TREATMENT OUTCOMES IN PATIENTS WITH OPIOID USE DISORDER

PREDICTORS OF TREATMENT OUTCOMES FOR PATIENTS WITH OPIOID USE DISORDER

By

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LAY ABSTRACT

Many people die from unintentional opioid overdose in North America. Treating patients with opioid addiction is very complicated, and we do not know who benefits most from these treatments. This is because people with opioid addiction often have complex health problems including the use of other drugs, such as cannabis, or medical and psychiatric problems that affect their treatment outcomes. The influence of these factors on patients' recovery has not been well studied. We therefore conducted three studies aimed to compare the effects of the common treatments for opioid addiction, and explore the role of cannabis use. These studies were done in a large group of patients with opioid addiction. We identified valuable information regarding potential factors that make someone at higher risk of not doing well in treatment, which are important to keep in mind as these individuals may benefit from more intensive treatment programs in addition to medications.

ABSTRACT

Background: Opioid-related mortality rates have steeply risen over the past decade, simultaneous to the increased prevalence of more potent synthetic opioids such as fentanyl in the street drug supply. Many patients with opioid use disorder (OUD) also use cannabis, which has been suggested to reduce opioid use in this population. The purpose of this thesis is to gain a deeper understanding of treatment outcