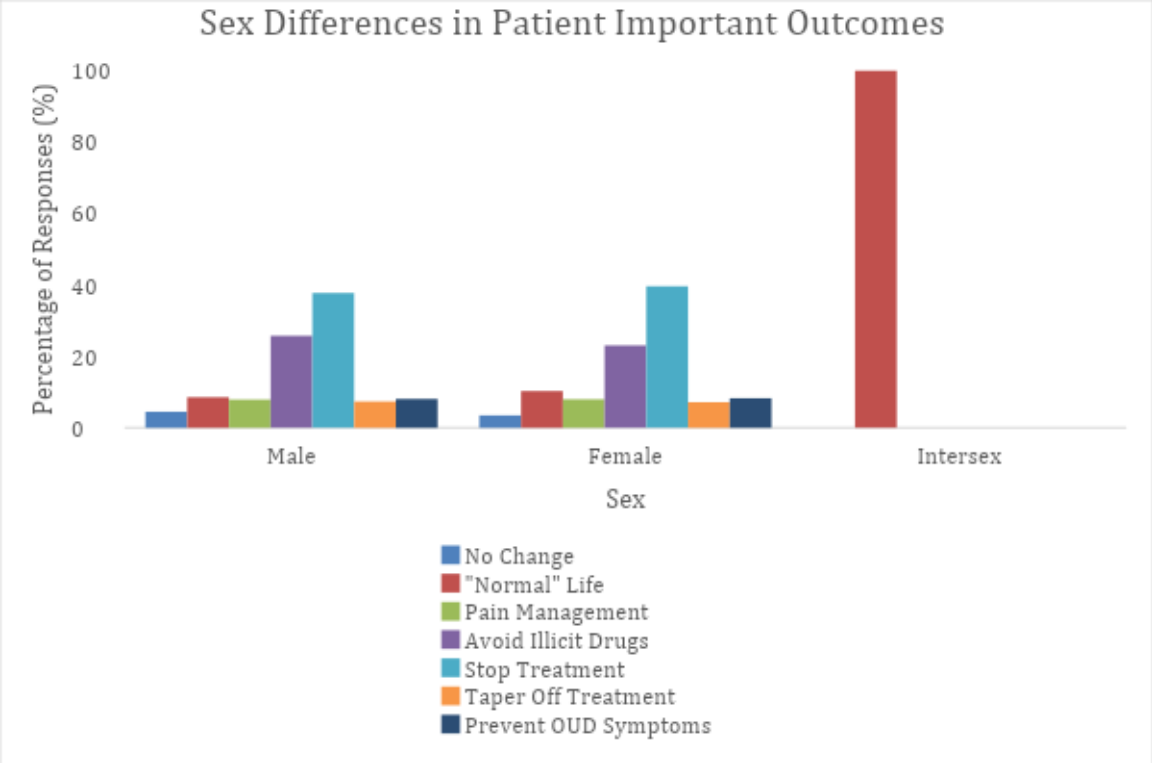
	n=2031
Age in years (SD)	39.1(10.7)
Sex, % female	44.0
Ethnicity, % European	71.3
Currently Employed, %	33.8
Marital Status	
Never married, %	50.4
Currently married/Common-law, %	28.9
Separated/Divorced/Widowed, %	20.7
Level of Education	
None/Elementary School, %	28.3
High school, %	43.1
Trade school, %	2.5
College/university, %	25.7
Postgraduate, %	0.4
Details of Opioid Use	
Age of opioid use onset in years (SD)	24.8 (9.25)
Treatment duration in months (SD)	54.5 (63.1)
Methadone Dose in mg/day (SD)	70.4 (41.3)
buprenorphine/naloxone Dose in mg/day (SD)	12.0 (6.73)
Participants with at least one positive opioid urine screen in past 3 months, %	68.2



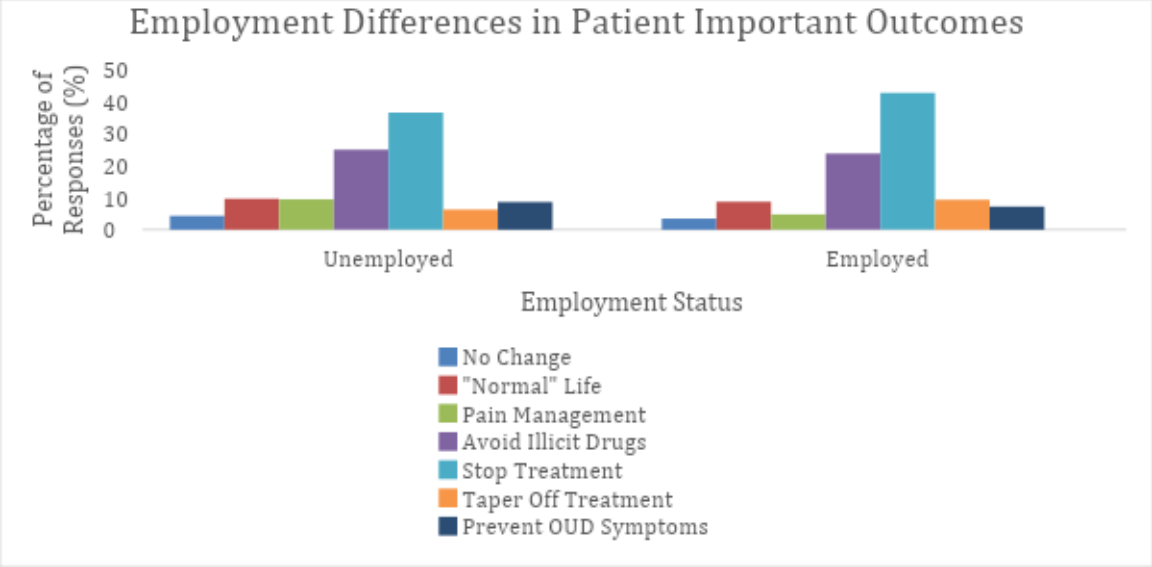
6.8.2 The percentage of responses per patient important outcome group



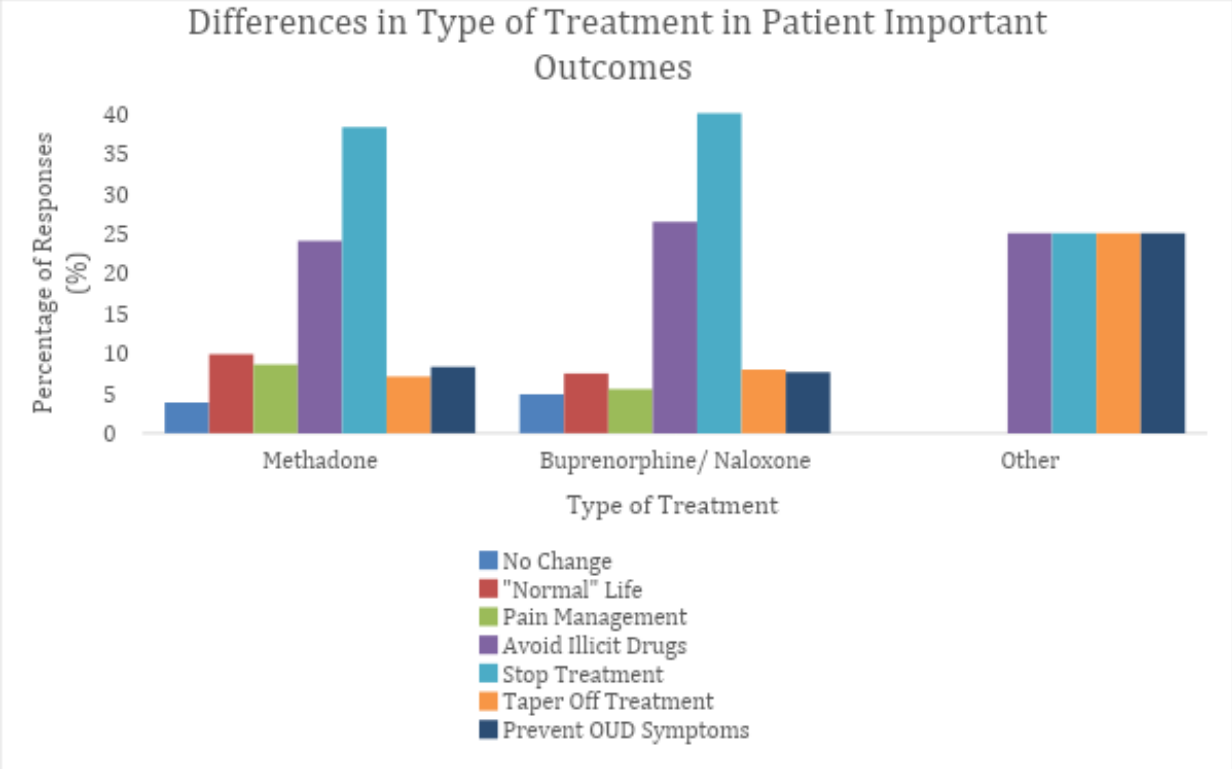
6.8.3 Desired treatment outcomes by age group



6.8.4 Sex differences in patient important outcomes



6.8.5 Patient important outcomes by employment status



6.8.6 Differences in type of treatment seen in patient important outcomes

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7 CHAPTER 7

Treatment with methadone compared to buprenorphine-naloxone: A cross-sectional study of patients with opioid use disorder

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7.1 Abstract

Introduction: Methadone and buprenorphine-naloxone are two of the most common medication assisted treatments (MAT) available for opioid use disorder (OUD). Unlike methadone, buprenorphine-naloxone has several properties that make it a safer option that is less likely to be abused. It is important to investigate if there are differences in treatment outcomes, including opioid, cannabis, cocaine, crack cocaine, benzodiazepine, amphetamine and alcohol use between these two groups.

Methods: Data was obtained from a large, observational study examining pharmacogenetics of MAT. Information regarding demographic information, treatment details, and substance use was collected at baseline. We conducted a multivariable logistic regression comparing the methadone and buprenorphine-naloxone groups. We also explored these differences by sex.

Results: We included a total of 2273 participants of which 1794 were receiving methadone and 479 were on buprenorphine-naloxone. We found that those receiving buprenorphine-naloxone were less likely to have used illicit opioids (OR=0.408, 95% CI 0.324,0.514, p=<0.001) and amphetamines (OR=0.653, 95% CI 0.462,0.923, p=0.016) in comparison to methadone patients. We also found that those on buprenorphine-naloxone where more likely to have consumed alcohol that those receiving methadone treatment (OR= 1.401 95% CI 1.122,1.750, p=0.003). Among males, those on buprenorphine-naloxone were less likely to have used amphetamines in comparison to those on

methadone (OR=0.421, 95% CI 0.258, 0.684, p=<0.001). In females, the buprenorphine-naloxone group where more likely to have used alcohol than those in the methadone group (OR=1.611, 95% CI 1.162,2.234, p=0.004).

Interpretation: This study identified significant differences between patients receiving methadone and buprenorphine-naloxone treatment for OUD. These differences are important to take into consideration when recommending what MAT may be suitable for someone with OUD.

Keywords: methadone, buprenorphine-naloxone, opioid use disorder, medication assisted treatment

7.2 INTRODUCTION

7.2.1 Background

Opioids are a class of drugs that can be found in both prescription drugs such as oxycodone and hydromorphone often prescribed for pain relief, and recreational drugs such as heroin. Despite the distinction present between prescribed and recreational opioids, all opioids deliver a euphoric feeling that can increase the risk of developing abuse and dependence[1]. Opioid misuse is a significant health concern that is associated with significant morbidity and mortality. A report released by the Centre of Disease Control and Prevention stated that approximately 128 people overdose on opioids daily in the United States. Approximately 2.1 million people have opioid use disorder (OUD) due to prescription opioids alone[3].

Evidently, OUD is a complex disorder that results in symptoms such as cravings and withdrawal from opioids, which has led to the development of Medication Assisted Treatment (MAT). The ability of methadone (an opioid agonist) to relieve withdrawal and craving symptoms led to the introduction of methadone treatment in 1964 and has made it one of the most widely used MATs for OUD in North America[4]. Past research has suggested that while methadone may be effective in treatment retention and reduction in illicit opioid use, there is treatment variability in health, social functioning and comorbid substance use[5–9]. In recent years, a newer MAT is gaining in popularity to be used as first line treatment for OUD[10]. It is a partial opioid agonist consisting of buprenorphine-naloxone (buprenorphine). Buprenorphine has similar effects when compared to

methadone, but it is also associated with added withdrawal benefits such as less sedation and respiratory depression[11–13].

Research exploring the differences between buprenorphine and methadone have found some support for buprenorphine to be a suitable recovery drug. More specifically, these studies have found buprenorphine to be significantly associated with greater clarity of thinking and a greater reduction in heroin use, when compared to methadone[14–16]. Other studies have explored differences between buprenorphine and methadone to find that buprenorphine and methadone have specific benefits for different patient groups. Methadone has been seen to have higher treatment retention rates than buprenorphine and is recommended for patients with higher risk of treatment dropout[17,18] and opioid misuse during treatment, both behaviors that are often seen in heroin users and opioid injectors[19]. In comparison, buprenorphine has a lower risk of overdose and is recommended for socially stable opioid users[17,20].

Despite identified differences in methadone versus buprenorphine treatment for opioid users, there is also evidence suggesting that these differential effects may have been affected by patient selection bias[21]. Some studies have also found no interactions between the type of OUD treatment and opioid use or treatment attrition[19,22,23]. Additionally, many of the studies that have looked at differences in methadone versus buprenorphine have been completed in non-Canadian populations or have not had large Canadian sample sizes. Considering the limitations and the inconclusive conclusions of the studies looking at differences in these treatment options, it is important to further examine differences in Canadian opioids users receiving either methadone or

buprenorphine as treatment. The importance of identifying differences present in the types of OUD treatment is also highlighted by the recent rise in popularity of buprenorphine as a treatment for OUD in Canada and the simultaneous shift in the profile of Canadian opioid users, both of which indicate a need for current, up-to-date research. Furthermore, studies have found differences in withdrawal effects, treatment attrition, risk of overdose, and cognitive abilities when examining methadone versus buprenorphine[19,22,23].

Many of these differences may have varying levels of importance to opioid users depending on their treatment goals and user profiles. Thus, not only is it important to examine differences in opioid users receiving methadone or buprenorphine as treatment, it is important to explore how treatment outcomes differ for OUD patients receiving both methadone and buprenorphine in order to develop and improve current treatment recommendations[24]. Therefore, the aim of this study is to assess the association between the type of medication assisted treatment and treatment outcomes in patients with OUD**.**

7.2.2 Objectives

Specifically, we aim to:

1. Explore the association between type of MAT (methadone or buprenorphine) and differences in illicit opioid, cannabis, cocaine, crack cocaine, benzodiazepine, amphetamine and alcohol use;
2. Examine sex differences in type of MAT received and treatment outcomes.

7.3 METHODS

This study adheres to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)[25].

7.3.1 Study Design

Cross-sectional data were obtained from the Pharmacogenetics of Opioid Substitution Treatment (POST) study, a collaboration between researchers at McMaster University and the Canadian Addiction Treatment Centres.

7.3.2 Participants, Study Setting and Measures

Participants were recruited from 30 outpatient MAT clinics throughout Ontario. In order to be enrolled in POST, participants had to be 16 years of age or older, diagnosed with OUD and receiving MAT. They also had to provide written, informed consent. Enrolled participants received a face-to-face baseline interview with trained research personnel and provided information related to demographics,

Study participants were asked about their current MAT information which included: what treatment were they on (i.e. methadone, buprenorphine), dosage, how long have they been on it and have they tried any other treatment before this and if they receive Ontario disability support program (ODSP). Participants were also administered the Maudsley Addiction Profile (MAP), which is a self-reported questionnaire that obtains information related to physical, mental and social functioning, risk-taking

behavior and substance use within the past 30 days[26]. The MAP asks about the following substances: cannabis, alcohol, heroin, illicit(non-prescribed) methadone, cannabis, cocaine, crack cocaine, benzodiazepines and amphetamines. Information on illicit opioid use was collected from the results of the urine drug screens conducted by the CATC clinics.

7.3.3 Statistical Analysis

We reported all demographic characteristics using descriptive statistics. Continuous variables are summarized as means with standard deviations (SD), while categorical or dichotomous characteristics are summarized with frequencies and percentages.

The main analysis examining the relationship between the type of MAT received (methadone or buprenorphine/naloxone) and various substance use treatment outcomes was conducted through a multivariable logistic regression. We controlled for age, sex and treatment duration (in months) as they are known covariates in this population. We also controlled for ODSP status because up until 2016, buprenorphine was not covered under Ontario's drug benefit program.

Substance use for cannabis, cocaine, crack cocaine, alcohol, illicit methadone, heroin, benzodiazepines and amphetamines were dichotomized using the MAP where it was any use of the substance in the past 30 days or no substance use in the past 30 days. Illicit opioid use was dichotomized using the urine drug screens with any positive opioids' screens or no positive opioid screens. Heroin was not included in the regressions

as it would have been accounted for in the positive opioid urine screens. Illicit methadone and benzodiazepines were not included in the regressions as these variables were underpowered. We also conducted a subgroup analysis by sex using the same multivariable logistic regression model.

Additionally, we did a sensitivity analysis by running the main model with participants that had started treatment before August 2016 and those that had started treatment August 2016 onwards. The reason we performed this analysis is because it is in July 2016 we see case series about micro-dosing for buprenorphine (Bernese method) appear[27,28]. With the introduction of the micro-dosing protocol, it was learned on how to start people on buprenorphine without patients having to be abstinent from opioids and without putting them into precipitated withdrawal. We explored if there were differences in these findings.

The data analysis was conducted using IBM SPSS Statistics Version 25[29]. The findings reported adjusted odds rations, 95% confidence interval with the significance for the main analysis set to an alpha of a=0.05 and a=0.025 for the subgroup analysis. We used the variance inflation factor (VIF) to examine multicollinearity and all variables have a VIF of less than two, indicating no collinearity amongst them.

7.4 RESULTS

The POST study recruited a total of 2392 patients that were potentially eligible for this study of which 36 were duplicates and 84 were prescribed opioids aside from their MAT. We included a total number of 2273 of participants in the analysis (Figure 7.7.1).

7.4.1 Demographics

In our study sample, we had a total of 1794 participants that were receiving methadone and 479 participants receiving buprenorphine. The percentage of females was similar in both methadone (44.1%), and buprenorphine (45.7%) groups. Those that were receiving buprenorphine had more people report being employed (40.5%) in comparison to those receiving methadone (31.8%). The participants in the buprenorphine group had an average age of 25.3 years (SD= 9.6) which was marginally higher than the average of 24.27 years (SD= 9.2) of those in the methadone group. Those in the methadone group reported treatment duration 59.9 months (SD=64.1) in comparison to the buprenorphine group 26.0 months (SD=34.2). The buprenorphine group reporter a lower mean % positive opioid urine screens at 11.0% compared to the methadone group at 17.0%. Heroin use within the past 30 days was higher in methadone (15.6%) than the buprenorphine group (9.4%). Illicit methadone use was not very prevalent in methadone or buprenorphine at 2.0% and 0.4%, respectively. Benzodiazepine use in the past 30 days was 8.1% methadone and 6.7% in buprenorphine. A complete summary of demographic and characteristics of the methadone and buprenorphine groups are described in Table 7.7.2.

7.4.2 Primary Analysis

The findings of the main analysis examining the association between type of MAT received and treatment outcomes are reported in Table 7.7.3. It was found that those that were on buprenorphine were significantly less likely to have a positive opioid urine screen (OR=0.408, 95% CI 0.324,0.514, p=<0.001) in comparison to those on methadone. The results also showed that the buprenorphine group was less likely to report using amphetamines in the past 30 days compared to the methadone group (OR=0.653, 95% CI 0.462,0.923, p=0.016). Those receiving buprenorphine were significantly more likely to report using alcohol in the past month than those receiving methadone (OR= 1.401 95% CI 1.122,1.750, p=0.003). Additionally, those on buprenorphine had a significantly shorter duration in treatment than methadone (OR=0.980, 9 5% CI 0.977, 0.984, p=<0.001). There were no associations found in cannabis, cocaine or crack cocaine use in the past 30 days along with no significant differences in age or sex.

7.4.3 Secondary Analysis

Our planned subgroup analyses by sex investigated the relationship between type of MAT and treatment outcomes. The results are reported in Table 7.7.4. We found that amongst both males and female, those receiving buprenorphine were significantly less likely to have a positive opioid urine screen and had shorter treatment duration. In males, we found that those receiving buprenorphine were less likely to have reported using amphetamines in the past 30 days when compared to methadone (OR=0.421, 95% CI 0.258, 0.684, p=<0.001).In females we found that the buprenorphine was more likely to

have reported using alcohol in the past month than the methadone group (OR=1.611, 95% CI 1.162,2.234, p=0.004). There were no significant associations found in age, cannabis use, cocaine use, or crack cocaine use within males or females.

In our sensitivity analyses, those that were enrolled in treatment prior to micro-dosing introduction (before August 2016) and those that were enrolled in treatment post micro-dosing showed similar significant differences for illicit opioid use, treatment duration and alcohol use. However, pre-micro-dosing, we found that those in the buprenorphine group were significantly more likely to be female, of an older age and not receiving ODSP. These findings were not replicated post micro-dosing. In the post micro-dosing participants, we found that those receiving buprenorphine were less likely to have used amphetamines. Additional details can be found in Table 7.7.5.

7.5 DISCUSSION

In this large cross-sectional study, we investigated treatment outcome differences between OUD patients receiving methadone or buprenorphine. We found that there were significant differences between the two groups for treatment duration, opioid, amphetamine and alcohol use. We also found that there were no significant differences for age, sex, ODSP status, opioid overdose, cocaine, crack cocaine, or cannabis use for participants receiving methadone or buprenorphine. When we explored these differences by sex, we found that in females, there were significant differences in alcohol use

between buprenorphine and methadone groups whereas in males, there were differences in amphetamine use between the two groups.

In Canada, buprenorphine has recently become the first-line treatment whereas has methadone shifted to second-line treatment recommendation in the management of OUD[30]. While buprenorphine is the recommended first-line treatment, we see that this is not reflected in our sample with approximately 80% being on methadone. This may be due to a variety of reasons including that in Ontario specifically, buprenorphine was not covered under the drug benefit plan and patients had to pay for the medication themselves if they wanted to start or switch over to it, whereas methadone was covered. In our secondary analysis, we can see that those that were on buprenorphine prior micro-dosing were less likely to be receiving ODSP, but this difference disappears once micro-dosing was introduced. This timeframe (August 2016) was approximately during the same time that ODSP started covering buprenorphine in the drug benefit plan.

Additionally, some research does suggest that patients may prefer buprenorphine over methadone in cases of not wanting the associated stigma associated with methadone clinics and in cases where they perceive methadone to have addictive properties that hinder the goal of not misusing opioids[31]. Another study examining patient preference for MAT found that those that preferred methadone over buprenorphine believed that they were overusing opioids and had a fear of going into withdrawal[32] suggesting that patients who continue to use opioids while receiving MAT may prefer methadone. While methadone may still be able to provide euphoric effects, buprenorphine has higher affinity of mu-opioid receptors and therefore is able to replace other opioids from mu-

receptors when ingested[11,33], which puts patients in precipitated withdrawal and protects against overdose.

Our results showed that those on buprenorphine were less likely to have used illicit opioids than those receiving methadone. This finding was replicated both pre- and post-micro-dosing. This may be because many OUD patients who currently receive buprenorphine had to be abstinent from all opioids before they started it, as before micro-dosing, if they were not abstinent, patients would experience withdrawal[17]. Additionally, patients generally seem to be ignorant of the strictly one-way withdrawal relationship between opioids and buprenorphine, where the use of opioids followed by ingestion of buprenorphine will lead to withdrawal. Patients are unaware that if they are already on buprenorphine and decide to use other opioids, they will not go into withdrawal. Thus, fear of precipitated withdrawal may discourage from opioid use. Additionally, it is of concern that those that are on methadone were more likely to have a positive opioid screen as there is a risk of QT prolongation, which is not present for buprenorphine[34,35]. This become a greater safety concern when combined with additional substances such as use of amphetamines, which we found in our results.

We also found that those receiving methadone had a significantly longer duration in treatment in comparison to those on buprenorphine. A Cochrane review examining differences between buprenorphine and methadone-maintained individuals found similar results, where buprenorphine had lower treatment retention compared to methadone[36]. There is evidence presented from randomized control trials that echo these findings, stating that treatment retention is lower in individuals randomized to buprenorphine[32,37,38],

possibly due to the more recent, unfamiliar uptake of it as a first-line treatment for OUD. However, these studies have polarizing findings on opioid use differences between groups, where some suggest there are negligible differences between groups[37], while others suggest that those receiving methadone are less likely to use opioids[36]. However, there is some evidence that indicates that individuals receiving buprenorphine are less likely to use opioids, providing support for our findings[32].

Significant differences were found between the two groups for amphetamine, where individuals on methadone showed higher levels of amphetamine use. This finding can be explained by evidence suggesting that individuals who engage in use of one substance are at a higher risk of using other substances[39], as seen in the methadone group's concurrent use of opioids and amphetamine. Furthermore, buprenorphine is often prescribed to individuals with moderate dependence and greater motivation, thus suggesting that the results may have captured a clinical bias rather than a difference between both groups[40,41]. Higher use of amphetamines was also seen in males on methadone treatment when data was analyzed by sex, which may be due to greater risk-taking behavior seen in males as they are more likely to use and have a greater mortality from using tobacco, alcohol and illicit drugs, compared to females[42].

In contrast to amphetamine, individuals on buprenorphine were found to have higher use of alcohol. Alcohol may cause increased risk of methadone toxicity as it is a sedating substance[17] which may explain why it seems to be consumed more by people on buprenorphine compared to people on methadone maintenance treatment[43,44]. More specifically, as buprenorphine is often a choice for individuals looking to taper treatment,

they may be using alcohol to self-medicate as they lower their use of opioids. When analyzed by sex, greater use of alcohol was seen in females, a finding that could also be explained by self-medication. It has been reported that female opioid users receiving treatment have higher rates of physical, physiological health problems, family history of psychiatric illness, and childcare responsibilities, which may lead to greater self-medication using exogenous substances such as alcohol[8].

As with all observational, cross-sectional research, we are limited in making any causal associations between type of MAT received and treatment outcomes. However, to our knowledge, this is one of the few studies with a large sample examining outcome differences between those receiving methadone or buprenorphine. We also may not be able to generalize our results to an OUD population receiving MAO outside of Ontario, Canada. Additionally, these findings may be more reflective of selection bias into methadone or buprenorphine treatment. We also used self-report for substance use using the MAP which may be of concern regarding social desirability bias. However, we have previously conducted a sensitivity analysis in this population using self-report MAP information and its reflection in the urine drug screens and found that the self-report through MAP was appropriate in capturing information[9].

There is a need for future research to examine long terms outcomes between OUD patients that receive methadone and buprenorphine treatment. With these medications being the first- and second-line treatments for OUD, there is a gap in the literature examining if one treatment is better than another when tackling the specific goals, preferences or needs of patients. Furthermore, there is a need for empirical evidence

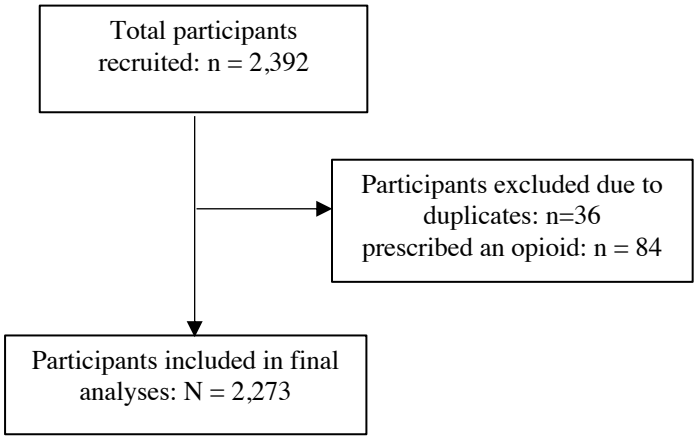
examining buprenorphine induction through micro-dosing. There is currently limited knowledge on the subject, and it may be through research that we are able to inform not just healthcare professionals but OUD patients that are hesitant in switching to buprenorphine only due to the fear of experiencing withdrawal.

7.6 Conclusion

With the continuing effects of the opioid epidemic on the Canadian population, it is important to examine if one MAT may be more beneficial in certain outcomes and goals compared to another one. Identification of the strengths and limitations of these treatments will allow for the improvement of OUD patient care, by aiding the revision of treatment guidelines and recommendations. We identified significant differences in the use of various substances between methadone and buprenorphine patients. Future research should examine long term outcomes between these groups and see if one treatment is more suitable for a specific type of OUD patient, thus leading to the development and possible implementation of personalized medicine approaches to OUD patient care.

7.7 Tables and Figures

7.7.1 Study Flow Diagram



7.7.2 Demographic characteristics of study sample

Characteristics (n=2273)	Methadone	Buprenorphine/naloxone
Total number of patients	1794	479
Mean Age (SD)	39.3(10.7)	38.2(10.8)
Sex, % female	44.1	45.7
Currently employed, n (%)	31.8	40.5
ODSP		
Marital status		
Never married, n (%)	899 (50.2)	241 (50.2)
Currently married/Common-law, n (%)	523 (29.1)	149 (31.1)
Separated/Divorced/Widowed, n (%)	372 (20.7)	89 (18.7)
Ethnicity		
European (%)	1323 (73.7)	318 (66.4)
Native North American (%)	176 (9.8)	84 (17.5)
Other (%)	295 (16.5)	77 (16.1)
Level of Education		
None/Elementary School (%)	521 (29.0)	119 (24.9)
High school (%)	778 (43.4)	213 (44.5)
Trade school (%)	42 (2.3)	12 (2.5)
College/university (%)	448 (25.0)	132 (27.6)
Postgraduate (%)	5 (0.3)	3 (0.6)

Details of Opioid Use		
Age of opioid use onset in years (SD)	24.7(9.2)	25.3(9.6)
Treatment duration in months (SD)	59.9(64.1)	26.0(34.2)
Treatment dose in mg/day (SD)	70.4(40.1)	11.9(6.8)
Baseline Illicit Opioid Use, mean % positive screens)	17.0	11.0
Opioid Overdose, %		
Self-reported drug use in past 30 days, %yes to at least one day		
Heroin	15.6	9.4
Illicit methadone	2.0	0.4
Illicit benzodiazepine	8.1	6.7
Cocaine	19.1	21.3
Crack Cocaine	15.2	13.8
Cannabis	54.1	52.2
Amphetamine	15.3	10.4
Alcohol	34.8	44.7

7.7.3 Multivariable logistic regression analysis

	OR	**95% CI**	**P-VALUE**
Older Age	1.010	0.999-1.021	0.063
Treatment Duration	.980	0.977-0.984	<0.001*
Female	1.123	0.904-1.395	0.293
Opioid Overdose	0.882	0.692-1.124	0.310
Receiving ODSP	0.839	0.691-1.081	0.174
Illicit Opioid Use	0.408	0.324-0.514	<0.001*
Cannabis Use	0.923	0.741-1.150	0.474
Amphetamine Use	0.653	0.462- 0.923	0.016*
Crack Cocaine Use	1.028	0.743-1.423	0.866
Cocaine Use	1.244	0.938-1.650	0.129

Alcohol Use	1.401	1.122-1.750	0.003*

7.7.4 Multivariable logistic regression by sex

	MALES			FEMALES		
	OR	95% CI	P-value	OR	95% CI	P-value
Older Age	1.007	0.992-1.022	0.345	1.014	0.999-1.030	0.071
Treatment Duration	0.973	0.967-0.978	<0.001*	0.986	0.982-0.990	<0.001*
Opioid Overdose	1.119	0.803-1.560	0.508	0.709	0.491-1.024	0.067
Receiving ODSP	0.680	0.470-0.985	0.041	0.982	0.688-1.403	0.922
Illicit Opioid Use	0.302	0.219-0.418	<0.001*	0.552	0.392-0.778	<0.001*
Cannabis Use	0.845	0.619-1.155	0.292	0.989	0.720-1.358	0.944
Amphetamine Use	0.421	0.258-0.684	<0.001*	1.035	0.623-1.720	0.895
Crack Cocaine Use	1.225	0.772-1.942	0.389	0.867	0.543-1.385	0.552
Cocaine Use	1.371	0.937-2.005	0.104	1.145	0.742-1.768	0.541
Alcohol Use	1.291	0.946-1.762	0.107	1.611	1.162-2.234	0.004*

7.7.5 Sensitivity Analysis by Micro-dosing Year

	PRE-MICRO-DOSING			POST MICRO-DOSING		
	OR	95% CI	P-value	OR	95% CI	P-value
Older Age	1.027	1.003-1.051	0.029*	1.007	0.995-1.020	0.249
Treatment Duration	0.989	0.983-0.994	<0.001*	0.976	0.966-0.987	<0.001*
Female	1.874	1.167-3.008	0.009*	0.987	0.769-1.267	0.919
Opioid Overdose	1.318	0.761-2.282	0.325	0.789	0.600-1.037	0.090
Receiving ODSP	0.529	0.306-0.915	0.023*	0.947	0.707-1.268	0.714
Illicit Opioid Use	0.565	0.350-0.912	0.019*	0.341	0.260-0.448	<0.001*
Cannabis Use	0.747	0.469-1.192	0.221	0.981	0.780-1.267	0.844
Amphetamine Use	0.862	0.372-1.999	0.730	0.610	0.416-0.895	0.011*
Crack Cocaine Use	1.514	0.799-2.867	0.203	0.905	0.620-1.322	0.607
Cocaine Use	1.059	0.564-1.987	0.858	1.303	0.945-1797	0.107
Alcohol Use	1.882	1.173-3.021	0.009*	1.341	1.035-1.737	0.026*

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8 CHAPTER 8

8.1 Concluding Remarks

8.1.1 Overview

Through this thesis, we have examined opioid use disorder treatment outcomes and predictors using three perspectives. Firstly, we appraised existing literature by conducting two systematic reviews and meta-analyses which addressed the shift in the demographic profile of an individual with OUD in relation to the shift in the demographic profile (Chapters 2,3 and 4). These systematic reviews were followed up with an observational study examining differences in the sociodemographic and health status profile of these two groups (Chapter 5). Characterization of the shift in the demographic profile of an individual with OUD lead to the identification of a variety of differences in the profile of someone with OUD. Thus, we ended our investigation with a look at the impact of generalized treatment, specifically MAT, on the ever-shifting demographic profile of an individual with OUD. More specifically, we examined what goals individuals with OUD would like to achieve from treatment (Chapter 6) and whether there are differences among patients by the type of MAT received (Chapter 7).

8.1.2 Role of demographic shift in OUD

The increase in the number of opioid prescriptions has not only contributed to the opioid epidemic and but it is also the reason for the shift in the demographic profile of people with OUD. While one of the most common reasons to be prescribed opioids is for

chronic, noncancer pain, we wanted to assess how this impacts those that were provided opioids for acute pain. Therefore, we looked at the literature investigating the adverse events and risks that are associated with prescribing opioids for a common acute pain condition, ALBP. Although we were not able to identify a great deal of studies examining this association, the meta-analysis we conducted suggested that prescribing opioids for ALBP may put patients at risk for recurrent opioid use. This review also revealed a need for good, empirical evidence through trials assessing the role of prescription opioids on the effectiveness of treating ALBP, and perhaps even acute pain conditions as a whole. Speaking to this, the 2017 Canadian guidelines for opioids for chronic noncancer pain has recommended nonsteroidal anti-inflammatory drugs as a first line of treatment for chronic pain conditions which last much longer than acute pain.

To further examine the shift in the demographic profile, we synthesized the literature on the method of introduction to opioids and treatment outcomes for patients receiving MAT for OUD. Results of this study showed that the those introduced to opioids through a legitimate prescription were less likely to use opioids, cannabis, cocaine, alcohol and injection drug use in comparison to those that were initially introduced through recreational means. As a follow-up to this study, we conducted an observational study investigating the socio-demographic and health functioning differences by method of introduction in those receiving MAT. We found that those introduced by prescription were less likely to have used cannabis and more likely to report chronic pain. These two studies highlight that there are significant differences between patients introduced via prescriptions and those who were introduced via other

means, suggesting that these patients may have different needs that need to be addressed through personalized care. Education, support, and availability of harm reduction resources could address the concerns of high-risk taking behaviour and consequently higher presence of health problems such as Hepatitis C and polysubstance use, seen in individuals introduced to opioids through non-prescription means. Individuals introduced via prescription could also benefit from targeted treatment as they have higher prevalence of conditions such as chronic pain that could be integrated into their treatment plan.

8.1.3 Association between ambiguous MAT outcomes and the Shifting Demographic profile

We conducted a study examining what are the goals of treatment that patients report that they want to achieve from receiving MAT as we wanted to identify any inconsistencies in the expectations from MAT. We found that the majority of participants wanted to either stop treatment completely or stop the use of all drugs. We also found that participants reported wanting to live a normal life, manage their pain, avoid withdrawal symptoms, taper off treatment or were satisfied and wanted no change. These findings are extremely important in OUD research as notably, trials (the gold standard for MAT research) often neglect patient-important outcomes in favour of more convenient surrogate outcomes when assessing effectiveness, despite the limited relevance of such outcomes to the patients themselves. Patient, clinician, and researcher perspectives may differ importantly on the outcomes to be considered when testing effectiveness. For example, one intervention may appear more effective as it pertains to outcomes of opioid

use, but produce worse outcomes on important psychosocial outcomes, pain management or withdrawal symptoms. While disagreement between key parties is a challenge in the selection of outcomes for clinical trials for numerous health conditions, the selection of outcomes of effectiveness is of particular concern for OUD and is likely compounded by the polarity in national clinical guidelines for MAT. Indeed, Canadian MAT guidelines reflect a harm reduction approach aimed at reducing illicit opioid use, while the United States of America guidelines for management of OUD are aligned with abstinence. The divided priorities established by national guidelines for management of OUD likely magnify the differences in the outcome sets investigated in trials of MAT, and lack of consensus on important outcome measures has led to the underreporting of patient-important outcomes in OUD trials. Identification of some type of consensus between patient and clinician perspectives on what are important outcomes in assessing MAT effectiveness is essential.

Lastly, we conducted a study examining treatment outcome differences among those receiving methadone and buprenorphine/naloxone. We found that those receiving buprenorphine/naloxone were less likely to use illicit opioids, amphetamines and more likely to use alcohol in comparison to those on methadone. This reveal important clinical implications in such that there are differences among these two groups that should be taken into consideration when recommending a specific MAT for an individual with OUD.

8.2 Future Directions

Given the great heterogeneity and differences we have demonstrated within the OUD population receiving treatment, it is necessary to push OUD research into to developing a core set of outcomes for OUD treatment which incorporates patient-important outcomes and further personalized care. The development of a set of core domains will improve the usability of future RCTs and trials and will inform the effectiveness of pharmacological treatments for OUD, thus leading to the development of evidence-based guidelines. The development of a set of core domains will specifically lead to the establishment of a consistent set of outcomes to assess effectiveness of treatments for OUD, which will help researchers complete meta-analyses and other cross-study comparisons. These comparisons will ultimately inform the evidence-based clinical management of OUD, which is a fundamental aspect of mitigating the current opioid crisis. Additionally, future research should aim to bridge the gap by developing some type of translational tool that providers of treatment can utilize in developing a personalized treatment plan that takes patient goals into consideration.

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Systematic Review

Adverse Outcomes Associated with Prescription Opioids for Acute Low Back Pain: A Systematic Review and Meta-Analysis

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Background: Acute low back pain (ALBP) is a common clinical complaint that can last anywhere from 24 hours to 12 weeks. In recent years, there has been an opioid epidemic which is linked to the increased availability of prescription opioids. Though guidelines recommend that in the treatment of ALBP, opioids should be used when other treatments fail, we have seen an increase in opioid prescriptions for ALBP. With this crisis, it is important to examine if there are any adverse outcomes associated with prescribing opioids for ALBP.

Objective: We aim to review the published literature to examine the adverse outcomes associated with opioid use for ALBP.

Study Design: We performed a systematic review with meta-analysis in accordance with our published protocol and PRISMA guidelines.

Setting: The review was conducted at McMaster University.

Methods: Various electronic databases for articles published from inception to September 30, 2017, inclusive. Both randomized clinical trials and observational studies on the impact of opioid use in ALBP in the adult population were included. Eight pairs of independent reviewers performed screening, data extraction, and assessment of methodological quality. The identified articles were assessed for risk of bias using sensitivity analysis. Trials with comparative outcomes were reported in a meta-analysis using a fixed effects model.

Results: A total of 13,889 studies were initially screened for the review and a total of 4 studies were included in the full review, of which 2 studies were meta-analyzed. Our results showed that prescribing opioids for ALBP was significantly associated with long-term continued opioid use (1.57, 95% CI, 1.06-2.33). There was no significant association found between unemployment duration and prescribing opioids for ALBP (3.54, 95% CI, -7.57 to 14.66).

Limitations: Due to the limited number of studies that considered unemployment, only an unpooled analysis was conducted. Among the included studies there was both statistical and clinical heterogeneity due to differences in methodology, study design, risk of selection or performance bias. Most of the studies had an unclear or high risk of bias and poorly defined side effects.

Conclusions: Due to the lack of literature examining long-term adverse outcomes associated with prescribing opioids for ALBP, no definitive conclusions can be made. However, with the literature available, there does seem to be risk associated with prescribing opioids for ALBP so there is a great need to conduct further investigations examining these adverse outcomes for ALBP patients.

Key words: Acute low back pain, opioids, prescriptions, low back pain, long-term use, opioid use disorder

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In general, low back pain causes discomfort and pain to a wide number of people each year (1,2) and has become an extremely common clinical complaint (3). Acute low back pain (ALBP) is a major cause of disability and is described as pain in the inferior gluteal and costal margin (3-5). This pain typically lasts between 24 hours and 12 weeks (5). Even though a large proportion of ALBP patients recover within 14 days, recurrent pain is experienced by about 70% of ALBP patients within one year of onset (6,7). Additionally, a previous study reported that 85% of all acute back pain is nonspecific and hence, it cannot be ascribed to a definite cause (8). However, research has shown that some of the main causes include trauma, malignancy or bone metastasis, infective cases like an abscess and osteomyelitis, and inflammatory conditions like HLA-B27 arthritis (9-11). ALBP remains a leading cause of disability as well as a major public health problem (12).

The use of non-opioid therapy is the main recommendation for the management of ALBP. The current framework given by the American College of Physicians, as well as the American Pain Society and the European guidelines for managing low back pain in primary care, recommend the use and application of non-opioid therapies like nonsteroidal anti-inflammatory drugs as the initial line of treatment for low back pain (5,10,13). The guidelines further propose that opioids need to be used for ALBP only in severe cases, particularly when other forms of medications and treatments are deemed ineffective (5,10). Opioid prescriptions for ALBP have greatly increased, though their effectiveness is yet to be supported by evidence (14). Moreover, research has indicated that work loss linked with back pain is more likely for people who have taken opioids compared to those who have not (15).

Deyo et al (16) found that over 2% of US adults reported regular prescription and use of opioids, and more than half of these have low back pain. The research suggests that many of the patients who use prescribed opioids have persistently high levels of low back pain. It has been suggested that despite uncertainties about their long-term safety and efficacy for ALBP, the use of prescription opioids for ALBP has risen rapidly in parallel with the opioid crisis (17).

In Canada, opioid misuse through physician prescription is rampant (18). The Canadian Center on Substance Abuse (CCSA) in 2013 devised a prevention strategy that involved education of the public, patients, and physicians (19). It also devised an evidence-based policy recommendation to avoid the harm of addiction and improve prescription practices. Despite the CCSA's efforts, the use of opioids is still high in some parts of Canada. In Ontario, mortality due to prescribed opioid use has increased (20). Opioid use disorder has also led to societal problems like criminality and increased disease infection rates (18,21,22). A recent investigation by Bawor et al found that more than half of the women as well as a third of the men diagnosed with opioid use disorder were first introduced to opioids through a legitimate prescription (23). There remains a gap in the literature investigating the incidence of abuse, misuse, or dependence (opioid use disorder) after being prescribed opioids for ALBP (24).

Evidence for long-term misuse of opioids, as well as other adverse outcomes following prescription of opioids for ALBP, have not been examined systematically. This lack of research makes it difficult for clinicians to make informed treatment-related decisions, and for patients to make informed decisions regarding their own treatment. This review will make a critical and significant contribution to the practice of prescribing and use of opioids for ALBP management –a common debilitating condition experienced by many people.

Objectives

The objective of this review was to conduct a systematic review and meta-analysis of the literature investigating adverse outcomes associated with prescribing opioids for ALBP. Adverse outcomes of interest included prescription abuse, misuse, continued long-term use, development of opioid use disorder, unemployment, social adversity, marital discord, criminal activity, and mortality.

Methods

Protocol and Registration

This systematic review was conducted to investigate adverse outcomes associated with prescription opioid use for adult ALBP patients. The Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines were followed (25). The protocol for this systematic review has been published previously and registered with PROSPERO (registration number CRD42016033090) (26).

Eligibility Criteria

We included studies reporting on patients 18 years or older, gender, and ethnicity. Patients with a primary diagnosis of ALBP (as defined by reporting low back pain of ≤ 12 weeks without a clear and specific attributable

cause) (4) in any setting were included. Inclusion criteria for participation were those studies describing prescription opioids for ALBP and reporting on the duration of use, follow-up, incident misuse, social adversity, side effects, and mortality. Eligible study designs included randomized controlled trials (RCTs), observational studies (including cohort and cross-sectional designs), pilot or feasibility studies (powered), and other trial designs (e.g., cross-over and cluster RCTs).

Information Sources and Search Strategy

The following electronic databases were searched from inception to September 30, 2017 with no language limitations: PubMed, EMBASE, PsycINFO, CINAHL, and Web of Science. In addition, we searched trial databases of the National Institutes for Health Clinical Trials Registry, Cochrane Trials Registry, and the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP). We also conducted a manual search of reference lists from identified studies, relevant articles, and systematic reviews; key journals; as well as grey literature. Search terms were related to ALBP, prescription opioids, and MeSH terms (Table 1, Appendix 1). Study authors were contacted when outcome data were insufficient for analysis.

Table 1. *Example of search strategy.*

MEDLINE = 669	1 exp Acute Pain
	2 exp Low Back Pain
	3 exp Analgesics, Opioid
	4 exp Morphine
	5 exp Codeine
	6 exp Fentanyl
	7 exp Tramadol
	8 exp Meptazinol
	9 exp Pentazocine
	10 exp Methadone
	11 exp Buprenorphine
	12 oxycodone.mp.
	13 dipipanone.mp.
	14 remifentanil.mp.
	15 papaveretum.mp.
	16 pethidine.mp.
	17 tapentadol.mp.
	18 1 or 2
	19 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17
	20 18 and 19 (728)
	21 limit 20 to humans (701)

Study Selection

Eight pairs of reviewers independently performed the initial and subsequent screenings and data extraction of the articles according to the set of inclusion and exclusion criteria. When there was disagreement, resolution was reached by either discussion to consensus, or by consultation with a third party if it remained unresolved.

Data Collection and Data Items

After identifying relevant studies, the following data were extracted from the full texts of the studies using piloted standardized forms: author, year of study, country, study design, patient demographics (number, age, and gender), intervention (type of prescription, dose and duration of treatment), comparators, and main outcome measures. In addition, we extracted data on statistical results obtained in each identified study. For the extraction form, please see Appendix 2.

Risk of Bias of Individual Studies

Two reviewers conducted independent assessments of the methodological quality of eligible studies; a modified version of the Newcastle-Ottawa Scale that has been modified for cross-sectional studies was used to assess the risk of bias for the observational studies (27). Eight items in the Newcastle-Ottawa scale were categorized into criteria based on study selection, comparability, and appropriateness of outcome measures. For randomized controlled studies, the Cochrane Risk of Bias tool was applied to eligible studies to assess all sources of bias (such as selection bias, attribution bias, reporting bias, etc.) (28). The quality and strength of evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria and summarized in Table 2 (29).

Statistical Analyses

We have presented our findings both qualitatively and quantitatively. Where possible we have reported on population characteristics associated with experiencing adverse events as well as intervention characteristics such as prescription patterns, doses and types of opioids, duration of treatment, and whether any specific guidelines were followed.

We have presented pooled dichotomized data as odds ratios (OR) with 95% confidence intervals and pooled continuous data as mean differences (MD) or stan-

Table 2. *Summary of findings.*

Certainty Assessment					No. of patients		Effect		Certainty	Importance
No. of studies	**Study Design**	**Risk of bias**	**Inconsistency/ Indirectness/ Imprecision**	**Other considerations**	**Early Opioid Use**	**No Opioid Use**	**Relative (95% CI)**	**Absolute (95% CI)**		
Unemployment										
2	observational studies	not serious	not serious / not serious / serious [a]	all plausible residual confounding would reduce the demonstrated effect	786	9189	-	MD 3.54 higher (7.57 lower to 14.66 higher)	⊕⊕◯◯ Low	Important
Late Opioid Use										
2	observational studies	not serious	serious [b] / not serious/ not serious	all plausible residual confounding would reduce the demonstrated effect	134/786 (17.0%)	932/9189 (10.1%)	RR 1.57 (1.06 to 2.33)	58 more per 1,000 (from 6 more to 135 more)	⊕⊕◯◯ Low	Critical
Side Effects										
2	randomised trials	not serious	serious [c] / serious [d] / serious [e]	none	One study reported that the group receiving opioids as treatment experienced worse side effects than the group receiving alternative drug whereas another study reported both groups experiencing a similar number of side effects.				⊕◯◯◯ Very Low	Important

CI: Confidence interval; MD: Mean difference; RR: Risk ratio
a. Imprecise as adjusted pooled estimates were not possible to conduct.
b. Inconsistent due to high heterogeneity and large variation across study characteristics, including population, sample size and method of measuring late opioid use.
c. High degree of variability in side effects reported.
d. Often looking at adverse events profile, not specifically exploring established opioid-related side effects.
e. Pooled estimate was not possible as there was large variation between studies as to what side-effects were measured and there was also variation in drugs that were being compared.

dardized mean differences (SMD) with 95% confidence intervals. We have quantified data heterogeneity using the I-squared statistics greater than 40% since Cochrane has indicated that a value less than 40% may not be a representation of significant heterogeneity (30). To account for confounding, adjusted analyses from observational studies were used. Meta-analysis was conducted using RevMan 5.2 (The Nordic Cochrane Centre for The Cochrane Collaboration, Copenhagen, Denmark). We were unable to assess publication bias, as studies have reported that this is not possible for fewer than 10 studies (31). We followed the PRISMA reporting guidelines (Fig. 1).

Types of Interventions

Experimental

The experimental intervention included prescriptions of any type of opioid for the treatment of ALBP. The types of opioids included morphine, diamorphine, fentanyl, alfentanil, remifentanil, methadone, oxycodone, pethidine, tapentadol, tramadol, codeine, dihydrocodeine, and meptazinol.

Comparators

The accepted comparators included placebo/not prescribed any opioids, any non-opioid analgesics, and any complementary therapies.

Outcome Measures

Continued Opioid Use

We have defined continued opioid use as ongoing opioid use beyond the needed time to treat for ALBP. ALBP is a pain condition that does not last more than 12 weeks by definition. Continued opioid use may be measured in a variety of ways, such as us-

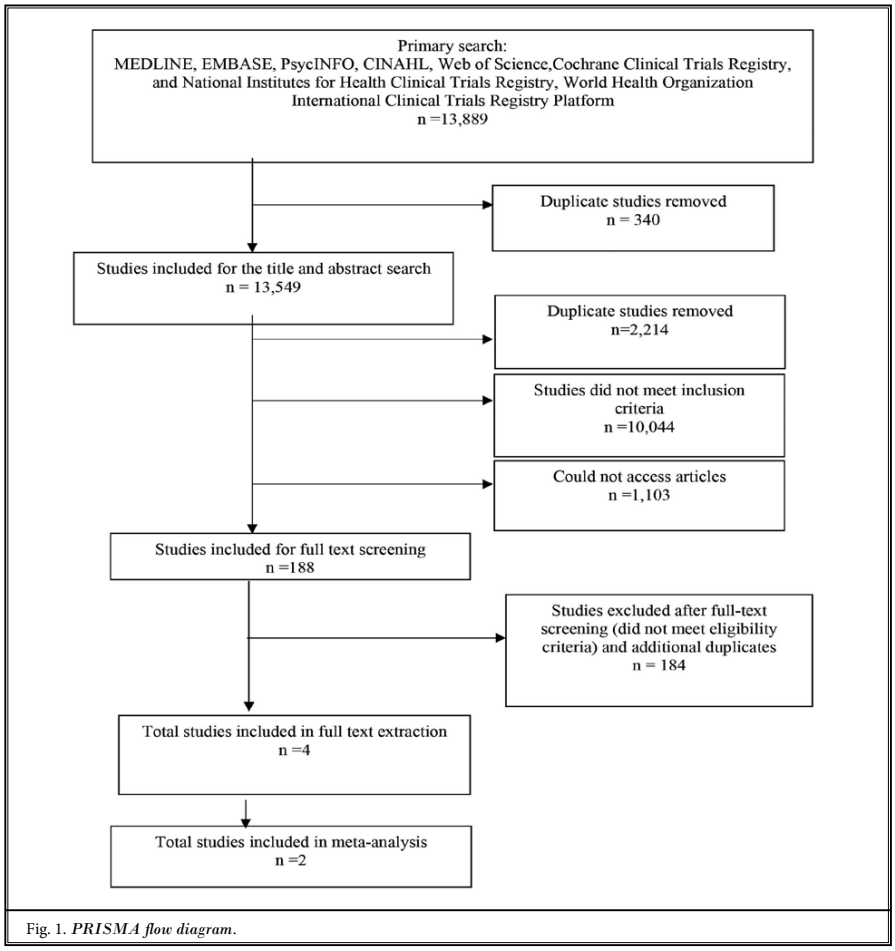

Fig. 1. *PRISMA flow diagram.*

ing a prescription monitoring system to determine if additional prescriptions were prescribed beyond the need to treat ALBP or through urine screens testing for opioids. A full list of outcome measures can be found in Table 3.

Unemployment

Unemployment is defined as the total time an individual has not worked since being diagnosed with ALBP. This can also be measured in varied ways including disability claims, self-report, and government records. A full list of outcomes for unemployment can be found in Table 3.

Table 3. *Summary of study characteristics.*

Study Name and Year	Methods (type of study, what is the study comparing, blinds, analysis, sample size)	Participants (age range, gender, exclusion criteria, primary diagnosis)	Interventions (Brief description of the two groups separated by arm)	Outcomes (Tools they use to measure it)
Innes 1998 (32)	Double-blind, randomized clinical trial comparing analgesic efficacy and adverse effects of ketorolac to acetaminophen–codeine in ED patients with acute musculoskeletal low back pain Continuous data analyzed using general linear model ANOVA; ordinal efficacy variables analyzed using Cochran-Mantel-Haenzel (CMH) test adjusted for centre effect and compared between groups using Mann-Whitney U-test; nominal data analyzed by χ^2 or Fisher Exact Probability tests as appropriate; within-group comparisons performed using Student's paired t-test for parametric data and Wilcoxon signed-rank paired tests for categorical data Sample Size: ketorolac 62, acetaminophen-codeine 60	n = 122 Mean age (SD) of ketorolac 33.1 (9.86); mean age of acetaminophen-codeine 36.0 (10.07) Gender: 26 females, 96 males Primary diagnosis: acute musculoskeletal low back pain Exclusion criteria: active peptic ulcer within 6 months; bleeding diathesis or anticoagulant use within 4 weeks; pregnancy or breastfeeding; chronic pain condition or recurring back pain; suspected or known alcohol or drug abuse; received any investigational drug within 4 weeks; co-existing injury or illness contraindicating study medications or interfering with evaluations (e.g. asthma or COPD); allergy, sensitivity, or contraindication to acetaminophen, opioids, ASA, or NSAIDs; fracture, dislocation, neurological impairment, or cause of back pain requiring treatment beyond analgesics; receiving medications that might influence pain intensity evaluations (e.g. analgesics, anesthetics, sedating antihistamines, antiemetics, anxiolytics, antidepressants, psychotropic)	Ketorolac tromethamine (KET): 10 mg orally, then 10 mg every 4–6 h as needed (up to 4 doses in 24 h); patients requiring fifth or sixth analgesic dose in any 24-h period given acetaminophen (650 mg per dose) Acetaminophen-codeine (ACOD): 600 mg acetaminophen/60 mg codeine orally, with same dose repeated every 4–6 h as needed (up to 6 doses in 24 h)	Adverse events recorded by research staff at ED discharge, telephone follow-up, and study termination and recorded by patients in their diaries; events occurring more than once for any given patient reported only once under worst recorded severity, outcome, and relation to study drug
Lee 2016 (35)	Retrospective cohort study examining effects of early opioid prescription for acute occupational low back pain in the emergency department on disability duration, long-term opioid use, total medical costs, and subsequent surgeries Cox proportional hazard analysis to quantify risk of early opioid use on cumulative disability duration; multivariate binomial log regression models to examine relationship between early opioid use and acute disability, chronic disability, and subsequent low back surgeries; multivariate linear regression models to determine impact of early opioid use on total medical costs Sample Size: early opioids 349, no early opioids 2538	n = 2887 Mean age (range) of early opioids 40.5 (39.3–41.6); mean age of no early opioids 41.4 (41.0–41.8) Gender: 1106 females, 1781 males Primary diagnosis: acute occupational low back pain Exclusion criteria: zero-cost cases (no payment of medical / indemnity services); medical-only cases (no paid temporary partial / total disability days); cases with WC claims within the year before their injury date; cases with <1 year of tenure; complex cases with initial hospitalization(s), fractures, or multiple injuries	Early opioids: Workers' Compensation claims with an initial ED visit within 3 days post-onset that received early opioid(s) within 2 days of initial ED visit date No early opioids: Workers' Compensation claims with an initial ED visit within 3 days post-onset without any early opioids	Total length of work disability was operationalized as the total number of compensated days lost from work that were covered by indemnity payments (i.e. wage replacement for lost work time) Long-term opioid use was defined as having medical bills for ≥ 3 opioid

Table 3 con't. *Summary of study characteristics.*

Study Name and Year	Methods (type of study, what is the study comparing, blinds, analysis, sample size)	Participants (age range, gender, exclusion criteria, primary diagnosis)	Interventions (Brief description of the two groups separated by arm)	Outcomes (Tools they use to measure it)
Videman 1984 (33)	Double-blind parallel trial comparing clinical efficacy and tolerance of orally administered meptazinol and diflunisal in treatment of lumbago Statistical significance of differences between the two groups evaluated with Student's t-test; differences in duration for which treatments were given in each group evaluated with Kolmogorov-Smirnov's test Sample Size: meptazinol 35, diflunisal 35	n = 70 Mean age (SD) of meptazinol 38 (14); mean age of diflunisal 35 (11) Gender: 29 females, 41 males Primary diagnosis: acute low back pain Exclusion criteria: pregnant or breastfeeding; significant haematological, renal, hepatic, respiratory, or circulatory disorders; history of peptic ulceration or GI upset; sensitive to narcotic analgesics and/or benzomorphan derivatives (dependent upon narcotic agents or any other drugs); weight < 45 kg or > 95 kg	Meptazinol: 1 tablet of 200 mg 4 times daily plus placebo resembling diflunisal capsule Diflunisal: 1 capsule of 250 mg 4 times daily plus placebo resembling meptazinol tablet	Details of any side-effects reported were also noted at each visit.
Webster 2007 (34)	Retrospective cohort study examining association between early opioid use for acute LBP and several outcomes: disability duration, medical costs, "late opioid" use (5 prescriptions from 30 to 730 days), and surgery in a 2-year period following LBP onset Multivariate linear regression to examine association between receipt of early opioid prescriptions, disability duration, total medical costs; logistic regression to examine association between receipt of early opioid prescriptions and undergoing low back surgery, late use of opioids Sample Size: 0 mg MEA* 6651, 1–140 mg MEA 437, 141–225 mg 494, 226–450 mg 423, 450+ mg 438 *morphine equivalent amount	n = 8443 Mean age (SD) of 0 mg MEA 40.3 (10.4); mean age of 1–140 mg MEA 39.6 (10.3); mean age of 141–225 mg MEA 40.8 (10.7); mean age of 226–450 mg MEA 40.6 (9.5); mean age of 450+ MEA 40.7 (9.7) Gender: 2381 females, 6062 males Primary diagnosis: acute occupational low back pain Exclusion criteria: <1 day of compensated lost time; <1 year of job tenure; any low back pain claims in prior year; lost time began >10 days after low back pain onset; received no paid medical service within 15 days post-onset; received treatment for a fracture or any other concurrent condition within 15 days post-onset	No early opioids: no opioid medications received within 15 days post-onset based on paid medical bills Early opioids: divided into 4 groups based on quartiles of MEA received (1–140 mg, 141–225 mg, 226–450 mg, 450+ mg)	Length of disability determined using indemnity (wage replacement) payments Late opioid prescriptions defined as cases receiving 5 or more opioid prescriptions between 30 and 730 days post-onset

Side Effects

Side effects are defined as any adverse symptoms experienced by individuals while on any medication that was treating their ALBP. There was much heterogeneity in the side effects being measured and therefore these results were presented in a narrative summary.

Results

Study Selection

From the electronic database searches, a total of 13,889 relevant abstracts were screened. After removal of 2,554 duplicates and exclusion of 11,147 studies that did not meet the inclusion criteria, the full texts of the remaining 188 articles were screened and 4 studies were included. The PRISMA flow chart for the selection process is exhibited in Fig. 1. Of the remaining 4 studies, 2 of the studies were excluded from the meta-analysis because they did not measure the outcomes of unemployment or continued opioid use (32,33). The final 2 studies that quantified outcomes of recurrent opioid use and unemployment were subjected to meta-analysis (34,35).

Study Characteristics

The characteristics of the included studies in this review are summarized in Table 3. Of the 4 studies included in the systematic review, 2 were retrospective observational studies (34,35) and 2 were clinical trials (32,33). The 2 observational studies compared groups that did not receive any opioids when diagnosed with ALBP to groups that did receive opioids for ALBP. The RCTs compared opioid groups (metzapinol and acetaminophen-codeine) to comparator drugs (ketorolac and diflunisal) for ALBP. The mean age (k = 4) across intervention groups was 38.5 years, and mean age across comparator groups (k = 4) was 37.5 years. The majority of the sample consisted of male patients (68.8%).

Only 2 studies reported on the outcomes of continued opioid use and disability duration (34,35). Two studies did not report on side effects experienced (34,35) while the other 2 studies reported on adverse symptoms profiles (32,33).

Risk of Bias Within Studies

The quality of each included study is shown in Table 2. Justifications for assessments are presented in Appendix III with the risk of bias tables. The Cochrane Risk of Bias and the modified Newcastle-Ottawa Scale (NOS) were used to rate the internal validity of the studies shown in Fig. 2. The Cochrane Risk of Bias tool was used to assess the quality of the RCTs and NOS was used to assess the quality of the observational studies.

Generally, the results of the RCTs included in this review should be interpreted with caution due to the risk of bias shown in Fig. 2. Some of the common issues were surprising. Specifically, one out of the 2 RCTs did not include any information on random sequence generation, blinding of patients or personnel, or blinding of outcome assessment or outcome data. This was especially surprising as blinding in drug studies is not unusual for investigators and patients. Neither RCT included any information on allocation concealment. One of the studies should especially be interpreted with caution as it was funded by the company that produces one of the drugs under investigation.

For the 2 observational studies, neither provided any information about how any missing data were handled. One of the observational studies did not adjust for confounding variables for unemployment, which places it at high risk of bias. Otherwise, the 2 studies were generally well reported on all other characteristics including an appropriate population, sample size, statistical analyses, and outcome measurement.

Results of Individual Studies

Recurrent Opioid Use

Our meta-analysis pooled results of 2 studies comparing the effects of opioid prescription use for ALBP on recurrent use of prescription opioids in the future by measuring the number of prescriptions given utilizing a prescribing database. The other 2 identified studies did not report on the outcome of recurrent opioid use (32,33) (Fig. 3). Opioid prescription in Lee et al (35) was defined as receiving and filling a prescription for ALBP within 2 days of the ED visit and it was defined by Webster et al (34) as receiving and filling a prescription within 15 days of the ED visit. The total sample size consists of 9,975 patients. In Webster et al (34), prescription opioid dosage was divided into 4 quartiles that ranged from 1 to 450+ morphine equivalent amount (MEA). In Lee et al (35), the mean for MEA was 145. In this analysis, we used the results for the entire population of Lee at al (35) and the results from the 1-140 MEA group of Webster et al (34). In our meta-analysis, we used the relative risk ratio to compare the groups that received no opioid prescription to the group that did receive an opioid prescription. The relative risk ratio is defined as the risk of an event, in this case recurrent opioid use, relative to an exposure, prescription for opioids. For recurrent opioid use, we see that those who were pre-

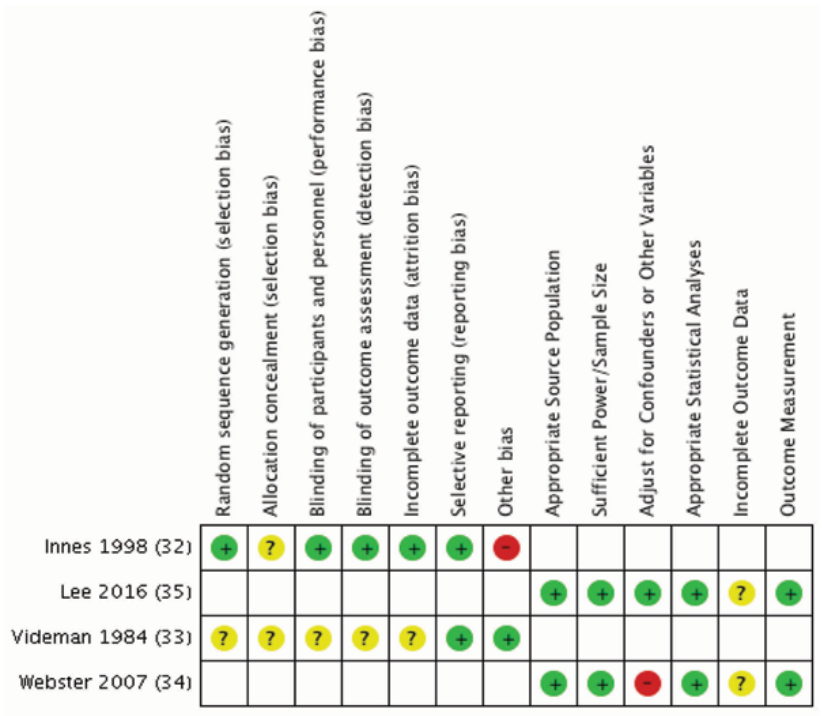

Fig. 2. *Risk of bias summary: review authors' judgements about each risk of bias item for each included study. The items from random sequence generation to other bias (inclusive) are from the Cochrane Risk of Bias Tool reflecting the 2 RCTs while items from Appropriate Source Population to Outcome Measurement (inclusive) are from the Newcastle-Ottawa Scale (NOS) reflecting the 2 observational studies.*

scribed opioids for ALBP were 57% (95% CI, 1.06-2.33) more likely to have recurrent opioid use than those who were not given an opioid prescription. However, significant heterogeneity (I^2 = 83%) is present.

Unemployment

Overall, our meta-analysis (Fig. 4) pooled results of 2 studies comparing the opioid prescription for ALBP and no opioid use, measuring outcomes of unemployment. The other 2 studies did not report quantitative data on the unemployment outcome. The total sample size consisted of 9,975 patients. Both Webster et al (34) and Lee et al (35) measured unemployment as days filed for worker's disability. Similarly, for the analysis of continued opioid use, we used the results for the 1-140 MEA from Webster at al (34) and the results of the full sample for Lee et al (35). In our meta-analysis, we used the standardized mean difference (SMD) to compare the effects of both groups. The SMD is the difference in mean effects between the intervention and comparator groups divided by the pooled standard deviation (SD). In our meta-analysis, an estimated SMD of 3.54

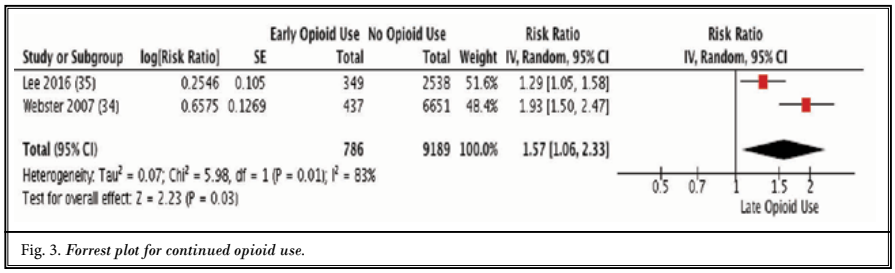

Fig. 3. *Forrest plot for continued opioid use.*

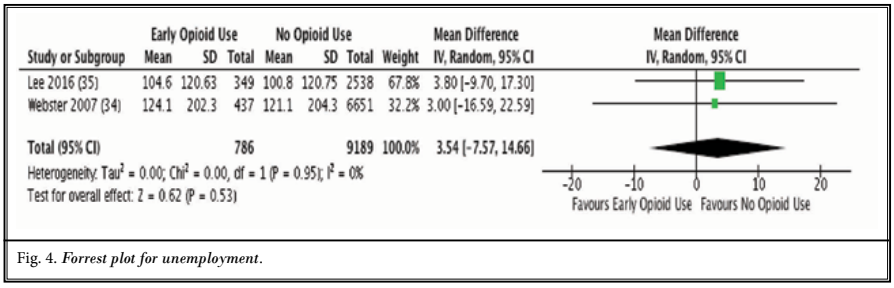

Fig. 4. *Forrest plot for unemployment.*

(95% CI, -7.57 to 14.66) was observed. These results suggest that in terms of unemployment, there is no significant association between those who had opioids prescribed for ALBP and those who did not have an opioid prescription.

Side Effects

The meta-analysis for side effects (SEs) was not possible due to high heterogeneity among the identified studies with respect to the variability of side effects considered; therefore, results have been qualitatively synthesized here. Only 2 eligible studies reported on SEs experienced. The assessment tools for measurement of SEs together with findings of the 2 studies are summarized in Table 2. While the SEs in Innes et al (32) were recorded at discharge, follow-up, and at the end of the study, Videman et al (33) only recorded the side effects at follow-ups for a total of 3 weeks. Furthermore, Innes et al (32) used a more structured approach by defining adverse drug events (ADEs) according to severity as well as employing a subjective rating scale at the termination of the study.

Both studies found a similar profile of SEs including mainly gastrointestinal and neurological symptoms experienced by patients (Table 2). Videman et al (33) also found that patients reported tiredness, sweating, and urinary symptoms. While both studies reported the number of patients affected by SEs, only Innes et al (32) described the proportion of patients with severe SEs during the study. Nevertheless, both trials reported the number of patients discontinuing treatment due to experiencing SEs during the study. In the Innes et al (32) study, twice as many SEs were reported in one intervention group compared to the other group while Videman et al (33) found comparable incidences of SEs in both of their study groups. At the study conclusion in one trial (32), the frequencies of patient self-reported overall ratings of drug tolerability as "very good" or "excellent" were 70% (95% CI, 59%-81%) and 46% (95% CI, 34%-58%] in the ketorolac and acetaminophen-codeine patient groups, respectively.

Risk of Bias Across Studies

When assessing risk of bias across studies (Fig. 5),

we noticed a few trends. First, in the RCTs, neither study provided any information on selection bias. One study did not provide any information on or analysis of detection bias or attrition bias. However, both studies were found to have reporting bias. One additional form of bias was an RCT that was being funded by a company that has developed one of the drugs used. Overall, our results show that the results from the RCTs should be interpreted carefully due to risk of bias.

In the 2 observational studies, neither study reported any information on how missing data were handled, and one study did not adjust for potential confounders. However, all studies reported the appropriate population, statistical analyses, sample size, and outcome measurement. Overall, our results show that the observational studies were generally well-reported but should still be interpreted with caution, as they are not without bias.

Additional Analyses

Due to the small number of studies identified for this review, no additional analyses were conducted.

Summary of Evidence

The main cause of deaths associated with drugs in North America is linked to opioid use with misuse of prescription opioids as the primary contributing factor to the global opioid crisis (36) and economic burden on health care systems (37). Currently, after the United States, the second largest user of pharmaceutical opioids is Canada (38,39). Despite recommendations from recent guidelines to perform a full risk assessment of ALBP patients before prescribing opioid analgesics (40,41), prescription of opioids and misuse of these medications continue (42).

Although the therapeutic efficacy of opioids for management of chronic pain in general is well-established (8,43), evidence for prescribing opioids for ALBP is largely lacking. It is uncertain whether opioid prescribing for patients with ALBP improves recovery rate or return to work and whether adverse SEs are associated with long-term overuse of opioids. To date, there are no systematic reviews on the evidence for long-term use of opioids and other adverse outcomes in patients affected by ALBP. Therefore, given the con-

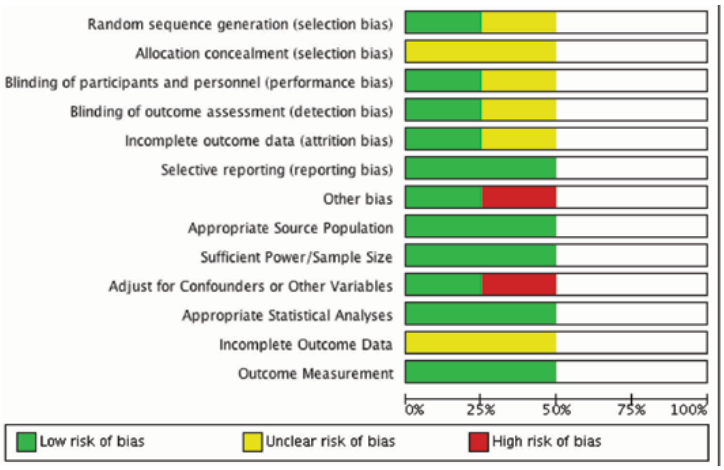

Fig. 5. *Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies. The items from random sequence generation to other bias (inclusive) are from the Cochrane Risk of Bias Tool reflecting the 2 RCTs while items from Appropriate Source Population to Outcome Measurement (inclusive) are from the Newcastle-Ottawa Scale (NOS) reflecting the 2 observational studies.*

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siderable negative impact of opioids and related-drug misuse outcomes, the evaluation of evidence regarding long-term functional outcomes associated with opioid overuse in ALBP patients is warranted. To the best of our knowledge, this study is the first reported meta-analysis on the synthesis of evidence for long-term opioid overuse and associated adverse outcomes in patients with ALBP. Our findings indicate that ALBP patients prescribed opioids are at risk for continuing to have long-term opioid prescription use and that opioid therapy for ALBP does not expedite return to work.

Continued Opioid Use

The meta-analysis of pooled evidence showed that there was a significant difference in recurrent opioid use in patients prescribed opioids versus non-opioid users. This suggests that opioid prescribing for patients affected by ALBP may constitute a risk factor for these patients to continue to use opioids beyond the time required for treatment of the acute condition. Previous studies have also indicated that prescribing opioids for acute pain management poses a high risk for long-term opioid overuse (44,45)

Furthermore, patients prescribed opioids for ALBP had double the risk of recurrent opioid use compared to those who were not given an opioid prescription. In support of our findings, several recent studies have also found higher risks of long-term opioid use and overdose associated with initial opioid exposure (46,47), especially prevalent in opioid-naïve patients with acute pain (48-50). However, due to the limited number of studies for this meta-analysis and the presence of significant heterogeneity, the results should be interpreted with caution.

Recent systematic reviews have shown that as a result of the limited number of trials there is no certainty regarding the efficacy and safety of opioids in ALBP individuals (42,51). There is also a lack of evidence in support of long-term opioid use at any dose in the treatment of ALBP. Our systematic review highlights the need for revising current guidelines related to prescribing opioids for ALBP treatment in light of the associated risk factors in prescribing opioids leading to recurrent and prolonged use of opioids.

Disability Duration and Opioid Use

We did not find a significant association between opioid prescription and disability duration for ALBP patients when combining study results. The findings of Webster et al (34) revealed that longer work disability was linked to prescribing as well as higher doses of opioids despite adjusting for injury severity and demographic factors. This could be due to the negative effect of opioids on physiological well-being or to patients' greater risk of poor outcomes independent of opioids (42). Lee et al (35), however, did not find an association between opioid prescribing and disability duration. These studies do not seem to indicate that opioids accelerate patients' return to work or improve functional outcomes. Previous studies showed that prescribing opioids for acute pain was associated with negative consequences; in a study of primary care patients, patients with acute pain who were prescribed opioids were found to have worsening of pain, function, and depression after 6 months compared to those who did not receive opioids (52). In a study of acute pain related to work injuries, patients receiving opioids for more than one week were twice as likely to experience long-term disability after one year (53).

Side Effects of Opioid Use for ALBP management

Although there was no quantitative analysis possible for SEs, this review included studies of both observational and nonplacebo designs. We found that the most commonly reported SEs of opioids in patients with ALBP were gastrointestinal and neurological symptoms. Other reported SEs included urinary symptoms, tiredness, and sweating (33). Other studies have reported similar SEs when patients were administered opioids for acute and chronic pain (54-56). The considerable heterogeneity and variability in SEs among the included studies and low number of eligible trials posed a challenge to comparing SEs of different opioids. In addition, the 2 identified trials were both randomized parallel group designs comparing opioids to other types of analgesics, with opioids demonstrating a significantly higher rate of SEs. The reported overall rates of SEs due to opioid medication (65%) were similar in the 2 randomized trials. SEs due to long-term use of opioids in patients with ALBP are not clear from the trials included, as the longest follow-up period was 3 weeks. There were also differences in the 2 included trials in terms of patient clinical demographics such as previous exposure to opioids, severity of pain, or dose of opioid medication administered during the trial. These factors may all impact the incidence of SEs and should be taken into account in the design of future trials.

The prevalence of SEs may also depend on methods used for collection of information (56), which varied

across the studies. Of note, both randomized clinical trials included mostly healthy young male patients who may recover more rapidly or have higher pain thresholds compared to the elderly or those with comorbid illness. Other factors that may explain the differences in the reporting of the 2 randomized clinical trials include differences in the duration of pain assessment, ranging from a few hours to weekly assessment. Therefore, these findings cannot be generalized to the wider population, and larger scale clinical trials with longer duration of follow-up are warranted to determine the influences of gender, age, or other demographic factors on reported SEs.

Limitations

Despite the strengths of this systematic review (such as adherence to PRISMA guidelines and publication of a protocol), there are potential limitations to consider. For the analysis of unemployment, we were only able to conduct an unpooled analysis. Although we did attempt a meta-analysis, publication bias could not be assessed due to the limited number of studies. There was both statistical and clinical heterogeneity among the included studies, due to differences in methodology, study design, risk of selection, or performance bias – which has been known to potentially affect meta-analysis (58). In addition, most of the studies had an unclear or high risk of bias and poorly defined SEs. Despite such limitations, the rapid rise in prescription-related opioid complications, including mortality due to overdose, makes this systematic review needed and raises the need for further studies to provide evidence on the efficacy and safety of long-term opioid treatment for patients with ALBP.

There is limited evidence to determine benefits and adverse effects of opioids in various subgroups of patients defined by clinical or demographic characteristics. When facing challenges with randomized clinical trials, well-designed observational studies with control of potential confounding factors are much needed to investigate the efficacy and safety of long-term opioid use in patients with ALBP. Moreover, additional research is needed to compare the benefits and safety of various opioids and dosages.

Therefore, definitive conclusions on the effectiveness of long-term opioid therapy for acute back pain are not possible due to the scarcity of clinical evidence. Within the limitations of this review, however, significant risks appear to be associated with opioid prescription for acute pain management, whereby no improvement is found in employment status and risk of continued use is evident.

Conclusions

This systematic review demonstrates that patients with ALBP who are prescribed opioids are at a significantly higher risk of continued opioid use. Furthermore, prescribing opioids for ALBP patients is associated with at least one adverse event and delayed recovery. The findings of this systematic review, in addition to the widespread opioid-prescribing trend, further highlight the urgent need to conduct randomized trials to provide (a) evidence on the efficacy and safety of pharmaceutical opioids in the treatment of patients with ALBP or (b) evidence-based guidelines to avoid prescribing opioids for ALBP.

Appendix 1. ***Complete search strategy.***

MEDLINE=669	1 exp Acute Pain 2 exp Low Back Pain 3 exp Analgesics, Opioid 4 exp Morphine 5 exp Codeine 6 exp Fentanyl 7 exp Tramadol 8 exp Meptazinol 9 exp Pentazocine 10 exp Methadone 11 exp Buprenorphine 12 oxycodone.mp. 13 dipipanone.mp. 14 remifentanil.mp. 15 papaveretum.mp. 16 pethidine.mp. 17 tapentadol.mp. 18 1 or 2 19 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 20 18 and 19 (728) 21 limit 20 to humans (701)
EMBASE=6,565	1 exp pain 2 exp low back pain 3 exp narcotic analgesic agent 4 exp morphine 5 exp codeine 6 exp fentanyl 7 exp tramadol 8 exp meptazinol 9 exp pentazocine 10 exp methadone 11 exp buprenorphine 12 oxycodone.mp. 13 dipipanone.mp. 14 remifentanil.mp. 15 papaveretum.mp. 16 pethidine.mp. 17 tapentadol.mp. 18 acute pain.mp. 19 1 or 2 or 18 20 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 21 19 and 20 22 1 and 18 23 2 or 22 24 20 and 23
PsycINFO=247	1 exp Pain 2 exp Back Pain 3 1 and 2 4 low back pain.mp. 5 acute pain.mp. 6 exp Opiates 7 exp MORPHINE 8 exp CODEINE 9 exp TRAMADOL 10 exp PENTAZOCINE 11 exp FENTANYL 12 exp METHADONE 13 meptazinol.mp. 14 exp BUPRENORPHINE 15 oxycodone.mp. 16 dipipanone.mp. 17 remifentanil.mp. 18 papaveretum.mp. 19 pethidine.mp. 20 tapentadol.mp. 21 3 or 4 or 5 22 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 23 21 and 22

Appendix 1 con't. ***Complete search strategy.***

Web of Science =5,511	1 TS=acute pain 2 TS=low back pain 3 TS=analgesics, opioid 4 TS=morphine 5 TS= codeine 6 TS= tramadol 7 TS= pentazocine 8 TS= fentanyl 9 TS= methadone 10 TS= meptazinol 11 TS= buprenorphine 12 TS= oxycodone 13 TS= dipipanone 14 TS= remifentanil 15 TS= papaveretum 16 TS= pethidine 17 TS= tapentadol 18 #2 OR #1 19 #17 OR #16 OR #15 OR #14 OR #13 OR #12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 20 #19 AND #18
CINAHL= 229	1 MM "Acute Pain (Saba CCC)") OR (MM "Pain Clinics") OR "acute pain" 2 MM "Low Back Pain" 3 MH "Analgesics, Opioid+" 4 MH "Morphine+" 5 MH "Codeine+" 6 MM "Tramadol" 7 MH "Fentanyl+" 8 "meptazinol" 9 MH "Pentazocine" 10 MH "Methadone" 11 MH "Buprenorphine" 12 MH "Oxycodone" 13 "dipipanone" 14 "remifentanil" 15 "papaveretum" 16 "pethidine" 17 "tapentadol" 18 S1 OR S2 19 S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 20 S18 AND S19
Cochrane Library and Clinical Trials Registry= 179	1 remifentanil 2 papaveretum 3 pethidine 4 tapentadol 5 MeSH descriptor: [Acute Pain] explode all trees 6 MeSH descriptor: [Low Back Pain] explode all trees 7 MeSH descriptor: [Analgesics, Opioid] explode all trees 8 MeSH descriptor: [Morphine] explode all trees 9 MeSH descriptor: [Codeine] explode all trees 10 MeSH descriptor: [Fentanyl] explode all trees 11 MeSH descriptor: [Tramadol] explode all trees 12 MeSH descriptor: [Meptazinol] explode all trees 13 MeSH descriptor: [Pentazocine] explode all trees 14 MeSH descriptor: [Methadone] explode all trees 15 MeSH descriptor: [Buprenorphine] explode all trees 16 MeSH descriptor: [Oxycodone] explode all trees 17 dipipanone 18 #5 or #6 19 #1 or #2 or #3 or #4 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or 15 or #16 or #17 20 #18 and #19
National Institutes for Health Clinical Trials Registry = 207	Condition or disease terms: acute pain, low back pain Intervention terms: opioids, analgesics, prescription
World Health Organization International Clinical Trials Registry Platform = 288	acute pain OR low back pain AND opioids

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Appendix 2.

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: _____

Definition of ALBP:_____

Exposure: _____ Intervention (if applicable): _____

Demographics

Number of participants: Total: _____ Men: _____ Women: _____ Per group: _____

Mean age (SD): Total: _____ Men: _____ Women: _____

Per group: _____

Ethnicity:_____

Outcome measurements:

Efficacy outcome

Schober test: _____

Pain measurement: _____

Oswestry disability questionnaire:

_____

Modified Zung questionnaire:

_____

Modified somatic perception questionnaire:

_____

Adverse events outcome:

Incidence of misuse:_____

Opioid withdrawal symptoms:

_____

Physical adverse events: _____

Social adversity:

_____

Mortality: _____

Comments:

_____

Results

Statistical methods: _____ Adjusted for: _____

Coefficient: _____95% CI: _____ p-value: _____

Findings: _____

Limitations: _____

Inclusion Criteria

RCT or observational study design examining outcome of prescription opioid use for ALBP Participants aged 18 years or older

Exclusion Criteria

Pilot or feasibility studies

Patients with comorbid use disorder

Additional Comments:

_____

_____

Appendix 3

Videman 1984 (33)		
Study Identification	**Author Judgment**	**Justification**
Random Sequence Generation	Unclear Risk	No information provided
Allocation Concealment (Selection Bias)	Unclear Risk	No information provided
Blinding of Participants and Personnel	Unclear Risk	Study described as double-blind, but no information on blinding provided
Blinding of Outcome Assessment	Unclear Risk	Study described as double-blind, but no information on blinding provided
Incomplete Outcome Data	Unclear Risk	No information provided
Selective Reporting	Low Risk	All prespecified outcomes were reported
Other	Low Risk	No other biases apparent

Innes 1998 (32)		
Study Identification	**Author Judgment**	**Justification**
Random Sequence Generation	Low Risk	Patients allocated to groups based on a computer-generated randomization code
Allocation Concealment (Selection Bias)	Unclear Risk	No information provided
Blinding of Participants and Personnel	Low Risk	All drugs were prepared in identical capsules to preserve double-blinding
Blinding of Outcome Assessment	Low Risk	A blinded consultant entered all data and performed statistical analyses
Incomplete Outcome Data	Low Risk	Missing values for efficacy assessments performed during the first 6 h interval were interpolated or extrapolated as follows: if one or more sequential evaluations were missing because the data were not recorded or the patients were not available to complete the assessment, then data were interpolated in a linear fashion; patients who required a second analgesic dose within 6 h of the first had their missing (5 and 6 h) values interpolated using the worst of the baseline rating or the last rating prior to the second dosing; patients withdrawing from the study before T = 6 h had missing values recorded as the last rating prior to discontinuation
Selective Reporting	Low Risk	All prespecified outcomes were reported
Other	High Risk	Study funded by company which produces one of the drugs under investigation (Ketorolac)

Lee 2016 (35)		
Study Identification	**Author Judgment**	**Justification**
Appropriate Source Population	Low Risk	Consecutive sample from a population representative of the condition under study
Sufficient Power/Sample Size	Low Risk	Large sample size (N = 2887)
Adjust for Confounders or Other Variables	High Risk	Several covariates included to adjust for individual characteristics and injury severity but did not adjust for covariates in all outcomes of interest.
Appropriate Statistical Analyses	Low Risk	Reported use of appropriate statistical analysis as required
Incomplete Outcome Data	Unclear Risk	No information provided
Outcome Measurement	Low Risk	Provided a detailed description of the outcome measures which are appropriate for the outcome of interest
Follow-up Bias	Unclear Risk	No information provided

Appendix 3 con't.

Webster 2007 (34)		
Study Identification	**Author Judgment**	**Justification**
Appropriate Source Population	Low Risk	Consecutive sample from a population representative of the condition under study
Sufficient Power/Sample Size	Low Risk	Large sample size (N = 8443)
Adjust for Confounders or Other Variables	High Risk	Covariates included age, gender, job tenure, and low back injury severity group
Appropriate Statistical Analyses	Low Risk	Reported use of appropriate statistical analysis as required
Incomplete Outcome Data	Unclear Risk	No information provided
Outcome Measurement	Low Risk	Provided a detailed description of the outcome measures which are appropriate for the outcome of interest
Follow-up Bias	Unclear Risk	No information provided

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Systematic Reviews

PROTOCOL Open Access

Treatment outcomes in patients with opioid use disorder initiated by prescription: a systematic review protocol

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Abstract

Background: In North America, opioid use has become a public health crisis with policy makers declaring it a state of emergency. Opioid substitution therapy (OST) is a harm-reduction method used in treating opioid use disorder. While OST has shown to be successful in improving treatment outcomes, there is still a great degree of variability among patients. This cohort of patients has shifted from young males using heroin to a greater number of older people and women using prescription opioids. The primary objective of this review is to examine the literature on the association between the first exposure to opioids through prescription versus illicit use and OST treatment outcomes.

Method: An electronic search will be conducted on the EMBASE, MEDLINE, PsycINFO, and Cumulative Index to Nursing and Allied Health Literature (CINAHL) databases. Two independent reviewers will conduct the initial title and abstract screenings using predetermined criteria for inclusion and exclusion. Reviewers will then conduct full-text data extraction using a pilot-tested data extraction form in duplicate. A third author will resolve disagreements if consensus cannot be reached. Quality and risk of bias assessment will be conducted along with a sensitivity analysis for all included studies. Qualitative summary of the evidence will be provided, and when possible, a meta-analysis will be conducted, along with heterogeneity calculation. The reporting of this protocol follows the PRISMA-P.

Discussion: We expect that this review will help determine whether patients that were initially exposed to opioids through a prescription differ in OST treatment outcomes in comparison to people who used opioids through illicit means. We hope that this review will provide evidence related to prescription opioids exposure and future treatment outcomes, which will aid clinicians in their decisions to prescribe opioids or not for specific populations at risk.

Systematic review registration: PROSPERO CRD42017058143

Keywords: Opioid substitution therapy, OST, Prescription opioids, Systematic review, Opioid use disorder, Protocol

Background

Rationale

The global opioid crisis is marked by a striking 32 to 36 million individuals who used opioids worldwide [1]. Illicit opioid use is associated with an increased risk of infections such as HIV and hepatitis C, dependency, poly-substance use, psychiatric comorbidity, criminal activity and death [2–4]. Opioids are now the primary cause of drug-related deaths in North America, with a 200% increase in the number of opioid-related deaths since 2000 [5]. Regular use of opioids can result in opioid use disorder (OUD), a chronic psychiatric disorder characterized by loss of control over the drug use, behavioural and psychological symptoms related to drug use and impairment in normal function of the affected individuals [2]. Treatment of OUD also takes an economic toll on the healthcare system [6]. The increased misuse of prescription opioids has contributed to these rising numbers of opioid use and its related consequences [5]. Historically, many individuals were first introduced to opioids through recreational drugs such as

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heroin [7, 8]. However, recent opioid use patterns have contributed to a demographic shift in which individuals developed OUD after being exposed to opioids by means of prescription drugs such as fentanyl, codeine, or oxycodone [9, 10]. Today, Canada is the world's second highest consumer of prescription opioids after USA [11].

Currently, opioid substitution therapy (OST) is used to treat OUD. OST is a harm reduction treatment that aims to limit adverse risks and events associated with illicit opioid use [12]. This entails the prescription of longer-acting opioids with less euphoric effects in order to minimize cravings and prevent withdrawal symptoms [12, 13]. The most commonly used opioid substitutes are methadone, buprenorphine, naltrexone and suboxone® (a combination of buprenorphine and naloxone) [12–14]. OST has a positive impact on OUD including a variety of social and health-related factors, such as a decline in the use of illicit substances, unemployment, HIV prevalence, criminal activities and mortality [2, 13, 15]. OST has also demonstrated improved social functioning and treatment retention [13–15]. However, while OST has demonstrated some success in managing OUD, there is still a great degree of variability in treatment outcomes [4].

This variability in treatment outcomes may be partially explained by a shifting OST population resulting from changes in the way in which an individual is first introduced to opioids. A recent study estimated that 52% of women and 38% of men are seeking treatment for OUD having first been exposed to opioids through a prescription [9]. Previous research demonstrates that patients in treatment for OUD were mainly young adult males, around 20 years of age, who injected heroin [8, 9, 16]. However, the patients receiving OST today are older and have a greater number of women [10, 17, 18]. This demographic shift warrants new investigation, as past research many no longer apply to this population.

Studies that look at the relationship between patients who initially started misusing opioids through a medical prescription and OST outcomes present conflicting findings. Some studies show that those in buprenorphine treatment that have misused prescriptions only have better treatment retention in comparison to people who have misused heroin [19] while other studies demonstrate that those that have misused prescriptions only do not differ in treatment retention from those misusing illicit opioids such as heroin [20].

The relationship between prescription opioids and OST outcomes may also be affected by physical health status. Opioids have become one of the most commonly used medications for pain in North America due to their analgesic effects [21]. Given the high prevalence of comorbid pain in the OUD population, it has been suggested that the chronic pain population is at risk for an increased likelihood to misuse prescription opioids [21–23].

It remains unclear, however, as to whether an association between initial exposure to opioids through a medical prescription and OST outcomes exists and if confounding variables heavily influence this relationship. Conducting a systematic evaluation of the literature on this topic is essential and can identify factors influencing treatment outcomes that may be overlooked in individual studies. We hypothesize that patients that were exposed to opioids through a prescription will have a different response to OST as defined by illicit opioid use and treatment retention.

Objectives

The aim of this systematic review is to synthesize and appraise the existing literature on the effects of initial exposure to opioids by prescription compared to those introduced through illicit opioid substitution therapy treatment outcomes in patients diagnosed with opioid use disorder.

Specifically, the study objectives are:

1. Summarize the literature examining the association between exposure to opioids through a medical prescription and OST outcome (primary: illicit opioid use, secondary: treatment retention and polysubstance use).
2. If possible, combine study findings in a meta-analysis comparing the OST treatment outcomes of those that were initially exposed to opioids through a legitimate prescription and those that were introduced through illicit means.
3. Conduct subgroup analyses based on age, sex, country and method of OST treatment outcome measurement.

Methods

Eligibility criteria

This review will consist of published observational cross-sectional and cohort studies and randomized control trials (RCTs) examining the association between opioid prescription misuse and OST outcomes. These studies may have been conducted in different settings including hospital, outpatient or community-based. Primary studies will include the main exposure to opioids through a prescription and OST treatment outcomes. The included studies will be comparing those introduced to opioids through a legitimate prescription and those introduced through illicit means. The individuals that began their use through a prescription not prescribed to them will be in the group of those that obtained opioids through other means (i.e. a family member, street or friend) as this can be defined as illicit use. There will be no age, sex, language or type of study population restrictions.

Studies will be excluded if they do not assess at least one of the primary or secondary outcomes of interest detailed below. Most of the research on OST treatment outcomes study the current type of opioid misuse (i.e. street drugs or prescription) and fail to identify the method of initial exposure to opioids. As such, these studies will be omitted from our analysis, as it will not be possible to make conclusions pertaining to the primary exposure of interest and the association with OST results. In addition, studies investigating patients in OST for other reasons apart from treatment of OUD will also be omitted.

Outcomes and prioritization

The primary study outcome, illicit opioid use, will be used to determine the effectiveness of the OST and may be quantified in various ways such as urine toxicology or self-reports as provided in the primary studies. Secondary outcomes will include treatment retention and poly-substance use. Treatment retention may be quantified as ratio of people who are still in treatment at the time the study completion or average period of time in treatment. Poly-substance use may be measured in similar ways to illicit opioid use (i.e. urine toxicology, self-reports).

Information sources

In order to identify the relevant articles that will be used in the review, a health sciences librarian (SS) was consulted to develop a search strategy. The databases to be searched from inception are EMBASE, MEDLINE, PsycINFO, and Cumulative Index to Nursing and Allied Health Literature (CINAHL). Articles will be identified using search terms related to prescription opioids and opioid use disorder together with their medical subject headings (MeSH) in different combinations (Table 1). An in-depth search will be carried out comprising of keywords found in the title, and abstract fields. To ensure that unnecessary restrictions on the search findings are avoided, the study findings will not be included in the search strategy. The searches will be restricted to studies conducted in human research participants. Gray literature will be searched using ProQuest Dissertations as well as the Theses Worldwide database. Lastly, a comprehensive hand search of reference lists of the relevant articles will be carried out to identify additional articles that may not have been captured in the original search.

Search strategy

Study records

Data management Articles identified by the search strategy will be uploaded to an online platform known as Google Forms. Google Forms will allow for management of the articles and will also allow the authors to collaborate simultaneously. The review team will be provided training on how to use Google Forms prior to the commencement of the study to ensure calibration of the forms and the data abstraction methods. A pilot of 20 studies will first be carried out to calibrate the study forms and assess level of agreement.

Selection process Two independent reviewers will carry out the title and abstract screening in duplicate to identify appropriate articles using previously established criteria. Eligible articles will then undergo full-text review in duplicate. Disagreements will be resolved by discussion and consensus, and in cases were no resolution is reached, a third author will be consulted. During each stage of screening, a kappa statistic will be used to establish inter-rater agreements. Exceptional agreement between reviewers will be demonstrated as a kappa value of at least 0.75 [24]. In cases were additional clarification is needed, the primary study authors will be contacted to help determine eligibility. The preferred reporting items for systematic reviews and meta-analyses (PRISMA) [25] flow diagram will be used when reporting the full systematic review.

Data collection process Independent reviewers will retrieve the data using a previously piloted data extraction form in duplicate (see Additional file 1). To ensure standardization, consistency among reviewers will be addressed by assessing completed pilot data extraction forms.

Data items For included data items, please see Additional file 1. The information to be retrieved by the reviewers will consist of details of the publication such as name of the first author, year of publication, journal and country of publication; research design that was used; demographics of the research participants; type and method of measuring opioid exposure (i.e. medical prescription or illicit); OST outcome measures; overall findings of the study and the study statistical results. In the case of missing data for any study, the authors will be contacted.

Risk of bias The risk of bias will be appraised using the modified Newcastle-Ottawa Scale (NOS) [26, 27] to appraise the likelihood of bias in studies that are mainly observational in nature. This modified scale comprises seven questions that assess bias in four realms: choice bias, performance bias, identification bias and information bias. Risk of bias is quantified on a scale 0 to 3 where 0 is high risk and 3 is low risk. The modified model has eliminated items concerning the comparability of groups. To assess risk of bias in RCTs, we will use the Cochrane Collaboration tool which will look at six domains including selection bias, reporting bias, attrition bias, performance bias, detection bias and other biases

Table 1 Search strategy

MEDLINE = 6250	1 exp Analgesics, Opioid/ 2 (opiate* or opioid* or fentanyl or narcotic* or dilaudid or oxycontin* or oxycod*).ti,ab. 3 1 or 2 4 exp Drug Prescriptions/ 5 (prescript* or prescrib* or pharmaceutical* or legal*).ti,ab. 64 or 5 73 and 6 8 ((prescript* or prescrib* or pharmaceutical*) adj2 (opioid* or opiate* or dilaudid or fentanyl or codeine or oxyco*)).ti,ab. 97 or 8 10 Opioid-Related Disorders/ 11 Heroin Dependence/ 12 Substance-Related Disorders/ 13 Substance Abuse, Intravenous/ 14 ((opiate* or opioid* or heroin* or oxyco* or codeine* or dilaudid or fentanyl or drug* or substance*) adj2 (use* or using or misuse* or abus* or dependence* or dependent* or addict*)).ti,ab. 1510 or 11 or 12 or 13 or 14 169 and 15 17 exp animals/ not (humans/ and exp animals/) 1816 not 17
EMBASE = 14,649	1 exp heroin dependence/ 2 opiate/ 3 exp opiate addiction/ 4 substance abuse/ 5 ((opiate* or opioid* or heroin* or oxyco* or codeine* or dilaudid or fentanyl or drug* or substance*) adj2 (use* or using or misuse* or abus* or dependence* or dependent* or addict*)).ti,ab. 61 or 2 or 3 or 4 or 5 7 ((prescript* or prescrib* or pharmaceutical*) adj2 (opioid* or opiate* or dilaudid or fentanyl or codeine or oxyco*)).ti,ab. 8 (prescript* or prescrib* or pharmaceutical* or legal*).ti,ab. 9 exp prescription/ 10 exp prescription drug/ 11 (opiate* or opioid* or fentanyl or narcotic* or dilaudid or oxycontin* or oxycod*).ti,ab. 12 exp narcotic analgesic agent/ 13 11 or 12 148 or 9 or 10 1513 and 14 167 or 15 176 and 16 18 limit 17 to human
PsycINFO = 2898	1 exp Opiates/ 2 (opiate* or opioid* or fentanyl or narcotic* or dilaudid or oxycontin* or oxycod*).ti,ab. 3 exp Prescription Drugs/ 41 or 2 5 (prescript* or prescrib* or pharmaceutical* or legal*).ti,ab. 63 or 5 74 and 6 8 ((prescript* or prescrib* or pharmaceutical*) adj2 (opioid* or opiate* or dilaudid or fentanyl or codeine or oxyco*)).ti,ab. 97 or 8 10 exp Heroin Addiction/ or exp Heroin/ 11 exp Intravenous Drug Usage/ 12 ((opiate* or oxyco* or opioid* or heroin* or codeine* or dilaudid or fentanyl or drug* or substance*) adj2 (use* or using or misuse* or abus* or dependence* or dependent* or addict*)).ti,ab. 1310 or 11 or 12 149 and 13
CINAHL = 1143	1 (MH "Drugs, Non-Prescription") OR (MH "Drugs, Prescription") OR (MH "Prescriptions, Drug") OR (MH "Drugs, Off-Label") 2 (MH "Substance Use Disorders") 3 (MH "Heroin") OR (MH "Substance Dependence") 4 (MH "Substance Abuse, Intravenous") 5 ((opiate* or opioid* or oxyco* or heroin* or codeine* or dilaudid or fentanyl or drug* or substance*) N2 (use* or using or misuse* or abus* or dependence* or dependent* or addict*)) 6 (MH "Analgesics, Opioid") 7 (opiate* or opioid* or fentanyl or narcotic* or dilaudid or oxycontin* or oxycod*) 82 OR 3 OR 4 OR 5 9 ((prescript* or prescrib* or pharmaceutical*) n2 (opioid* or opiate* or dilaudid or fentanyl or codeine or oxyco*)) 101 OR 6 OR 7 11 (prescript* or prescrib* or pharmaceutical* or legal*) 121 OR 11 1310 AND 12 149 OR 13 158 AND 14 (limtiters- human)

[28]. These results will be displayed in a table to facilitate easy comparison between the quality of studies included in this review.

Data synthesis All included studies will be appraised with a qualitative summary, and then if possible, a meta-analysis will be undertaken. Our primary analysis will compare treatment outcomes for patients that initiated opioid use by prescription (and continue to use prescription opioids) to those patients that started using opioids through illicit means. If studies further report that the patients who initially began through prescription have transitioned to using non-prescription opioids (or both), we will conduct a sensitivity analysis by removing these studies to determine whether it has an effect on the

outcomes. Studies will be merged in a meta-analysis depending on the similarity between design of the study and the measurements of the outcomes. Depending on the design of the research, direct estimates will be pooled separately as pooling data from observational studies as well as RCTs is not advisable [29].

To account for the anticipated heterogeneity in the included studies, a random effect model for the meta-analysis will be used. This model takes both within-study and between-study variance into consideration to offer a modest estimate in comparison to a fixed-effect model. The outcomes will be featured on a forest plot. Moreover, a sensitivity analysis might also be carried out to compare the outcomes of the studies with high or low risk of bias.

Heterogeneity will be computed among the pooled articles through the use of I^2 statistic. It is recommended that cut-off values are not enforced since the significance of heterogeneity relies on a variety of factors, although Cochrane has recommended that a value of < 40% might not signify a noteworthy amount of heterogeneity [29]. Therefore, likely sources of heterogeneity are going to be evaluated as long as there is an I^2 statistic > 40%. In this case, subgroup analyses will also be conducted.

Some of the likely sources of heterogeneity include age, sex, types of opioids and outcome measurements. These are going to be examined through the use of subgroup analyses. We also plan to conduct a subgroup analysis if possible examining the differences in treatment outcomes for individuals who obtained opioids through different sources (i.e. street, family members, friend).

Meta-bias Egger's plot will be created to assess the likelihood of publication bias in the included articles.

Confidence in the cumulative evidence The grading of recommendations, assessment, development and evaluation (GRADE) framework will be used to assess the quality of the evidence [30]. This scale evaluates evidence based on five realms: risk of bias, publication bias, consistency, directness and accuracy.

Presenting and reporting of the study results This systematic review will be reported in compliance with PRISMA reporting guidelines [25]. A flow diagram will be used to demonstrate the selection of studies including reasons for exclusion. The present protocol follows the preferred reporting items for systematic review and meta-analysis protocol (PRISMA-P) guidelines which is attached (see Additional file 2) [31].

Discussion

Using the evidence obtained from this systematic review, we expect to draw conclusions regarding the presence of an association between being exposed to opioids through a medical prescription and opioid substitution therapy outcomes. Examining the current literature in a systematic way will allow us to summarize existing findings on this topic and to critically appraise the risk of bias and methodological quality of these studies. The present literature primarily focused on the cohort of patients that were exposed to opioids through illicit means and little is known about the cohort of patients that started misusing opioids after using a prescription. This new shift in demographic profile of opioid users and the predominance of prescription opioid use over heroin in different parts of the world including Canada and the USA, the highest opioid-consuming countries in the world, warrants a detailed examination of the literature.

Given the rise of prescription opioid use in Canada and the USA, it is important that we evaluate factors that may affect the effectiveness of opioid substitution treatment for this cohort of patients.

Additional files

Additional File 1: Data extraction form in. This form includes all the information we intend to extract from the included studies. (PDF 54 kb)

Additional File 2: PRISMA-P checklist. These are the guidelines that this protocol was reported by. (PDF 92 kb)

Abbreviations

GRADE: Grading of Recommendations Assessment, Development and Evaluation; NOS: Newcastle-Ottawa scale; OST: Opioid substitution therapy; OUD: Opioid use disorder; PRISMA-P: Preferred reporting items for systematic review and meta-analysis protocols; PRISMA: Preferred reporting items for systematic reviews and meta-analyses; RCT: Randomized control trials

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Availability of data and materials

Not applicable

Authors' contributions

NS contributed to the conception and design of the study, development of data extraction forms, search strategy, manuscript writing and final review of the manuscript. MB contributed to the methodological design, critical revision and final review of the manuscript. LZ contributed to the methodological design, critical revision and final review of the manuscript. SS contributed to the development of the search strategy and final review of the manuscript. HS contributed to the critical revision and final review of the manuscript. BB contributed to the critical revision and final review of the manuscript. CS contributed to the critical revision and final review of the manuscript. RS 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 approval of the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable

Consent for publication
All authors consent and approve the manuscript for publication.

Competing interests
The authors declare that they have no competing interests.

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SYSTEMATIC REVIEW
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Treatment Outcomes in Patients With Opioid Use Disorder Who Were First Introduced to Opioids by Prescription: A Systematic Review and Meta-Analysis

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Objective: Prescription opioid misuse has led to a new cohort of opioid use disorder (OUD) patients who were introduced to opioids through a legitimate prescription. This change has caused a shift in the demographic profile of OUD patients from predominantly young men to middle age and older people. The management of OUD includes medication-assisted treatment (MAT), which produces varying rates of treatment response. In this study, we will examine whether the source of first opioid use has an effect on treatment outcomes in OUD. Using a systematic review of the literature, we will investigate the association between source of first opioid introduction and treatment outcomes defined as continuing illicit opioid use and poly-substance use while in MAT.

Methods: Medline, EMBASE, CINHAL, and PsycInfo were searched from inception to December 31st, 2019 inclusive using a comprehensive search strategy. Five pairs of reviewers conducted screening and data extraction independently in duplicate. The review is conducted and reported according to the PRISMA guidelines. A random-effects model was used for meta analyses assuming heterogeneity among the included studies.

Results: The initial search results in 27,345 articles that were screened, and five observational studies were included in the qualitative and quantitative analyses. Our

results found that those who were introduced to opioids through a legitimate prescription were significantly less likely to have illicit opioid use (0.70, 95% CI 0.50, 0.99) while on MAT. They were also less likely to use cannabis (0.54, 95% CI 0.32, 0.89), alcohol (0.75, 95% CI 0.59, 0.95), cocaine (0.50, 95% CI 0.29, 0.85), and injection drug use (0.25, 95% CI 0.14, 0.43) than those introduced to opioids through recreational means.

Conclusion: This study shows that the first exposure to opioids, whether through a prescription or recreationally, influences prognosis and treatment outcomes of opioid use disorder. Although the increased pattern of prescribing opioids may have led to increased OUD in a new cohort of patients, these patients are less likely to continue to use illicit drugs and have a different prognostic and clinical profile that requires a tailored approach to treatment.

Systematic Review Registration: PROSPERO CRD42017058143.

Keywords: opioids, prescription, opioid use disorder, systematic review, meta-analysis

INTRODUCTION

North America is experiencing an opioid crisis in which the illicit use of opioids is at an all-time high. Opioids are a class of drugs that are often prescribed to relieve pain and can be highly addictive (1). They include licit substances such as oxycodone, Percocet, hydromorphone, and street drugs such as heroin. The Center for Disease Control (CDC) reports that in the United States, approximately 115 people die every day from an opioid-related overdose (2). In 2017 alone, more than half the drug-related deaths in the States were due to opioids (2). Opioids are controlled substances and are classified by Drug Enforcement Administration (DEA) into various classes according to their abuse potential and medical utility (3). Opioids such as heroin are a Schedule 1 substance indicating high abuse potential and no medical utility, and fentanyl, oxycodone being Schedule II (3). In response to the opioid crisis, Substance Abuse and Mental Health Services Administration (SAMHSA) conducted a national survey and revealed that over 2.1 million people are suffering from an opioid use disorder (OUD) involving prescriptions opioids alone (4). OUD, previously classified as opioid abuse and dependence, is a disorder that affects the psychological, social and physical aspects of an individual's life (5). Dependence to a substance (i.e. opioids) typically refers to a physical response in the form of withdrawal symptoms when an individual stops using that substance (6). Addiction refers to not being able to resist the urge to use a substance despite there being negative consequence (6). OUD encompass opioid addiction and dependence that signify a problematic use of opioids impacting health and social functioning (5) Withdrawal symptoms experienced due to OUD may include sweating, shakes, anxiety, irritability, and restlessness amongst others (7).

There are several treatments available for OUD which include pharmacological and psychological options. Medication-Assisted Treatment (MAT) includes opioid agonist, antagonists, and partial agonists (8). Some of the more frequently used MATs for OUD are naltrexone, buprenorphine, and methadone (8). Methadone, a synthetic opioid agonist, is one of the most common MAT for treating OUD (8, 9). While research investigating the effectiveness of methadone maintenance treatment (MMT) has shown that it can reduce opioid cravings as well as other symptoms related to opioid withdrawal (i.e. shakes, sweating) through acting on the opioid receptors (8, 10), there is still a high degree of variability for treatment outcomes between individuals such as treatment retention (11–13). Research has suggested that some of this variability may be related to age (14), sex (15), and gender (16) but outcomes are also likely influenced by the increasing prevalence of prescription opioid misuse (17–19).

Current research is suggesting that one reason for the opioid epidemic is the rise of prescription opioid misuse. In 2016 alone, Canada and the United States prescribed over 440 million opioids to patients (20, 21). The National Institutes on Drugs Abuse (NIDA) suggest that anywhere from 8 to 12 percent of individuals prescribed opioids are at risk of developing OUD (22). With the rise of prescription opioid misuse, this has led to a shift in the profile of the "typical" illicit opioid user. Twenty years ago, this demographic profile would have consisted of primarily males in their 20s, misusing heroin intravenously (23, 24) but now, we are seeing a separate cohort of incoming OUD patients that are female, older in age and misusing prescription opioids (25, 26). Prescription medications including opioids are available on the illegal drug market through diversion (27, 28). Diversion of prescription medications may occur at any level from the direct pharmaceutical manufacturing site to patients selling the prescriptions themselves. This has been occurring for many decades for many types of substances (i.e. opioids, benzodiazepines) and with prescription opioids being readily available on the illegal drug market, this has contributed to a demographic shift.

This change in the demographic is substantial because there is evidence that suggests that different types of opioids users have varying experiences while in MAT (29). Previous research suggests that opioid prescription users differ in

their treatment outcomes compared to individuals who used heroin (29). Additionally, there is also support for the idea that poly-substance use differs within the OUD population receiving treatment. Poly-substance use has been suggested as a factor that is associated with decreased abstinence from opioids, treatment retention, and related to methadone-related mortality (30–33). Recent research found that cocaine, alcohol, and other substances were used significantly more by heroin users than prescription users (34). Prescription opioid users attending pharmacological treatment for OUD also had significantly longer treatment retention in comparison to heroin users (35). However the previous research is inconclusive as other studies suggested that there is no significant difference in treatment outcomes between prescription introduced and recreational opioid users (36). The magnitude to which this demographic shift has impacted treatment outcomes in specific MAT patient groups has yet to be investigated in a systematic way, and there are conflicting findings in the current literature.

Additionally, there are new, synthetic opioids (i.e. designer fentanyl and its' analogs) that are available on the street and have been found to be mixed in other illicit substances such as cocaine, methamphetamines and heroin (37). There has been an 88% increase in synthetic opioid-related deaths from 2013 to 2016 whereas the number deaths due to heroin alone use seem to remain consistent (38–40). Prescription opioids are also readily available on the illegal drug market through methods such as prescription resales and theft of prescriptions/prescription pads (28). In recent years, various governments have come up with legislative changes to control access and prescribing patterns for opioids (41–43). With there being new types of synthetic opioids and prescription opioids readily available on the street, it is important to examine if method of introduction to opioids impacts OUD treatment outcomes.

The purpose of this review is to examine differences in patients with OUD on MAT by those introduced to opioids through prescription versus by recreational means on outcomes of continued opioid use, poly-substance use and treatment retention.

This review will fill this knowledge gap and aims to have an important impact in how treatments are designed and tailored to various subgroups within the OUD population. Tailored treatments to address specific concerns in this population may improve MAT outcomes.

OBJECTIVES

The aim of this systematic review is to examine if opioid use disorder patients introduced to opioids through legitimate prescription differ in methadone maintenance treatment outcomes in comparison to those that were introduced to opioids through recreational means.

Specifically, we wanted to examine if these two cohorts differed in:

1. Continued opioid use while in MAT
2. Poly-substance use while in MAT
3. Treatment retention while in MAT

METHODS

Protocol and Registration

This systematic review was conducted to investigate OUD treatment outcomes by comparing those introduced to opioids through legitimate prescriptions and those introduced through recreational means. The Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines were followed (44). The protocol for this systematic review has been peer reviewed, published previously (45), and registered with PROSPERO CRD42017058143.

Eligibility Criteria

This review investigates the association between method of introduction to opioids and MAT outcomes in different settings (i.e. hospital, outpatient, community based) by examining published observational cross-sectional and cohort studies, as well as randomized control trials (RCTs). Included studies compared legitimate prescription opioid introduction to recreational opioid introduction, which can be defined as the use of opioids obtained through means outside of a prescription (i.e. family member, street, using another's prescription)

Studies that failed to measure the initial method of introduction to opioids were not included. Studies that did not assess at least one of the primary or secondary outcomes of illicit opioid use, poly-substance use and treatment retention were excluded. There were no restrictions on age, sex, or **language.**

Information Sources and Search Strategy

A search strategy was developed by a health science librarian (SS) to search for studies in the EMBASE, MEDLINE, PsycINFO, and Cumulative Index to Nursing and Allied Health Literature (CINAHL) databases. These databases were searched from inception until December 31, 2019. Search terms were related to prescription opioids and opioid use disorder together with their medical subject headings (MeSH) in different combinations. We also did a manual search of the references of relevant articles to identify any studies that may have been missed. The search strategy has been published in the protocol (45). We have also included the search strategy in the Appendix. Please see **Appendix Table 1**.

Study Selection

Previously established selection criteria were used by five pairs of reviewers in order to independently complete the title and abstract screening and subsequent full-text review of the eligible articles. Both stages of screening were carried out in duplicate. Upon the occurrence of a disagreement on the status of an article eligibility, resolution was reached through discussion to consensus between the pair, or with the consultation of a third party. Inter-rater agreements were established using a kappa statistic, where a kappa value of at least 0.75 is indicative of exceptional agreement between reviewers (46). The mean kappa value between pairs was 0.88.

Data Collection and Data Items

A piloted data extraction form was used by reviewers to retrieve data in duplicate. These forms extracted information relating to

the author, year of publication, journal, and country of publication. Details of the study's methodology and results were also retrieved. More specifically, information on research design used, demographics of the research participants, type and method of measuring initial type of opioid introduction (i.e. medical prescription or recreational), MMT outcome measures, overall findings of the study, and the study's statistical results was included. If data pertaining to the aforementioned items was missing, the authors were contacted.

Risk of Bias of Individual Studies

The risk of bias was independently assessed by two reviewers who reviewed the methodological quality of the eligible studies using the Newcastle-Ottawa Scale (NOS), used mainly for observational studies to assess choice bias, performance bias, identification bias, and information bias (47). A modified model was used that has eliminated items concerning the comparability of groups (48). It consists of 7 questions and is quantified on a scale of 0 to 3, where 0 is high risk of bias and 3 is low risk of bias. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria was utilized to assess the quality and strength of the evidence (49). This is provided in **Table 1**.

Statistical Analyses

All included studies were qualitatively summarized. A meta-analysis was conducted on the primary outcome of illicit opioid use and the outcome of poly-substance use. Review Manager 5.2 was used to conduct the meta-analyses. The substances included in this were cannabis, alcohol, injection drug use, cocaine, and benzodiazepines. These were the substances that were examined in the included studies. Two of the included studies investigated treatment retention but were unable to be meta-analyzed as they were reported in different ways. The outcomes are presented in a forest plot. The meta-analyses reflect the associations found between the outcomes and method of introduction to opioids (legitimate prescription and recreational). Due to the limited number of studies, we were not able to conduct any subgroup analyses for age, sex, country, and type of MAT treatment.

We have shown our pooled dichotomized data as odds ratio (OR) with 95% confidence intervals. The I^2 statistic was used to compute heterogeneity. Cochrane suggests that a value of <40% might not signify a noteworthy heterogeneity (50). A random effect model, which considers both within study and between study variance in comparison to the fixed-effect model, was used to account for expected heterogeneity in the included studies. We were not able to conduct an adjusted analysis as covariates were not controlled for. We were unable to examine publication bias as we have less than 10 included papers. Previous studies have reported that it is not possible to assess publication bias with less than 10 studies (51). PRISMA reporting guidelines were followed throughout this process (44).

Types of Interventions

Experimental

The experimental intervention includes those participants that were introduced to opioids through recreational use and are now in MAT for OUD.

TABLE 1 | Summary of findings.

		Illicit opioid use	Marijuana use	Cocaine use	Any injection drug use	Alcohol use	Benzodiazepine use
Certainty assessment	№ of studies	3	3	3	2	2	2
	Study design	observational studies	observational studies	observational studies	observational studies	observational studies	observational studies
	Risk of bias	not serious	not serious	not serious	not serious	not serious	not serious
	Inconsistency	not serious	not serious	not serious	not serious	not serious	not serious
	Indirectness	not serious	not serious	not serious	not serious	not serious	not serious
	Imprecision	serious[a]	serious[a]	serious[a]	serious[a]	serious[a]	serious[a]
	Other considerations	strong association	strong association	strong association	very strong association	none	none
№ of patients	Prescription opioid	339/691 (49.1%)	399/651 (61.3%)	175/651 (26.9%)	122/167 (73.1%)	259/607 (42.7%)	73/551 (13.2%)
	Illicit opioid introduction	309/709 (43.6%)	258/540 (47.8%)	91/540 (16.9%)	32/81 (39.5%)	185/509 (36.3%)	53/500 (10.6%)
Effect	Relative (95% CI)	OR 1.42 (1.01 to 2.00)	OR 1.87 (1.12 to 3.12)	OR 2.01 (1.17 to 3.46)	OR 4.07 (2.31 to 7.15)	OR 1.34 (1.05 to 1.71)	OR 1.21 (0.79 to 1.86)
	Absolute (95% CI)	**87 more per 1,000** (from 2 more to 171 more)	**153 more per 1,000** (from 28 more to 263 more)	**121 more per 1,000** (from 23 more to 244 more)	**332 more per 1,000** (from 206 more to 429 more)	**70 more per 1,000** (from 11 more to 131 more)	**19 more per 1,000** (from 20 fewer to 75 more)
Certainty		⊕⊕◯◯ LOW	⊕⊕◯◯ LOW	⊕⊕◯◯ LOW	⊕⊕⊕◯ MODERATE	⊕◯◯◯ VERY LOW	⊕◯◯◯ VERY LOW
Importance		CRITICAL	IMPORTANT	IMPORTANT	IMPORTANT	IMPORTANT	IMPORTANT

CI, Confidence interval; OR, Odds ratio.

[a]*Imprecise as adjusted pooled estimates were not possible to conduct.*

Comparator
The accepted comparators include those that were introduced to opioids through a legitimate physician's prescription and are now in MAT for OUD.

Outcome Measures
Continued Opioid Use
We have defined continued opioid use to be the use of any opioids while the patient is in methadone maintenance treatment.

Poly-Substance Use
We defined poly-substance use as the use of any of the previously defined substances before or during MMT.

Treatment Retention
We defined treatment retention as the length of time a patient stayed in their MAT without dropping out.

RESULTS

Study Selection
From the databases searched, a total of 27,345 articles went through the title and abstract screening process. After removing 3,264 duplicates and 24,076 studies that did not meet the inclusion criteria, a total of five studies were included. **Figure 1** is the PRISMA flow diagram of the screening process. All five studies were included in the meta-analyses of the outcomes. Three out of five studies were subjected to the meta-analysis of the primary outcome of illicit opioid use (36, 52, 53).

Study Characteristics
The characteristics of the included studies are summarized in **Table 2**. Five papers were included in this systematic review, all of which were observational studies looking at patients in MAT for opioid use disorder. Two studies looked at patients receiving buprenorphine or methadone treatment (36, 54). One study included patients undergoing methadone treatment (53). One study only looked at buprenorphine treated patients (55) while the final study looked at buprenorphine-naloxone patients (52). All five of these studies compared individuals initially introduced to opioids for prescription use with individuals introduced to opioids *via* recreational use. The majority of the sample consisted of male participants (57.4%).

Three out of five studies looked at the primary outcome of illicit opioid use (36, 52, 53). Two studies examined injection drug use (36, 55), three studies examined cannabis use, two studies examined alcohol use (53, 55), two studies examined benzodiazepine use (53, 54), and three studies examined cocaine use (53–55). Additionally, two studies examined treatment retention (30, 32).

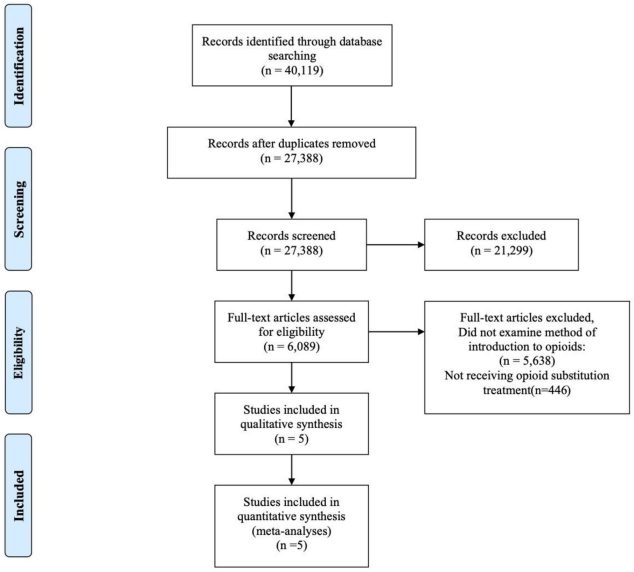

FIGURE 1 | PRISMA Flow Diagram.

TABLE 2 | Summary of characteristics.

Study	Country	Study Design and type of opioid substitution treatment	Participants (sample size in each group, age range, sex, inclusion/exclusion criteria, primary diagnosis)	Physicians prescription and recreational use Definitions	Outcomes (definition and how they were measured)	Statistical Analysis	Results
Canfield et al. (54)	United States	Cross-sectionalType of OST: N/A (patients recruited from inpatient detoxification unit)	N = 75 (physician prescription: n = 31, illicit opioid: n = 44)Mean age (range): 31.5 (18–70)Sex: 49 male (65%), 26 female (35%)Inclusion criteria: met DSM-IV criteria for opiate dependence, wished to become abstinent from opioids, at least 18 years old, able to understand spoken English, able to provide informed consent, had urine toxicology positive for opiates on day of admissionExclusion criteria: none (other than patient refusal)	Physician prescription: participants who reported that their addiction began with opioids that were prescribed for them (i.e., licit use)Recreational use: participants who traced the onset of their addiction to either diverted prescription medications or from "street drugs" (i.e., illicit drug use)	Collected self-report data related marijuana, cocaine and benzodiazepine use	Fisher exact test for between group comparisons of categorical variables; Student t-test for between group comparisons of continuous variables	First time Licit users were less likely to have ever used marijuana [27/31 (87%) vs. 44/44 (100%) p = 0.026]No significant association found between method of introduction to opioids and use of cocaine or benzodiazepines.
Cooper et al. (36)	Australia	Prospective cohortType of OST: not reported	N = 108 (physician prescription: n = 41, illicit opioid: n = 67)Mean age: 41 (range not reported)Sex: 52 male (48%), 56 female (52%)Inclusion criteria: had entered treatment for pharmaceutical opioid dependence, were competent in EnglishExclusion criteria: not reported	Participants were classified as having "iatrogenic dependence" if their first opioids of concern were prescribed by a doctor for a legitimate medical reason	Collected self-report data on participants' opioid use history (including past month illicit opioid use)Injection drug use history (including heroin, non-medical/non-prescribed opioids)Treatment retention was reported as median number of years on treatment	χ^2 tests, independent *t*-tests, and Mann-Whitney *U* tests used to examine baseline differences between those who initiated opioid use for iatrogenic and non-iatrogenic reasons	No significant difference between iatrogenic dependence vs. non-iatrogenic dependence in unsanctioned opioid use in the past month [19.5 vs. 25.4%, odds ratio 0.71, 95% CI (0.28, 1.84)]Iatrogenic dependence associated with a lower prevalence of lifetime injection of any drug [41.5 vs. 68.7%, odds ratio 0.32, 95% CI (0.14, 0.73)]No significant difference between iatrogenic dependence vs. non-iatrogenic dependence in median length on current treatment, p = 0.739

(Continued)

TABLE 2 | Continued

Study	Country	Study Design and type of opioid substitution treatment	Participants (sample size in each group, age range, sex, inclusion/ exclusion criteria, primary diagnosis)	Physicians prescription and recreational use Definitions	Outcomes (definition and how they were measured)	Statistical Analysis	Results
Dreifuss et al. (52)	United States	Cross-sectionalType of OST: sublingual buprenorphine/ naloxone	N = 360 (physician prescription: n = 199, illicit opioid: n = 117)Mean age: 32.5 (range not reported)Sex: 209 male (58%), 151 female (42%) Inclusion criteria: met DSM-IV criteria for current opioid dependence; were at least 18 years old; unsuccessful in Phase 1 of POATS study (returned to opioid use) and subsequently enrolled in Phase 2Exclusion criteria: heroin use on ≥4 days in past month; lifetime diagnosis of opioid dependence due to heroin alone; history of ever injecting heroin; concurrent formal ongoing substance abuse treatment	Physician prescription: first obtained opioids *via* a legitimate prescriptionRecreational use: given their first opioids by someone, or initially bought them from a drug dealer	Substance Use Report (corroborated by weekly urine drug screens) administered weekly duringtreatment and every two weeks during follow-up as primary measure todetermine "successful outcome" in Phase 2 (abstinence from opioids during final week of treatment and ≥2 of 3 weeks prior)	Bivariate analyses compared patients who were successful at end of treatment with those who were not	Patients who first used opioids to relieve physical pain were more likely to succeed (have a successful outcome of abstinence from opioids), while those who had first used to get high were less likely to do so
Sanger et al. (53)	Canada	Prospective CohortType of OST: methadone maintenance treatment	N = 976 (physician prescription: n = 469, illicit opioid: n = 507)Mean age: 40.8 in physician prescription group, 36.9 in illicit opioid group (ranges not reported)Sex: 535 male (54.8%), 441 female (45.2%)Inclusion criteria: over 18 years of age; met DSM-IV criteria for opioid dependence (modified in DSM-5 to opioid use disorder); on methadone maintenance treatment; able to provide informed, written consent, undergo urine drug screens, and provide information on source of initiation to opioidsExclusion criteria: receiving an alternate opioid substitution therapy; currently taking prescription opioids; currently on suboxone; unable to provide a urine sample	Physician prescription: initial exposure to opioids through a medical prescriptionRecreational use: initial exposure to opioids through other means including at home, family member, street, school, or friend	Maudsley Addiction Profile (MAP) administered to measure specific details of self-reported drug use for cocaine, cannabis, alcohol, and benzodiazepine,illicit opioid use measured by regular urine drug screens at baseline and 6-month follow-upTreatment retention was reported as mean number of months on treatment	Multivariable logistic regression used to examine relationship between illicit drug use and treatment retention in relation to source of initial opioid use	Those initiated *via* prescription were less likely to have used cannabis (OR = 0.66, 95% CI 0.49–0.90, P = .008) in comparison to those introduced by recreational meansNo significant association between method of introduction and illicit opioid use, cocaine, alcohol, benzodiazepine use.No significant association between method of introduction and current length of treatment

(Continued)

TABLE 2 | Continued

Study	Country	Study Design and type of opioid substitution treatment	Participants (sample size in each group, age range, sex, inclusion/exclusion criteria, primary diagnosis)	Physicians prescription and recreational use Definitions	Outcomes (definition and how they were measured)	Statistical Analysis	Results
Tsui et al. (55)	United States	Cross-sectionalType of OST: buprenorphine	N = 140 (physician prescription: n = 40; illicit opioid: n = 100)Mean age: 38 (range not reported)Sex: 106 male (76%), 34 female (24%) Inclusion criteria: age 18–65; DSM-IV diagnosis of opioid dependence; Hamilton Depression Revised Scale (MHDRS) score > 14; absence of significant suicidal ideation; willingness and ability to complete 3-month treatment with buprenorphine; no history of severe mental illness (bipolar disorder, schizophrenia, schizoaffective, or paranoid disorder); no currently prescribed medications for depression (participants not specifically excluded if taking tricyclic anti-depressant only for pain); ability to complete the study assessment in EnglishExclusion criteria: NR	Participants' responses to the question: "Who introduced you to opiates?" (possible responses included physician, sexual partner, friend, family member, stranger, and no one)	Collected self-report data on current (last 30 days) and past use of prescription opioids and heroin (including route of administration) using Addiction Severity Index (ASI) Collected self-report data on regular use of alcohol, marijuana and cocaine by asking, "Prior to starting opiates, did you ever have daily or regular use of (drug)?"	Descriptive analyses comparing individuals who reported physician introduction to opioids to those who did not report physician introduction; examined differences in demographic, clinical, and substance use-related variables between participants using Student t-tests and Pearson chi-square tests	Participants introduced by physician were more likely to be currently using prescription opioids only, less likely to have injected drugs (38 vs. 76%, $p < 0.01$), half as likely to currently inject drugs (28 vs. 57%, $p < 0.01$), and significantly less likely to report prior use of marijuana (53 vs. 72%, $p = 0.03$) and cocaine (23 vs. 45%, $p = 0.01$) Regular use of alcohol prior to starting opioids was equally reported among those who were and were not introduced by a physician to opioids

Risk of Bias Within Studies

The quality of the studies included are shown in **Figure 2**. Justifications for assessments are presented in **Appendix Table 1** with the risk of bias tables. The modified NOS was used to rate the internal validity of the studies shown in **Figure 2**, and assess the quality of these observational studies (47, 48). Generally, most of the studies included have relatively low to moderate risk of bias, except for one (54). Specifically, this study shows a high risk of bias when adjusting for confounders or other variables as the researchers did not adjust for confounders, instead opting to perform student t-tests. Another study also shows an unclear risk of bias when adjusting for confounders or other variables since the information they provide is unclear (52). Two of the studies included show an unclear risk of bias in terms of incomplete outcome data, simply because they do not provide any information about this (52, 54). Aside from these biases, all five of the observational studies were generally well reported on all other characteristics, including appropriate source population, sufficient power and sample size, appropriate statistical analysis, valid outcome measurement, and objective assessment of the outcome of interest.

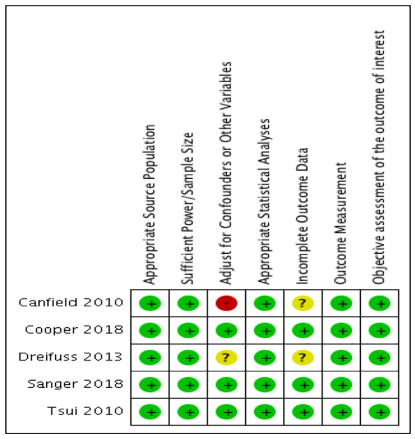

FIGURE 2 | Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Results of Individual Studies

Illicit Opioid Use

Our meta-analysis pooled results from three studies comparing the continuation of opioid use among individuals first introduced to opioids by a legitimate prescription vs. a recreational source. Cooper et al. (36) collected self-reported data on past month and lifetime opioid use. We used the data provided on the past month opioid use. Dreifuss et al. (52) collected data on the continued use of opioids using weekly substance use reports and urine drug screens. Sanger et al. (53) used urine drug screens to investigate illicit opioid use. The remaining two studies did not report on the outcome of continued opioid use (54, 55). Canfield et al. (54) examined progression of opioid use over time, but not as an outcome of the means of opioid use introduction. Tsui et al. (55) reported on the different patterns in type of opioids the groups would use (i.e. prescription, street drugs, or both) but did not provide information pertaining to the exact number of patients that were currently using opioids between licit and illicit method of introduction groups.

The studies included in our meta-analysis comprise a total sample size of 1,400 participants. Cooper et al. (36) reported that those introduced through a prescription were associated with a lower prevalence of lifetime heroin use, but no difference in past-month illicit opioid use. Dreifuss et al. (52) found that those introduced to opioids by means of a prescription were associated with discontinued opioid use in the final weeks of treatment, whereas those introduced through illicit means were associated with continued opioid use in treatment. In Sanger et al. (54), there was no significant association between the source of opioid introduction and continued opioid use. We conducted an unadjusted analysis using odds ratios to compared continued opioid use during treatment among those who were first introduced to opioids through a prescription versus an illicit source. We found that individuals who were introduced to opioids through prescription means were significantly 70% less likely to have continued to use opioids while in MAT (OR 0.70, 95% CI 0.50, 0.99, p-value 0.04). Please see **Figure 3**.

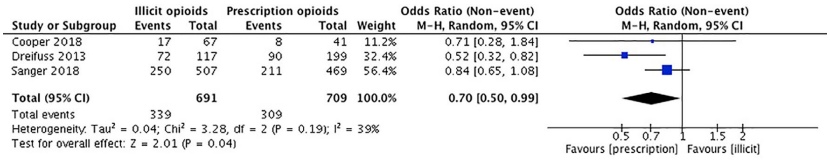

FIGURE 3 | Forest Plot for Illicit Opioid Use.

Injection Drug Use

Our meta-analysis pooled results from two studies comparing injection drug use among participants first introduced to opioids through a prescription versus an illicit source. Cooper et al. (36) collected self-reported data on injection drug use history. Tsui et al. (55) used the Addiction Severity Index (ASI) to collect self-reported data on current and past use of prescription opioids and heroin, including the route(s) of administration. The remaining three studies did not report on the outcome of injection drug use (52–54). Canfield et al. (54) reported a combination of intranasal and intravenous routes of administration and intravenous drug use could not be extrapolated. Dreifuss et al. (52) and Sanger et al. (53) did not report any data on intravenous drug use.

The studies included in our meta-analysis comprise a total sample size of 248 participants. In Cooper et al. (36), those introduced to opioids through a prescription have a lower prevalence of any injection drug use. Tsui et al. (55) reported that those introduced to opioids by a physician were less likely to have any injection drug use. We conducted an unadjusted analysis using odds ratios to compare any injection drug use among those who were introduced to opioids through a prescription vs. an illicit source. We found that individuals who were introduced to opioids through a prescription source were significantly less likely to engage in injection drug use in comparison to those introduced through recreational means (OR 0.25, 95% CI 0.14, 0.43, p-value < 0.001). Please see **Figure 4**.

Cannabis Use

Our meta-analysis pooled results from three studies comparing cannabis use in the initiation source of opioid use, by means of prescription vs. an illicit source. Canfield et al. (54) collected self-reported data on cannabis use history. Sanger et al. (53) used the Maudsley Addiction Profile (MAP) to acquire self-reported data on cannabis use in the past 30 days. Tsui et al. (55) acquired self-reported data on regular use of cannabis. The remaining two studies did not report on the outcome of cannabis use (36, 52).

The studies included in our meta-analysis comprise a total sample size of 1,191 participants. In Canfield et al. (54), participants who were first introduced to opioids by means of a prescription were less likely to have ever used cannabis. Sanger et al. (53) reported that those first introduced to opioids by a prescription were less likely to have used cannabis in the past 30 days than those first introduced to opioids by a recreational source. In Tsui et al. (55), participants who were introduced to opioids by a physician were less likely to report prior use of cannabis. We conducted an unadjusted analysis using odds ratios to compare cannabis use among those who were introduced to opioids by a prescription versus an illicit source. We found that those who initiated the use of opioid(s) through a prescription source were significantly less likely to use cannabis (OR 0.54, 95% CI 0.32, 0.89, p-value 0.02). Please see **Figure 5**.

Alcohol Use

Our meta-analysis pooled results of two studies comparing the effect of opioid introduction on alcohol use. Sanger et al. (53) used the MAP to acquire self-report data on alcohol use within the past 30 days. Tsui et al. (55) collected self-report data on regular use of alcohol by asking participants the question "prior to starting opiates, did you ever have daily or regular use of alcohol?". The remaining three studies did not report on the outcome of alcohol use (36, 52, 54). Cooper et al. (36) asked participants about injection use of alcohol and reported their results as a measure of injection history of any drug. Dreifuss et al. (52) examined alcohol use as a predictor of treatment

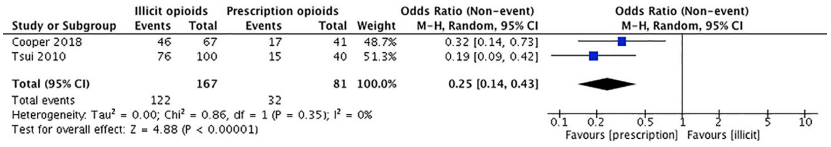

FIGURE 4 | Forest Plot for Any Injection Drug Use.

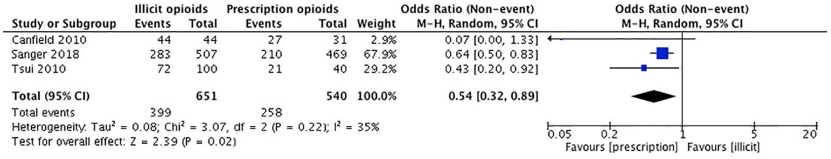

FIGURE 5 | Forest Plot for Cannabis Use.

success but not as an outcome of initial exposure to opioids. Canfield et al. (54) did not report any data on alcohol use.

The studies included in our meta-analysis comprise a total sample size of 1,116 participants. In Sanger et al. (53), there was no significant association between source of opioid initiation and alcohol use. In Tsui et al. (55), there was no significant difference in regular use of alcohol prior to opioids between those who were introduced to opioids by a physician versus those who were not. For this meta-analysis, we used the results for the entire population from both Sanger et al. (53) and Tsui et al. (55). We conducted an unadjusted analysis using odds ratios to compare alcohol use among those who first initiated opioids through a prescription versus an illicit source. We found that individuals who were introduced to opioids through a legitimate prescription were significantly less likely to have used alcohol (0.75, 95% CI 0.59, 0.95) (OR 0.75, 95% CI 0.59, 0.95, p-value 0.02). Please see **Figure 6**.

Cocaine Use

Our meta-analysis pooled results of three studies investigating cocaine use. Canfield et al. (54) collected self-reported data on any previous cocaine use. Sanger et al. (53) used the MAP to acquire self-report data on cocaine use within the past 30 days. Tsui et al. (55) collected self-report data on regular use of cocaine by asking participants the question "prior to starting opiates, did you ever have daily or regular use of cocaine?". The remaining two studies did not report on the outcome of cocaine use (36, 52). Cooper et al. (36) collected data on the use of cocaine only in the context of injection drug use and reported their results as a measure of injection history of any drug. Dreifuss et al. (52) examined cocaine use as a predictor of treatment success but not as an outcome of initial exposure to opioids.

The studies included in our meta-analysis comprise a total sample size of 1,191 participants. In Canfield et al. (54), there was no significant difference in use of cocaine between those who reported obtaining their first opioid through a prescription versus an illicit source. In Sanger et al. (53), there was no significant association between source of opioid initiation and cocaine use. In Tsui et al. (55), participants who were first introduced to opioids by an illicit source were significantly more likely to report prior use of cocaine. For this meta-analysis we conducted an unadjusted analysis using odds ratios to compare cocaine use among those who first initiated opioids through a prescription versus an illicit source. We found that individuals who were introduced to opioids through prescription were significantly less likely to use cocaine (OR 0.50, 95% CI 0.29, 0.85, p-value 0.01). Please see **Figure 7**.

Benzodiazepine Use

Our meta-analysis pooled results of two studies comparing benzodiazepine use among participants first introduced to opioids through a prescription versus an illicit source. Canfield et al. (54) collected self-report data on any previous benzodiazepine use. Sanger et al. (53) used the MAP to acquire self-report data on benzodiazepine use in the past 30 days. The remaining three studies did not report on the outcome of benzodiazepine use (36, 52, 55). Cooper et al. (36) collected data on previous injection use of benzodiazepines and reported their results as a measure of injection history of any drug. Dreifuss et al. (52) examined the use of sedatives as a predictor of treatment success but did not specifically assess benzodiazepine use as an outcome of initial exposure to opioids. Tsui et al. (55) did not collect any data on benzodiazepine use.

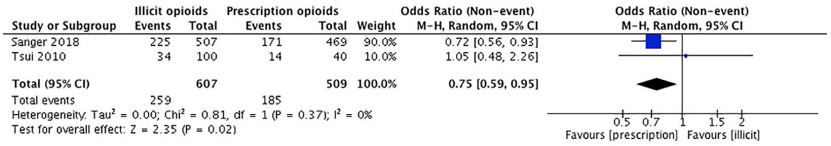

FIGURE 6 | Forest Plot for Alcohol Use.

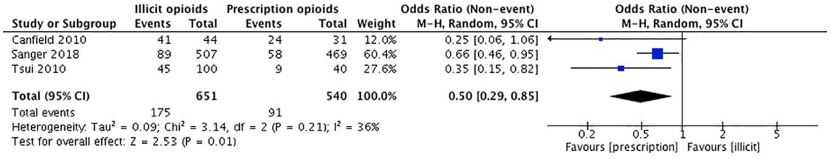

FIGURE 7 | Forest Plot for Cocaine Use.

The studies included in our meta-analysis comprise a total sample size of 1,051 participants. In Canfield et al. (54), there was no significant difference in benzodiazepine use among those who reported obtaining their first opioid through a prescription vs. an illicit source. In Sanger et al. (53), there was no significant association between source of opioid initiation and benzodiazepine use. We conducted an unadjusted meta-analysis using odds ratios to compare benzodiazepine use among those who first initiated opioids through a prescription vs. a recreational source. We found that there was no significant association between individuals who were introduced to opioids through prescription and those that were introduced through recreational means (OR 0.82, 95% CI 0.54, 1.26, p-value 0.37). Please see **Figure 8**.

Treatment Retention

Two studies examined treatment retention (36, 53) however we were unable to combine study results to conduct a meta-analysis. Sanger et al. (53) examined the mean length in treatment and found that there was no significant association between the prescription introduction and recreational introduction groups (53). Cooper et al. (36) reported the length of treatment in median years. They reported no significant association between those introduced to opioids through a prescription in comparison to those introduced by recreational means for length of current treatment in median years (36).

Risk of Bias Across Studies

When assessing risk of bias across studies (**Figure 9**), we noticed a few trends. First, two of the studies show an unclear or high risk of detection bias, which indicates that the studies either did not adjust for confounders and other variables, or did not properly report that they did so (52, 54). Secondly, two of the studies also show an unclear risk of detection bias as they fail to provide outcome data, or the data provided is unclear (52, 54). Overall, our findings show that the results from these two observational studies should be interpreted carefully due to risk of bias. Further, our results show that the other three observational studies were generally well reported and bias free (36, 53, 55). Please see **Figure 9**.

Additional Analysis

As there were a small number of studies included in this review, it was not possible to conduct any additional analyses.

DISCUSSION

Summary of Evidence

Opioid use disorder is a serious illness that affects approximately 26 to 36 million people across the globe (2). Not only does this illness affect the individual in multiple aspects of their lives, it places a great economic burden on healthcare systems (56). We have recently seen a dramatic increase in the number of people misusing opioids, a significant proportion of whom misuse prescription opioids specifically. While this crisis has global impacts, North America has experienced the majority of the burden of illness. The United States alone consumes 80% of the global supply of prescription opioids, and it is estimated that their use has increased by 300% since 1991 (57). Research has suggested that those prescribed an opioid prescription for chronic pain have a risk of up to 60% of misusing prescriptions (58). It is critically important to investigate the emerging cohort of patients who were introduced to opioids by legitimate prescriptions to see whether they fare differently in MAT compared to those who were introduced to opioids recreationally. To our knowledge, this is the first systematic review to synthesize the literature examining this question.

Our meta-analysis found that those that were introduced to opioids through a legitimate prescription were less likely to use illicit opioids while in treatment than those that were introduced to opioids through recreational means (OR 0.70, 95% CI 0.50, 0.99, p-value 0.04). Our findings also revealed that the prescription introduction to opioids cohort were less likely to have used cocaine (OR 0.50, 95% CI 0.29, 0.85, p-value 0.01), alcohol (OR 0.75, 95% CI 0.59, 0.95, p-value 0.02), cannabis (OR 0.54, 95% CI 0.32, 0.89, p-value 0.02), and injection drugs (OR 0.25, 95% CI 0.14, 0.43, p-value <0.001). There was no association found between the source of introduction to opioids and benzodiazepine use (OR 0.82, 95% CI 0.54, 1.26, p-value 0.37).

Those introduced to opioids through prescriptions were found to be less likely to continue using opioids during treatment than those whose first introduction was through recreation. This suggests that first introduction to opioids through illegal means predicts continued use during treatment, and that the first introduction may explain trends in subsequent opioid use. Brands et al. demonstrated that patients in MMT who used only prescription opioids had significantly less experience with sharing opioid injection equipment in comparison to those

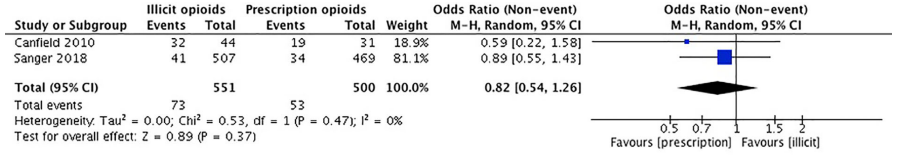

FIGURE 8 | Forest Plot for Benzodiazepine Use.

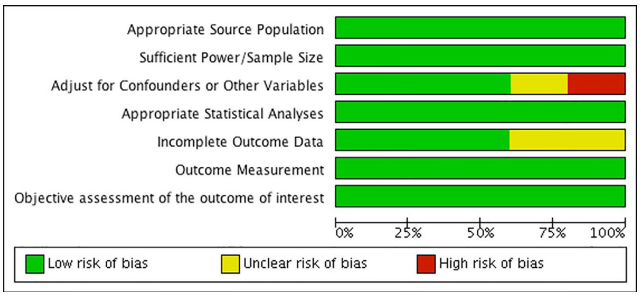

FIGURE 9 | Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

patients who used heroin only or initially (59). While this study did not ask patients about their first introduction to prescription opioids, most patients using prescription opioids only (86%) or initially (61.9%) indicated that their initial reason for using opioids was to manage pain. They conclude that those who were likely introduced to opioids through prescription as a means of treating pain tend to engage in less risk-taking behavior, and are less likely to continue using opioids during treatment in comparison to those not using opioid drugs to manage pain (59). Further, in another study of patients in treatment for OUD, those using only prescription opioids had a higher treatment retention, fewer opioid-positive urine samples, and were more likely to complete treatment than those patients using a combination of heroin and prescription opioids or those using heroin exclusively (35). Taken together, first introduction and reason for use, perhaps mediated by risk-taking behaviors, may predict future opioid use and explain our finding that those who were not first introduced to opioids through a prescription have an increased likelihood of continued use in treatment. People whose opioid use was first initiated through prescription also tend to be demonstrate lower risk-taking behavior, further supporting the observation that those who initiate opioid use from a prescription tend to be less likely to continue use during treatment. Prescription-introduced opioid users are more likely to be female, generally have an older age of opioid use onset, and are more like to have completed a post-secondary education (53). These factors likely influence the level of continued use of illicit opioids in treatment as women in general are less likely to use opioids (60) and are shown to engage in fewer risks than men in terms of both everyday risk-taking behaviors (61) as well as in financial, recreational, ethical, and recreational domains (62). Risk-taking attitudes are found to be reduced with age (62), and older adults are also less likely to partake in risk-taking behavior and illegal opioid use while in treatment. A study of treatment outcomes for opioid use found that 61% of older adults had no positive urine screens for opioids, compared to 35% in younger adults after initiating treatment (63).

Our finding that those introduced to opioids through recreational means are more likely to engage in using other substances such as alcohol, marijuana, and cocaine, is also congruent with the literature. Studies have found that the nonmedical use of opioids was significantly associated with the use of other illicit substances (56). Specifically, there is research that suggests that there are differences in polysubstance use between prescription users and recreational users, and that this poly-substance use in recreational opioid users may be associated with risk-taking behaviors. A study investigating HIV risk-taking behavior found that men who are recreational, poly-substance drug users were more likely to engage in risky behaviors such as the sharing of needles and sex without protection (64). Morely et al. took a closer look at recreational drug users and found that different mental disorders and behavior patterns are predictive of the type and degree of polysubstance use a recreational user engages in (65). Depression and anxiety disorders were found to be predictive of medication and cannabis use, whereas violent and risky behavior suggested the use of illicit or all drugs. In contrast, participants in the non-polysubstance class were more likely to be female, have a lower desire to use drugs, and were less likely to have a diagnosis of anxiety or depression, or engage in violent risk-taking behaviors. Thus, risk-taking behavior and the presence of mental illness may be predictive of polysubstance use in recreational drug users, which would explain our finding that recreational drug users have a higher likelihood of misusing more than one illicit substance. A study reported that respondents who had experienced at least one major depressive episode in the past year were more likely to engage in non-medical use of prescription pain relievers (66). Providing support and resources for comorbid mental health concerns within this population may be an area that clinicians and policy makers should consider implementing within OUD treatment plans.

With the increased availability of prescription opioids contributing to the opioid epidemic, countries across the globe have taken initiatives to control access and prescribing patters of opioids. Some of these initiatives include legislative changes through guideline recommendations in opioid prescribing for

chronic, non-cancer pain, acute pain conditions, and prescription monitoring programs (42, 67). Research examining these changes have suggested that there is a decrease in opioid prescribing with these measures in place such as using the recommendation of nonsteroidal anti-inflammatory drugs (NSAIDs) over opioids for acute pain (28, 67–70). These findings in combination with the ever-changing synthetic opioids drug market would suggest that is important to continue to tailor recommendations to fit the ever-changing opioid user.

These findings are important as they can help develop tailored MAT programs for patients. It may be important to consider comorbid medical conditions such as pain that may have led to being introduced to opioid by prescription or concurrent substance use when creating a treatment plan. This systematic review has highlighted that those introduced to opioids by prescription means are less likely to use other substances including opioids. This cohort of individual are most likely people that did not intend to engage in risk-taking behavior. They ended up dependent to opioids because of the associated addictive properties. They may benefit from being treated in different settings and with the use of different approaches to addiction philosophy. Addiction specialists should consider addressing harm reduction strategies such as hepatitis C treatment awareness and provision of clean needles to those still engaging is IV drug use while in treatment. Pain specialists and pharmacists may want to consider including a brief educational component and treatment plan to mitigate problematic use potential surrounding opioids when prescribing opioids to a patient is necessary. Additionally, those who were introduced through recreational means likely have a different set of problems to address than those whose use began with prescriptions. Perhaps there should be additional support provided for patients that desire to stop using additional substances alongside illicit opioids. The current lack of data present on poly-drug use, the associated risks and individual goals is limited and should be expanded on in order to develop personalized support for poly-drug users. Some research has predicted that the increased strictness of prescribing opioids will not have a huge impact on the number of opioid overdoses and deaths (71). Targeting illicit opioid use in treatment is where focus should also be. Policy makers may want to provide different treatment settings for OUD patients and, by identifying patients with high risk behavior patterns who were introduced to opioids recreationally, can take advantage of opportunities for interventions to reduce patients' hazardous use of other substances. It is also important to address the lack of information on the emergence of novel opioid substances and their apparent popularity with illicit opioid users as it limits the level of insight current literature can provide to drug addiction services and clinicians. Due to the lack of information on current opioid related changes future directions may include updating this paper to possibly highlight novel data on poly-drug use and opioid derivatives. Furthermore, due to the extended focus on North American and Australian data present in this paper future studies could explore ethnic and socioeconomic differences present in method of introduction to opioids.

Strengths and Limitations

This systematic review has some clear strengths, with the most notable being the methodological strengths. Firstly, this is the first systematic review to our knowledge that compares the method of introduction to opioids and treatment outcomes in OUD patients while in MAT. We were able to conduct six different meta-analyses on illicit opioid use, cocaine use, alcohol use, cannabis use, benzodiazepine use, and injection drug use. We employed rigorous screening methods to ensure all possible studies were included. Additionally, we presented our findings in a qualitative and quantitative method. Despite having a small number of studies included, the heterogeneity of the meta-analyses was less than 40%.

As with most systematic reviews, ours is not without limitations. The first limitation is that we were not able to conduct adjusted analyses. Unfortunately, not all the studies adjusted for confounding variables, which necessitates a more cautious interpretation of the findings. It is also important to mention that the included studies are before 2018, which may limit the impact of findings on the current opioid climate. Also, the analysis conducted was focused on North American or Australian data (the most available data), which minimizes the generalizability of the findings. We were also unable to conduct any analysis to detect publication bias due to a paucity of included studies. There is a lack of research on examining treatment outcome differences by the method of introduction to opioids as well as limited data on novel opioids and fentanyl derivatives. There is a need to not only to continue to examine this association through additional primary studies, but to also to investigate whether the type of opioids initially prescribed has ramifications on the risk of subsequently developing OUD. Additionally, standard urine screens may not be able to detect novel opioid. However, regardless of being able to detect novel opioids, our results did find a significant association for illicit opioid use and method of introduction to opioids. This finding may be a moderate estimation of the association and the actual association may be greater.

CONCLUSION

This review highlights the differences found in illicit opioid use, cocaine use, alcohol use, injection drug use, and cannabis use in found in the cohort of patients that were introduced to opioids through a legitimate prescription and those introduced to opioids by recreational means. These differences are important for health policy makers and can help shape the success of these patients through further investigation.

DATA AVAILABILITY STATEMENT

All datasets presented in this study are included in the article/ **Supplementary Material**.

AUTHOR CONTRIBUTIONS

NSa: contributed to the conception and design of the study, search strategy, screening and data extraction, analysis of

results manuscript writing, and final review of the manuscript. MBh contributed to the conception and design of the study, screening and data extraction, analysis of results, and critical revision and final review. NSi, BP, AD'E, MT, HS, AH, NB-M, VR, DS, MB, EL: contributed to the methodological design, manuscript writing, critical revision, and final review of the manuscript. RD, MS, LT: contributed to the methodological design, critical revision, and final review of the manuscript. SS: contributed to the development of the search strategy and final review of the manuscript. ZS: contributed to the conception and design of the study, critical revision, and final approval of the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2020.00812/full#supplementary-material

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Prospective Study

Association Between Socio-Demographic and Health Functioning Variables Among Patients with Opioid Use Disorder Introduced by Prescription: A Prospective Cohort Study

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Background: Prescription opioid misuse in Canada has become a serious public health concern and has contributed to Canada's opioid crisis. There are thousands of Canadians who are currently receiving treatment for opioid use disorder, which is a chronic relapsing disorder with enormous impact on individuals and society.

Objectives: The aim of this study was to compare the clinical and demographic differences between cohorts of patients who were introduced to opioids through a prescription and those introduced to opioids for non-medical purposes.

Study Design: This was an observational, prospective cohort study.

Setting: The study took place in 19 Canadian Addiction Treatment Centres across Ontario.

Methods: We included a total of 976 participants who were diagnosed with Opioid Use Disorder and currently receiving methadone maintenance treatment. We excluded participants who were on any other type of prescription opioid or who were missing their 6-month follow-up urine screens. We measured the participants' initial source of introduction to opioids along with other variables using the Maudsley Addiction Profile. We also measured illicit opioid use using urine screens at baseline and at 6-months follow-up.

Results: Almost half the sample (n = 469) were initiated to opioids via prescription. Women were more likely to be initiated to opioids via a prescription (OR = 1.385, 95% CI 1.027-1.866, $P = .033$). Those initiated via prescription were also more likely to have post-secondary education, older age of onset of opioid use, less likely to have hepatitis C and less likely to have use cannabis. Chronic pain was significantly associated with initiation to opioids through prescription (OR = 2.720, 95% CI 1.998-3.722, $P < .0001$). Analyses by gender revealed that men initiated by prescription were less likely to have liver disease and less likely to use cannabis, while women initiated by prescription had a higher methadone dose.

Limitations: This project was limited by its study design being observational in nature; no causal relationships can be inferred. Also, the data did not allow determination of the role that the prescribed opioids played in developing opioid use disorder.

Conclusions: Our results have revealed that almost half of this methadone maintenance treatment (MMT) population has been introduced to opioids through a prescription. Given that the increasing prescribing rates of opioids has an impact on this at-risk population, alternative treatments for pain should be considered to help decrease this opioid epidemic in Canada.

Key words: Opioid use disorder, chronic pain relief, methadone maintenance treatment, prescriptions, male, female

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In 2015, a report conducted by the United Nations Office on Drugs and Crime reported that approximately 32 to 36 million people worldwide abuse opioids (1). Opioids are the leading cause of drug-related death worldwide and are an even bigger concern for North America (2,3). Recent research has shown that this surge in illicit use is associated with the availability of opioids through medical prescriptions (4). Opioid use disorder (OUD) is a chronic, relapsing disorder that is categorized by serious psychological, social, and physical adversities (5). Negative consequences that may result from OUD include increased risk of infection and death, polysubstance use, psychiatric comorbidity, as well as criminal activity (5–7). OUD also creates an economic toll on the health care system, specifically due to the high costs of managing the disorder (8). In 2015, it was estimated that treatment for OUD in methadone clinics in Ontario alone cost $156 million (8,9).

Ontario has experienced an unprecedented increase in the number of patients undergoing methadone maintenance treatment (MMT) for OUD in the last 10 years, with over 50,000 individuals reported to be in MMT programs in 2016 (6,8). While MMT may be successful in treating OUD in some patients (10–12), treatment outcomes are highly variable, with other patients exhibiting poor health and social functioning and continuing use of illicit substances (7). The majority of the research conducted in the MMT population has focused on heroin and street users and fails to compare them to patients who were initiated to opioids via prescription. Differentiating between patients with prescription-influenced OUD and nonmedically influenced OUD is important for establishing a socio-demographic profile and determining unique risk factors for treatment failure in this population. Few studies have looked at the MMT population and dichotomized the study population by source of initiation to opioids. With recent research also finding that there is now an increase in women misusing opioids, with 52% of women and 38% of men seeking treatment having first been exposed to opioids through a prescription (13) , an investigation into gender differences is also warranted.

The objective of this study was to investigate clinical and socio-demographic differences of patients with OUD who were introduced to opioids via prescription compared to those who obtained opioids by other means (i.e., family, friends, street). We also aimed to examine gender differences between the 2 groups, which, to our knowledge, has not been done before.

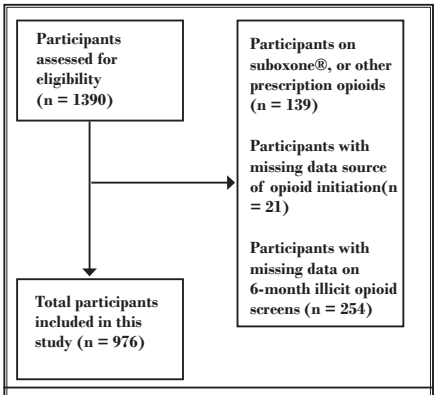

Fig. 1. *Flow diagram for eligibility and inclusion of participants*

Methods

Participants and Study Design

The data for this study was obtained from a larger project called the Genetics of Opioid Addiction (GENOA) study program, which is an ongoing multicenter cohort in collaboration with the Populations Genomics Program at McMaster University and Canadian Addiction Treatment Centres (CATC) (14). Patients were recruited from 19 different CATC clinics across Ontario from May 2013 through November 2016. This project was approved by the Hamilton Integrated Research Ethics Board (HIREB; Study ID 11-056).

To be eligible for GENOA, patients had to meet the following inclusion criteria: be over 18 years of age; meet the criteria for opioid dependence using the DSM-IV criteria (modified in DSM-5 to opioid use disorder); receive methadone maintenance treatment; able to provide informed, written consent; and undergo urine drug screens. In addition, patients also had to provide information on source of initiation to opioids. Patients who were receiving an alternate opioid substitution therapy, currently taking prescription opioids, currently on suboxone®, or unable to provide a urine sample were excluded from this study (Fig. 1).

Eligible patients provided informed consent and participated in a structured face-to-face interview at baseline, during which they were asked to provide basic demographic information and answer questions about

their health and social functioning. Specifically, the data collected consisted of information on socio-demographics, family background, psychiatric background, and details on drug use. Details of illicit opioid use were collected through regular urine drug screens at baseline and 6 months.

Measures

All patients in the study were asked about the initial source through which they were introduced to opioids (i.e., physician prescription, family, street) and this information was recorded on case report forms. For this study, this variable was dichotomized into prescribed opioids (initial exposure to opioids through a medical prescription) and illicit opioids (initial exposure to opioids through other means including at home, family member, street, school or friend). Demographic information, including age of onset of opioid use, methadone dose, treatment duration, education, and employment status, was also collected.

The Maudsley Addiction Profile (MAP) was administered to measure health and social functioning (15). Within the MAP, specific details of self-reported drug use were collected, including the number of times the drug was used within the past 30 days, typical dose, and the route(s) of administration. The illicit drugs included heroin, cocaine, illicit methadone, benzodiazepines, amphetamines, and cannabis. Frequency and amount of alcohol use was also collected. The MAP also collected medical history, which asked if the patient had been diagnosed with the following physical health conditions: HIV, hepatitis, chronic pain, liver disease, diabetes, and epilepsy.

Illicit opioid use was measured by regular urine drug screens and reported as the percentage of positive opioid screens (positive opioid screens divided by total urine screens). Illicit opioid use was measured at baseline and at a 6-month follow-up.

Statistical Analysis

To summarize the demographic data of the study population, descriptive statistics were used. The continuous variables are presented as means and standard deviations, while dichotomous variables are depicted as percentages.

The primary analysis used multivariable logistic regression to examine the relationship between socio-demographic factors, health functioning, and illicit drug use in relation to source of initial opioid use. Covariates included age, gender, methadone dose, and treatment duration. The variables of ethnicity, marital status, education, and drug use (heroin, cocaine, illicit methadone, alcohol, benzodiazepines, and amphetamines) were transformed into dichotomous variables. Ethnicity was categorized as Caucasian and other. Education was categorized as high school or less and post-secondary education (trade school/college/university/postgraduate). Marital status was grouped into currently with a partner (currently married/common-law) or no current partner (never married/separated/divorced/widowed). Drug use was categorized as any drug use within the past 30 days or no drug use. A secondary analysis that looked at gender differences was conducted using the same model, variables, and covariates.

The data analysis was conducted using SPSS Version 23.0 (16). The results reported a 95% confidence interval, adjusted odds ratio, and the alpha level of significance set to $\alpha = .05$ for the primary analysis. For the secondary analysis looking at differences between men and women, $\alpha = .025$ was set. Collinearity was considered by looking at the variance inflation factor (VIF); none of the variables had a VIF of 10 or greater. This study adheres to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) (17).

Sample size was calculated by using the logistic regression rule of having at least 10 events per predictor variable (18). This rule was satisfied, as we included 976 participants in the primary regression with 23 predictors. In the secondary analysis, we included 441 women and 535 men with 22 predictors each.

Results

A total of 1390 patients were potentially eligible for this study. A total of 82 patients were excluded, as they were on suboxone®, and 57 patients were excluded, as they were taking additional prescribed opioids. Additionally, 21 patients were excluded for missing data on initial opioid exposure and 254 patients were missing data on their 6-month urine screens. A total of 976 patients were included in the analysis (Fig. 1).

Demographics

Our sample included comparable numbers of prescription-initiated opioid users (n = 469) and illicit opioid users (n = 507). Approximately half of all patients in the prescription-initiated opioids group were women (51.0%), which was considerably higher in comparison to the illicit opioids group (39.8%). The prescribed opioids group's average age of onset of opioid use was 27.4 years (SD = 8.87), which was higher than the illicit opi-

oids group's mean age of onset, 23.1 (SD = 8.04). The average daily methadone dose for prescribed opioid-users was 78.2 mg (SD = 41.8), which was marginally greater than the average dose of 74.1 mg (SD = 46.0) for the illicit opioids group. The prescribed opioids group also had approximately twice as many patients experiencing chronic pain (51.8%) in comparison to the illicit opioids group (25.6%). We had a total of 0.9% of patients with HIV in the prescription-initiated and 0.2% of patients in the illicit opioids group. With these numbers being very small, we had to remove these patients from the primary and secondary analyses. A complete summary of demographic and clinical characteristics comparing prescribed opioid-users and illicit opioid-users is reported in Table 1.

Primary Analysis

The results of the multivariable logistic regression for the association between source of opioid initiation and other socio-demographic and health functioning variables are provided in Table 2. There was a significant association between being female and being initiated to opioids via prescription, after adjusting for current age, methadone dose, and treatment duration (OR = 1.385, 95% CI 1.027-1.866, *P* = .033). Education was found to be significantly associated with being initially prescribed opioids, suggesting that patients in the prescribed group were more likely to have post-secondary education in comparison to the illicit opioids group (OR = 1.76, 95% CI 1.78-2.44, *P* = 0.001). Patients who were initiated to opioids via prescription were almost 3 times as likely to have been diagnosed with chronic pain (OR = 2.72, 95% CI 1.97-3.75, *P* < .001). Age of onset of opioid use was significantly higher in those introduced to opioids through a prescription (OR = 1.05, 95% CI 1.03-1.08, *P* < .001). Patients who had been introduced to opioids through nonmedical means had significantly higher rates of hepatitis (OR = 0.64, 95% CI 0.44-0.94, *P* = .022) and were more likely to have used cannabis in the past 30 days (OR = 0.66, 95% CI 0.49-0.90, *P* = .008).

Secondary Analysis

Our secondary analyses by gender looked at the relationship between source of opioid and a variety of variables (Tables 3 & 4). Similar to the primary analyses, chronic pain, education, and age of onset of opioid use were associated with initiation to opioids via prescription for both men and women. Among men, liver disease was associated with illicit opioid use (OR = 0.278, 95% CI = 0.104-0.742 , *P* = 0.011). There was no significant association in the subgroup analyses by gender for continued illicit opioid use at 6 months.

Interpretation

This prospective cohort study compared individuals in MMT who were initiated to opioids via medical prescription versus those introduced through illicit means with respect to social-demographic characteristics, health functioning, and continued illicit substance use. Almost half of the sample was introduced through a medical prescription (n = 469); these patients were more likely to have older age of onset of opioid use, have post-secondary education, be female, and less likely to use cannabis. We also found that the prescription-initiated group was less likely to have hepatitis C and more likely to have chronic pain. When we explored these differences by gender, we found that among men, the prescription-initiated group had a lower prevalence of liver disease and cannabis use. Among women, those in the prescription-initiated group were less likely to have hepatitis and more likely to have a higher methadone dose.

Our findings highlight important distinguishing characteristics for the prescription-initiated group, consistent with the literature. The literature has suggested that with increased physician-prescribing of opioids, there has been a rise in older-age patients misusing opioids (19–21). Opioids are most commonly prescribed for chronic, non-cancer pain conditions (19,21) typically prevalent among older adults, such as low back pain, arthritis, and fibromyalgia (22,23). Some studies have suggested that up to 60% of chronic pain patients are at high risk for prescription misuse (24). The prescription-initiated group was more likely to have post-secondary education. There may be many factors influencing this, but a significant one may be that the recreationally-initiated group was younger at age of onset of opioid use; their early start to recreational drug use may have influenced further education. Research has found that youth who begin to use heroin at a young age have significantly higher high school drop-out rates in comparison to the prescription-using group (25). Additionally, women are more susceptible to chronic pain for a variety of factors, including greater amounts of estrogen in comparison to men. Estrogen has been shown to increase pain sensitivity and the risk of developing inflammation-related diseases (23,26,27). Recent research shows that women are more likely to be prescribed painkillers such as Percocet®, OxyContin,

Table 1. *Demographic characteristics of study sample*

Variables (n = 976)	Prescribed Opioids	Illicit Opioids
Total number of patients	469	507
Age (SD)	40.8 (10.4)	36.9 (11.2)
Gender, % women	51.0	39.8
Currently employed, n (%)	158 (33.7)	183 (36.1)
Marital Status		
Never married (%)	177 (37.7)	270 (53.3)
Currently married/Common-law (%)	150 (32.0)	156 (30.8)
Separated/Divorced/Widowed(%)	142 (30.2)	81 (16)
Ethnicity		
Caucasian (%)	418 (89.1)	438 (86.4)
Native North American (%)	28 (6.0)	34 (6.7)
Other (%)	23 (4.9)	35 (6.6)
Level of Education		
None/Elementary School (%)	96 (20.5)	115 (22.7)
High school (%)	208 (44.3)	278 (54.8)
Trade school (%)	21 (4.5)	11 (2.2)
College/university (%)	140 (29.9)	98 (19.3)
Postgraduate (%)	2 (0.4)	2 (0.4)
Details of Opioid Use		
Age of onset of opioid use in yrs (SD)	27.4(8.87)	23.1(8.04)
Methadone treatment duration in mos (SD)	51.3(49.2)	48.1(48.7)
Methadone dose in mg/day (SD)	78.2(41.8)	74.1(46.0)
Baseline illicit opioid use, % positive screens	17.0	18.8
Medical History, %		
HIV	0.9	0.2
Hepatitis	21.7	28.8
Diabetes	6.2	4.9
Liver disease	4.1	6.1
Chronic pain	51.8	25.6
Epilepsy	2.1	2.0
Other medical conditions*	52.9	40.2
Self-reported Drug Use At Least Once in Past 30 Days, %		
Heroin	5.8	12.8
Illicit methadone	1.3	1.2
Illicit benzodiazepine	7.3	8.0
Cocaine	12.4	17.5
Cannabis	44.7	55.8
Amphetamine	3.0	3.1
Alcohol	36.4	44.4

*The "other medical conditions" category consists of any other responses, the most common being hypertension, acid reflux, asthma, cancer, celiac disease, Crohn's disease, migraines, colitis, degenerative disc disease, hyperthyroidism, hypothyroidism, gout, heart murmur, and ulcers.

Table 2. *Multivariable logistic regression analysis on factors associated with source of opioid initiation (n = 976)*

	OR	95% CI	P Value
Age	1.008	0.988-1.027	.443
Gender	1.385	1.027-1.866	.033*
Currently Working	0.847	0.612-1.172	.316
Methadone Dose (mg/day)	1.000	0.997-1.004	.802
Treatment Duration	1.000	0.996-1.003	.842
Currently Married/Common-law	1.108	0.746-1.389	.909
Ethnicity	0.810	0.522-1.255	.345
Education	1.765	1.278-2.437	.001*
Age of Opioid Use Onset	1.049	1.028-1.072	<.001*
Epilepsy	1.252	0.471-3.326	.653
Hepatitis	0.616	0.424-0.893	.011*
Liver Disease	0.480	0.232-0.994	.048
Chronic Pain	2.720	1.998-3.722	<.001*
Diabetes	0.872	0.455-1.672	.680
Other medical condition	1.213	0.902-1.632	.201
Heroin	0.605	0.343-1.066	.082
Illicit Methadone	1.251	0.483-3.242	.605
Alcohol	0.838	0.622-1.128	.244
Cannabis	0.671	0.501-0.900	.008*
Benzodiazepine	1.106	0.671-1.821	.694
Amphetamine	1.112	0.553-2.236	.766
Cocaine	0.865	0.587-1.295	.481
Illicit Opioid Use at 6 Mos (% Positive Screens)	1.112	0.510-2.427	.789

Heroin, illicit methadone, alcohol, cannabis, benzodiazepines, amphetamine, cocaine interpreted as categorical variables consisting of 2 levels: no days drug used and used drug at least once in 30 days.
Ethnicity interpreted as a categorical variable: Caucasian and other.
Marital status interpreted as a categorical variable: currently with a partner and currently not with a partner.
*Significant at $P < .05$
Abbreviations: OR, odds ratio; CI, confidence interval.

and Vicodin, with higher dosages in emergency settings (28). We found that women initiated by prescription were likely to have a higher methadone dose, which has been shown to help with chronic pain, as methadone is a synthetic opioid (29). There is stereotyping towards men which assumes that men are more likely to misuse substances (30); however, this may not hold true in the OUD population. This study suggests that women diagnosed with OUD are more likely to have been prescribed an opioid and to be older, more educated, and have a history of chronic pain.

We found that those initiated to opioids through a prescription were less likely to have hepatitis C and less likely to use cannabis (31,32). In our analysis by gender, we also found that men initiated to opioids through a prescription were less likely to have liver disease. Injection drug use increases the likelihood of contracting hepatitis through the sharing of needles; hepatitis has a significant impact on the liver, as does use of multiple substances (33–35).

Men introduced to opioids through a legitimate prescription were also less likely to use cannabis. Though we cannot infer any causal relationship from our results due to the cross-sectional nature of the study, this finding suggests that those who began opioid use through illicit means may require additional care to manage ongoing use of cannabis. Previous research has shown that it is important to manage cannabis use, as it is as-

Table 3. *Multivariable logistic regression analysis on factors associated with source of opioid initiation in women (n = 441)*

	OR	95% CI	P value
Age	1.015	0.984-1.047	.357
Currently Working	0.901	0.536-1.514	.694
Age of Opioid Use Onset	1.065	1.029-1.102	<.0001
Methadone Dose (mg/day)	1.006	1.001-1.012	.031
Treatment Duration	0.998	0.993-1.003	.417
Epilepsy	1.545	0.408-5.855	.533
Hepatitis	0.551	0.308-0.986	.045
Liver Disease	1.149	0.346-3.817	.821
Chronic Pain	2.267	1.381-3.719	.001
Diabetes	0.477	0.184-1.236	.128
Other medical conditions	1.259	0.794-1.995	.328
Ethnicity	0.959	0.508-1.809	.897
Marital Status	1.035	0.641-1.673	.888
Education	1.683	1.044-2.712	.033
Alcohol	0.810	0.504-1.301	.383
Heroin	0.401	0.135-1.187	.099
Illicit Methadone	1.216	0.267-5.536	.801
Benzodiazepine	1.271	0.561-2.879	.565
Cocaine	0.677	0.364-1.259	.218
Amphetamine	1.614	0.432-6.030	.477
Cannabis	0.677	0.430-1.064	.091
Illicit Opioid Use at 6 Mos (% Positive Screens)	0.375	0.099-1.416	.148

Heroin, illicit methadone, alcohol, cannabis, benzodiazepines, amphetamine,ocaine interpreted as a categorical variables consisting of 2 levels: no days drug used and used drug at least once in 30 days.
Ethnicity interpreted as a categorical variable: Caucasian and other.
Marital status interpreted as a categorical variable: currently with a partner and currently not with a partner.
*Significant at $P < .025$
Abbreviations: OR, odds ratio; CI confidence interval.

sociated with ongoing opioid use during MMT among a subset of the population (36).

Limitations

This study is limited by its observational design, such that we cannot make any causal inferences about the association between the source of opioid use and health functioning. We also could not determine the extent to which prescription opioids contribute to the development of opioid use disorder from our collected data. However, the concept of identifying the initial source of introduction to opioids is novel, and, to our knowledge, no other study looking at a large MMT population has examined this. The information collected on illicit drug use was mainly reliant on self-report, and therefore susceptible to social desirability bias. In an attempt to reduce this bias, all research assistants were trained to build rapport with the study participants and administer the questionnaire in a standardized manner.

Conclusion

Few studies have compared functioning and treatment outcomes for MMT patients who were exposed to opioids by medical prescription versus recreational use. Our study shows that important differences exist between these groups of patients, including significantly greater comorbid chronic pain in the prescription opioid group, which has implications for developing specific treatment plans for these groups of patients. Given that approximately half of the MMT sample was initiated to opioids by a physician prescription, it is important to note the differences between this group

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Table 4. *Multivariable logistic regression analysis on factors associated with source of opioid initiation in men (n = 535)*

	OR	95% CI	P value
Age	1.003	0.977-1.030	.829
Currently Working	0.751	0.505-1.208	.267
Age of Opioid Use Onset	1.045	1.016-1.074	.002
Methadone Dose (mg/day)	0.997	0.992-1.002	.197
Treatment Duration	1.002	0.997-1.006	.463
Epilepsy	0.934	0.208-4.318	.930
Hepatitis	0.721	0.431-1.206	.212
Liver Disease	0.278	0.104-0.742	.011
Chronic Pain	3.146	2.062-4.798	<.0001
Diabetes	1.251	0.500-3.130	.633
Other medical conditions	1.196	0.798-1.796	.386
Ethnicity	0.596	0.310-1.144	.120
Marital Status	1.024	0.667-1.571	.915
Education	1.941	1.221-3.085	<.0001
Alcohol	0.875	0.586-1.305	.512
Heroin	0.732	0.359-1.494	.392
Illicit Methadone	1.097	0.280-4.298	.894
Benzodiazepine	1.012	0.521-1.965	.973
Cocaine	0.999	0.569-1.754	.998
Amphetamine	0.817	0.344-1.943	.648
Cannabis	0.646	0.428-0.974	.037
Illicit Opioid Use at 6 Mos (% Positive Screens)	2.292	0.825-6.370	.112

Heroin, illicit methadone, alcohol, cannabis, benzodiazepines, amphetamine, cocaine interpreted as categorical variables consisting of 2 levels: no days drug used and used drug at least once in 30 days.
Ethnicity interpreted as a categorical variable: Caucasian and other.
Marital status interpreted as a categorical variable: currently with a partner and currently not with a partner.
*Significant at $P < .025$
Abbreviations: OR, odds ratio; CI, confidence interval.

of patients and those who obtained opioids by other means. Differences in education level, comorbid medical issues, and concurrent substance use may be important to consider when developing treatment programs as well as specific goals of care for MMT patients. Many recent investigations, including our study, have shown the heterogeneity among the MMT patient population indicating a need for personalized care for these patients. The source of initial opioid use may be useful in clinical practice to promote discussion about specific concerns, such as hepatitis C treatment, concurrent substance use, and chronic pain; and to recommend appropriate harm reduction strategies to patients.

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ORIGINAL ARTICLE

The future of precision medicine in opioid use disorder: inclusion of patient-important outcomes in clinical trials

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Opioid use has reached an epidemic proportion in Canada and the United States that is mostly attributed to excess availability of prescribed opioids for pain. This excess in opioid use led to an increase in the prevalence of opioid use disorder (OUD) requiring treatment. The most common treatment recommendations include medication-assisted treatment (MAT) combined with psychosocial interventions. Clinical trials investigating the effectiveness of MAT, however, have a limited focus on effectiveness measures that overlook patient-important outcomes. Despite MAT, patients with OUD continue to suffer negative consequences of opioid use. Patient goals and personalized medicine are overlooked in clinical trials and guidelines, thus missing an opportunity to improve prognosis of OUD by considering precision medicine in addiction trials. In this mixed-methods study, patients with OUD receiving MAT (n=2,031, mean age 39.1 years [SD 10.7], 44% female) were interviewed to identify patient goals for MAT. The most frequently reported patient-important outcomes were to stop treatment (39%) and to avoid all drugs (25%). These results are inconsistent with treatment recommendations and trial outcome measures. We discuss theses inconsistencies and make recommendations to incorporate these outcomes to achieve patient-centered and personalized treatment strategies.

Keywords: Opioid; outcomes; clinical trials; patient important

Introduction

Substance use disorder is a chronic and complex behavior with multifaceted health and social consequences. Prescription opioid misuse has become a public health crisis in the United States and Canada, with its reach spreading to other societies at a global level.[1-3] The root and progression of the opioid crisis in North America have been covered in all types of media as the crisis has touched the lives of many, and its detrimental effects are seen daily in the form of increased mortality and healthcare utilization. In a recent outlook on the rationale for opioid overprescription patterns that began in the 1980s and have continued since, managing pain was found to be the catalyst for the wide distribution of opioids, based on weak evidence contained in a letter to the editor published in the *New England Journal of Medicine*.[4,5] Nonetheless, the rate of opioid prescribing and use continues to rise, leading to an increased incidence of opioid use disorder (OUD). A report compiled by the Substance Abuse and Mental Health Services Administration (SAMHSA) found that over 2.1 million people in the United States are suffering from an OUD related to prescription opioids.[6]

OUD is a chronic, relapsing disorder that effects all aspects of an individual's life – physical, social, and psychological.[7] A central feature of OUD are the withdrawal symptoms that are experienced when opioids are abruptly stopped, or their dose reduced. Examples of these symptoms are sweating, agitation, shakes, and muscle pains.[7] Research has also suggested that the severity of withdrawal symptoms experienced may be associated with why patients who are receiving treatment for OUD relapse.[8]

There are various treatment options available for OUD, which are usually a combination of psychological and pharmacological interventions. The pharmacological intervention includes medication-assisted treatment (MAT), which

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can include opioid agonists, partial agonists, and antagonists.[9,10] One of the most common types of MAT is methadone maintenance treatment (MMT). Methadone is a synthetic opioid that can have long-lasting effects for up to 24 hours[9] and helps to alleviate withdrawal symptoms, usually without the euphoric effects associated with opioids.[9] While studies have shown that MMT is effective, there is still great variability in treatment response,[11,12] and outcome measures to assess the effectiveness of methadone are inconsistent.[13]

As OUD can affect people in multiple ways, including physical and mental health, social impact, economic burden, quality of life, and life expectancy, it is therefore difficult to identify which of these aspects clinical trialists, healthcare services, and providers should focus on when developing treatment programs. There are many challenges to consider when deciding on an outcome measure for a chronic disorder with multifaceted impact such as OUD. There is also a need to consider what patients want as a successful and desirable treatment outcome for them to ensure better prognosis and implement a personalized medicine approach. More specifically, the challenges that need to be addressed include how a personalized medicine approach impacts MAT clinical trials and guideline recommendations. Important questions to consider in tackling this challenge include: what is an outcome of treatment success, who selects the desired outcome? How should treatment programs be evaluated? What is the best use of limited healthcare and social-services resources in managing OUD? How do personal characteristics affect treatment outcomes? And finally, how might addressing these challenges support incorporation of precision medicine into addiction clinical trials?

Guidelines for the management of OUD make recommendations for treatment based on findings from clinical trials, expert opinions, and literature reviews. Guidelines strongly recommend the use of MAT to reduce opioid use and/or retain patients in treatment.[14] These strong recommendations and the selected outcomes do not consider patient-important goals or the different sociodemographic profiles of patients. Thus, these guidelines are based on the notion that the same treatment is recommended for every patient. Although these recommendations and treatment outcomes are important and reduce harm for many patients with OUD, there remains an important aspect of patient-relevant treatment goals, such as a focus on personalized treatment, that is not being considered in current evidence-based practice.

The overwhelming variation in the selection of MAT outcomes in trials, as well as the lack of inclusion of patient-important outcomes in current guidelines, demand further research to establish a set of treatment outcomes that considers patients' goals and preferences. This will allow future trials to measure the effectiveness of MAT and tailor treatment recommendations based on personalized profiles to improve OUD prognosis and move toward precision medicine in clinical trials of addiction treatment.

Within this context, the objectives of this study were: to identify treatment goals of patients with OUD receiving MAT; and to investigate if there are differences in patient-reported treatment goals by age, sex, gender, ethnicity, employment, treatment duration, and type of treatment received.

Our ultimate purpose is to provide suggestions for the inclusion of patients' goals (patient-important outcomes) in clinical trials as a way of promoting the use of precision medicine in managing OUD.

Methods

This is a mixed-methods study, using qualitative and quantitative data collection and analyses.

Eligibility criteria

Participants were eligible for this study if they were 16 years of age or older, if they fulfilled the DSM-5 criteria for OUD, were receiving MAT for OUD at the time of recruitment, and provided written informed consent.

Data collection

Data were part of a large research program designed to investigate factors associated with OUD. The current study is a primary study that was planned *a priori* within a large program of OUD-related research. Participants were recruited from community-based addiction treatment centers in Canada and interviewed face-to-face at these centers by research personnel. Data collection for this study occurred between May 2018 and August 2019. The data collected included sociodemographic details, current and past substance use, and psychological and physical health symptoms using structured questionnaires. Demographic information included age, gender (social construct), sex (biological construct), ethnicity, marital status, employment, education, and MAT. Urine drug screen results for the past 3 months were collected at the time of study enrollment. Study participants were also asked an open-ended question: "What are your goals of treatment?" Answers related to this question were written by research personnel at the time of the interview in a free text format, with no restrictions on text length or content.

Quantitative statistical methods

The participants' demographic information was summarized using descriptive summary measures, expressed as mean (standard deviation) or median (minimum-maximum) for continuous variables and number (percent) for categorical variables.

Patient-important outcomes were defined on the basis of participants' goals and were compared by six variables: age, sex, gender, ethnicity, employment, and type of current MAT. Age was trichotomized into age groups defined by Statistics Canada[15]: "youth" (16-24 years), "adults" (25-64 years), and "senior" (65+). Sex was coded as male, female, and intersex. Gender was coded as cisgender male, cisgender female, and other (transgender male, transgender female, two-spirit, non-binary, genderfluid, genderqueer, and agender, as reported by participants in response to the question "what gender do you most identify with?"). Ethni-

city was self-reported by participants and was coded as European, East Asian (Chinese, Japanese, Malaysian, Korea, Papua New Guinea, Thailand, Philippines, Indonesia, Vietnam, Cambodia, Laos, Myanmar/Burma, Bhutan, Singapore), Persian and Arab, African, South Asian (Indian, Sri Lanka, Pakistan, Nepal, Bangladesh), Indigenous (Native North American, Native South or Latin American, Australian Aborigine), and other/mixed. Employment was coded as currently working or not working. Type of treatment was defined as methadone, buprenorphine/naloxone (Suboxone), or other.

Qualitative data analysis methods

Nvivo 12 qualitative data analysis software (QSR International) was used to perform a deep-level analysis of the participants' treatment goal response data.[16] The data management and analyses plans are described in steps 1-3.

Step 1: cleaning and importing the data

For qualitative analysis, data were first cleaned in Microsoft Excel to minimize typographical errors present in the free-text responses to the question asking participants about their treatment goals. The data were imported into Nvivo, with the text pertaining to participant goals imported as an open-ended question while attribute-assigning data, such as age and sex, were imported as closed-ended questions. The latter are not codable in Nvivo, and were not analyzed using this software.

Step 2: word frequency query and text search queries

The free-text data were run through a word frequency query to logically arrange the information and determine the most common four-letter words. The words that occurred most frequently were considered to be representative of the participants' perspectives, as it is assumed that important and significant words are used more often.[17] The word count query helped identify initial patterns in the data, and there is evidence that this function improves analytic accuracy when compared to manual qualitative word frequency analyses.[17] In order to avoid decontextualization of the free-text answers, the minimum number of letters permissible in the word frequency query was four. Any word with a frequency weighting of greater than 0.5% was coded as a node. A node is a collection of references found in the free-text data that corresponds to a particular theme or word.[18] Words with a word frequency percentage above 0.5% that were related to a similar theme were grouped in the same node. Words with word frequency percentages above 0.20% were scanned and included in existing nodes with which they shared similarities.

The text search query allows words and their stemmed variants to be identified as references found in the free-text data responses. Text search queries were conducted for words identified in the word frequency queries to identify related-stemmed words. Results from the text search query were then coded into the appropriate nodes. Patterns and coding strategies emerged as a result of grouping similar words into nodes; these nodes were then labelled as themes.

Step 3: matrix coding queries

Matrix coding queries help compare participant responses across and between different demographic categories.[18] Before comparing demographic categories, this query was run between coded references (text that had already been coded at a node) and participant responses, to identify any responses that had not been coded at a node. If a participant had a free-text response but was missing a corresponding coded reference at any of the different nodes, the free-text response was reviewed, and a reference was added to the appropriate node. This process brought forth new words and themes that were eventually combined with existing nodes. Any new words that were identified were also put through a text search query to ensure all the stemmed words were identified and coded into a node. The process of conducting a matrix query to identify any missing references and new/stemmed words was completed iteratively until all participant responses had a coded reference(s).

Another matrix coding query was run between different demographic categories and the nodes to identify the attributes associated with each node. The demographic categories included were age, sex, gender, employment, ethnicity, and type of treatment. The output of a matrix coding query is a chart that displays the number of references coded at each node and the corresponding demographic attributes for each participant.

Quantitative data analyses methods

Univariate exploratory analyses were conducted to identify statistical differences among the groups in their desired treatment outcomes. The themes used in these analyses were derived from the completed Nvivo analysis of the free text goals. A chi-square analysis was completed for each Nvivo identified treatment outcome (stop MAT, avoid illicit drugs, live a "normal" life, manage pain, prevent OUD symptoms, taper off MAT, no changes in treatment) with age, sex, gender, ethnicity, employment, type of treatment, and source of first exposure to opioids (licit vs. illicit). An alpha of 0.05 was used to establish significance. All analyses had a degree of freedom (df) of 1 and created a 2×2 output. The associated phi value (φ) was reported for these analyses. Age had a df of 2. For these analyses, Cramer's V value was reported.

Ethics statement

The study was approved by the Hamilton integrative Research Ethics Board (HiREB #4556). All patients provided written informed consent.

Results

Study participants' characteristics

A total of 2,032 participants were recruited for this study. One participant had treatment goal data missing, which

resulted in a sample of 2,031 participants (1,135 males, 896 females, and one intersex) whose treatment goals were analyzed qualitatively. The mean age was 39.1 years, 71.3% were of European ethnicity, and 66.2% were not currently working. Demographic details are presented in Table 1. Most participants had at least one positive urine drug screen for illicit opioids while on MAT (68.2%), and 44.1% were first exposed to opioids through licit means (i.e., they were prescribed opioids for medical reasons).

Objective 1: Qualitative patient important outcome data results

Seven major themes were identified using Nvivo analysis, in order of frequency:

1. Stop MAT (includes stop methadone or buprenorphine/naloxone treatment completely or to not be dependent on MAT);
2. Avoid illicit drugs (includes wanting to get clean, stay clean, abstinence, or sobriety from a variety of drugs, not just opioids);
3. Live a "normal" life (includes wanting a stable life, normal life, education, job or work, good mental health, or wanting to support their family or stay alive);
4. Manage pain (includes chronic pain or pain management);
5. Prevent OUD symptoms (includes withdrawal and craving);
6. Taper off MAT (includes wanting to taper off, wean off, or reduce dose);
7. No changes in treatment (includes keep everything as is, stabilize the dose, or nothing to add).

Table 1 Demographic characteristics (n=2,031)

Characteristic	
Age (years), mean (SD)	39.1 (10.7)
Sex (female)	44.0
Ethnicity (European)	71.3
Currently employed	33.8
Marital status	
Never married	50.4
Currently married/common-law	28.9
Separated/divorced/widowed	20.7
Level of education	
None/elementary school	28.3
High school	43.1
Trade school	2.5
College/university	25.7
Postgraduate	0.4
Details of opioid use	
Age onset (years), mean (SD)	24.8 (9.25)
Treatment duration (months) (SD)	54.5 (63.1)
Methadone dose (mg/day), mean (SD)	70.4 (41.3)
Buprenorphine/naloxone dose (mg/day), mean (SD)	12.0 (6.73)
Participants with at least one positive opioid urine screen in past 3 months	68.2

Data presented as percentage, unless otherwise specified.
SD = standard deviation.

Participants were free to provide multiple desired treatment outcomes; therefore, the total number of responses exceeds the number of participants. Participants who had goals corresponding to both the stop MAT treatment and the taper off MAT treatment themes were grouped under the stop MAT treatment theme and removed from the taper off MAT treatment theme. These themes were separated as one implies getting off the program entirely (stop MAT), while the other theme implies, they may stay on the program, but at a lower dose. This resulted in the total number of responses decreasing from 3,310 to 3,020.

Figure 1 shows the distribution of the seven different outcomes. The most desired goal was to stop MAT (39% of responses), followed by avoiding illicit drugs (25%), whereas the lowest percentage was for the goal to have no changes in treatment (4% of responses).

Objective 2: Distribution of patient-important outcomes by predefined groups

Patient responses were analyzed in comparison with age, sex, gender, ethnicity, employment and treatment duration, and type. Results are shown below.

Age

There were 203 responses from youths, 2,780 from adult, and 37 from seniors (Figure 2). The most common goal for all three age groups was to stop treatment (youth, 39.9%; adults, 38.6%; seniors, 32.4%). The least common goal for the youth group was pain management (1.5%).

Sex

The most common goal for both female and male participants was to stop treatment (females, 39.6%; males, 37.8%) (Figure 3). To live a normal life was the one response for intersex (100%).

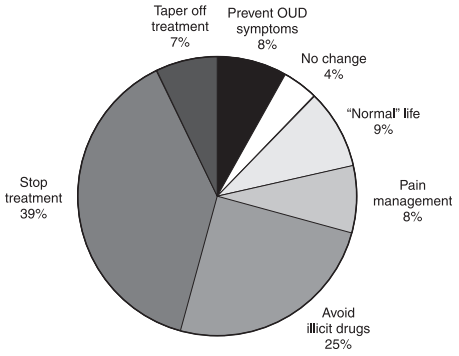

Figure 1 Percentage of responses per patient-important outcome group. OUD = opioid use disorder.

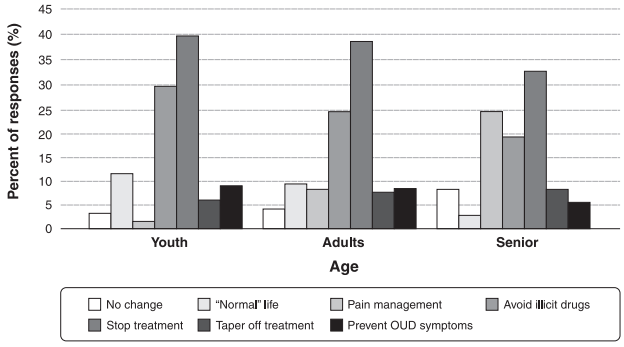

Figure 2 Desired treatment outcomes by age group. OUD = opioid use disorder.

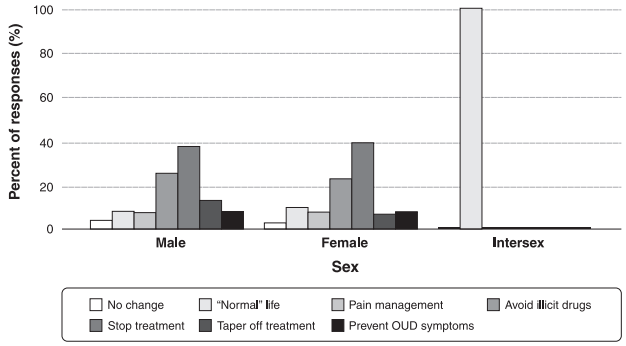

Figure 3 Sex differences in patient-important outcomes. OUD = opioid use disorder.

Gender

There were a total of 1,351 cisgender female responses, 1,646 cisgender male responses, and 23 other responses. The most common goal for both cisgender female and cisgender male participants was to stop treatment (cisgender females, 39.7%; cisgender males, 37.7%). The most frequent goal identified by participants grouped under the ''other'' category was to stop treatment (39.1%).

Ethnicity

The majority of participants were European (n=2,154) followed by ''other'' (n=437) and Indigenous (n=367) (Figure S1, available as online-only supplementary material). The most common goal for all ethnicities was to stop treatment.

Employment

The highest reported outcome by both unemployed and employed participants was to stop treatment (unemployed, 36.6%; employed, 42.7%). (Figure 4). The greatest difference in response by employment was seen in the pain management theme (unemployed, 9.47%; employed, 4.78%).

Type of treatment

There were 2,399 responses corresponding to methadone treatment, 616 responses relating to buprenorphine/naloxone treatment, and four responses for other forms of treatment (Figure 5). The most common goal for both methadone and buprenorphine/naloxone treatment was to stop treatment (methadone, 38.2%; buprenorphine/naloxone, 40.1%).

Length of treatment

The most common goal at all lengths of treatment was to stop treatment (1 year or less, 34.2%; 1-5 years, 40.5%; 5-10 years, 42.6%; 10-15 years, 36%; 15+ years, 41.4%) (Figure S2, available as online-only supplementary material).

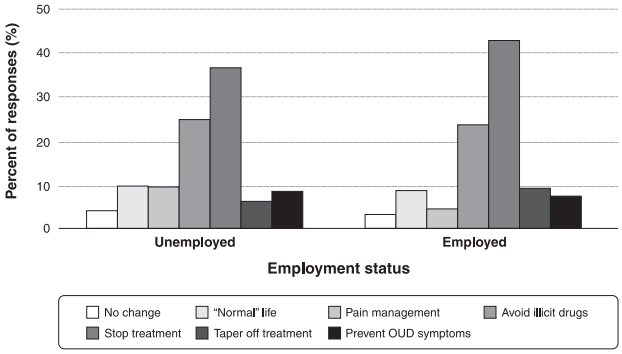

Figure 4 Patient-important outcomes by employment status. OUD = opioid use disorder.

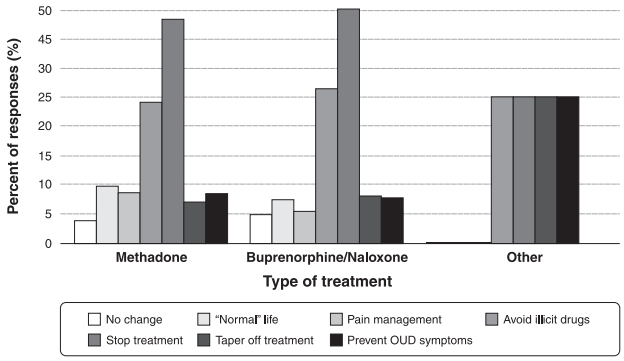

Figure 5 Differences in type of treatment seen in patient-important outcomes. OUD = opioid use disorder.

First exposure to opioids: legitimately prescribed (licit) vs. recreational exposure (illicit)

The most common goal, regardless of the source of first exposure to opioids, was to stop treatment (licit, 37.9%; illicit, 39.1%). Participants who were first exposed to opioids through licit means had more responses listing pain management as their goal compared to those who were first exposed to opioids through illicit means (licit, 12.4%; illicit, 4.3%) (Figure S3, available as online-only supplementary material).

Correlation analyses

Univariate exploratory analyses to identify statistical differences among the groups in the outcomes they identified as important showed that all groups had stop MAT and avoid illicit drugs as the leading treatment goals. However, some differences among groups were also observed. Specifically, the following associations were found to be significant: pain management and age ($p \leqslant 0.001$), stop MAT and sex ($p = 0.047$), stop MAT and ethnicity ($p = 0.001$), taper off MAT and ethnicity ($p = 0.007$), pain management and employment ($p \leqslant 0.001$), stop MAT and employment ($p = 0.013$), taper off MAT and employment ($p = 0.008$), live a "normal" life and type of treatment ($p = 0.030$), pain management and type of treatment ($p = 0.005$), pain management and source of first exposure to opioids ($p \leqslant 0.001$), and live a "normal" life and source of first exposure to opioids ($p = 0.021$) (for additional details, see Table S1, available as online-only supplementary material).

Discussion

In this large study of 2,031 patients with OUD, we identified that 39% of patients wanted to stop MAT and 25% wanted to stop all drugs, not just opioids. Yet, current MAT programs are focused on treatment retention and stopping or reducing illicit opioid use. This suggests that 64% of patients in this cohort are not meeting treatment goals for traditional MAT programs. This may be an important consideration when assessing MAT effectiveness measures, as well as considering individual patient

preferences based on sociodemographic factors and personalized medicine.

Patients of all ages wanted to stop MAT and avoid illicit drugs. While older adults had pain management as their second most frequent goal, the majority of patients – regardless of their sociodemographic variables – wanted to stop or taper off MAT.

Current OUD management guidelines recommend the use of MAT to manage OUD; however, these guidelines do not include patient-related goals and do not specify the length of time for which MAT should be considered.[19] In this study, patients' most frequently reported goal of OUD treatment was to stop MAT (39%). However, in the absence of recommendations based on evidence from clinical trials on the duration of MAT and the desire of patients to stop MAT, treatment adherence and the prognosis of OUD are unlikely to be favorable.

Guidelines also strongly recommended that withdrawal management only without transition to a MAT should not be used in managing OUD,[19] as this is suggested to be associated with relapse, overdose, and risk of unsafe substance use compared to no treatment at all, while patient-important goals identified in our study stated that only 8% of responses were related to OUD symptoms management. Most participants in this study had at least one positive urine drug screen for opioid while on MAT (68.2%) during the preceding 3 months, despite being on MAT for an average of 4.5 years. The risk of relapse and overdose are real challenges in OUD, but many trials use short-term, narrowly focused outcome measures, such as urine drug screens, to determine treatment effectiveness. If efficacy of MAT is based on opioid-negative urine drug screens, then MAT is ineffective in 68% of patients in this study. The use of urine drug screens to measure the effectiveness of MAT in clinical trials fails to capture important outcomes associated with the chronicity of OUD, which limits the scope of treatment.

A frequently mentioned treatment goal (25%) was to avoid all illicit drugs, not just opioids. We previously reported that comorbid substance use in this population is common, with 42% having a comorbid substance use disorder.[20] Despite this, clinical trials of MAT for OUD exclude patients with co-substance use.[14] This exclusion is leaving a significant proportion of patients with OUD with unmet needs and unmeasured treatment outcomes.

Another factor we explored that may influence patients' treatment goals is the type of MAT prescribed. In this study, we reported patient-important goals by the type of MAT they are receiving. Patients' desire to be off treatment may be explained by the stigma attached to methadone.[21] However, the results of this study showed that patients on other MAT also wanted to be off treatment. Therefore, stigma alone may not explain why the most frequent patient-important outcome is to stop treatment.

Our findings also suggest that patients who were first exposed to opioids through licit vs. illicit means may have different goals to achieve out of MAT. We found that those who were exposed to opioids through licit means were significantly more likely to have pain management as a goal, perhaps because their first exposure to opioids was probably for pain management. In addition, MAT, including methadone, is used for pain management; therefore, it is expected that patients with chronic pain conditions may wish to continue using MAT to relieve pain. Additionally, those that were introduced to opioids through illicit means were likely to list "live a normal life" as a goal. Previous research that has looked into the sources of introduction to opioids has found differences in substance use and demographic characteristics in those introduced to opioids by prescription vs. other means.[22,23] This suggests that participants who were introduced to opioids through illicit means may have vulnerability factors for substance use disorder, such as novelty-seeking and risk-taking behavior, compared to people with pain who were prescribed opioids to manage it and would be more likely to have treatment goals pertaining to stability/living a normal life.[23]

Although the reasons why patients wanted to be off MAT cannot be explained in this study, a treatment plan that includes patient-important goals and evidence-based, informed precision medicine is needed to improve treatment outcomes in OUD. While it may seem challenging to achieve a consensus between patients and treatment programs on what constitutes a good treatment outcome, previous studies showed that it is possible to obtain such agreement.[24] Nevertheless, there is a lack of patient-important and patient-identified outcome sets in clinical research and practice.[25] No previous work on patient-important outcomes in OUD to inform clinical trials has been completed, despite the ongoing opioid crisis.

Comparisons of treatment plans and goals vary greatly across clinical care settings, patients' expectations, and services delivered.[26] For example, the duration of treatment may have an impact on patient engagement in services whose patients perceive these services as more helpful than short-term treatment.[27] Furthermore, patients' suggestions on their treatment goals often differ from their clinicians' opinions. One study found that patients with addiction saw physical health as a goal more often than their clinicians did.[28] Thus, patient and clinician communication about the goals and expectations of treatment may be beneficial to translate patients' opinions and choices of what constitutes a relevant outcome for them into the course of treatment. Communication may also help patients' positive opinions on long-term goals become a part of their service plan, potentially leading to achievable goals. This concept was summarized by stating that limiting discrepancies between patients' and clinicians' goals of addiction service might lead to convergence, which is likely necessary for positive treatment goals and better care of patients with addiction.[28]

Discrepancies are often related to the concept that existing treatments and clinical trials in OUD have used convenience outcomes that are objectively measurable (such as urine drug screens) without consideration for patient-important outcomes, sociodemographic differences, and patients' goals or group differences. Additionally, guidelines also indicate that there is little consistent evidence to evaluate the effectiveness of OUD treatment.[29] Reviews evaluating OUD treatment effectiveness have found great variability in the selected goals between studies,[30-32] leading to difficulty in establishing a

real treatment effect. Each study measures a different set of goals that define success in arbitrary or accessible terms, limiting cross-study comparisons. This is an important limitation in addiction research that must be overcome if a consensus on what works for OUD management and how to assign a treatment goal is to be achieved.

Despite being the largest study to date and including unrestricted responses from patients receiving active treatment, some limitations of our work should be considered. The study cohort may not be representative of all patients with OUD, as there is an expected self-selection bias in voluntary participation in research compared to those who do not participate. The study findings may not be generalizable to the entire Canadian population, as our study sample was recruited from community clinics in the province of Ontario. It is important to note that our mean age and sex distribution resembles data collected by Public Health Ontario in 2018, where age groups and sex distribution were similar to those of the study participants.[33]

Other limitations to consider are other variables that may play a role in determining patient-oriented goals and which are not measured in this study, such as personality type. Previous research suggests that there may be a relationship between specific traits and chronic substance use.[34] There is also the possibility that patients who no longer attend treatment programs and achieved sustainable recovery may have a different outlook on treatment goals compared to patients in the active phase of substance use disorder. Despite these limitations, the responses provided by 2,031 patients in active treatment are important findings that at least will apply to a similar population in the active phase of the disorder.

In conclusion, in this mixed-methods study, we analyzed answers to an open-ended question – letting participants express their opinions without any constraints on the type, length, or direction of the answer – on what participants wanted out of treatment for OUD. We identified patient-important outcomes for OUD that may inform future trials of MAT for OUD. Despite implementation of many different measures, opioid use has not seen adequate control. Therefore, identifying effective ways to manage OUD remains both urgent and timely. Treatment guidelines and programs rely on well-conducted clinical trials; when these begin to include patient-important outcomes, their results may lead to a paradigm shift in what treatments outcomes should be considered, what medications are truly effective, for what goal these results apply and to what patients, and how treatment programs should be evaluated when it comes to resource allocations and policy making. We need a shift in how these treatments are tested for effectiveness to incorporate patient-important outcomes and provide a precision medicine approach to managing the OUD epidemic.

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Disclosure

The authors report no conflicts of interest.

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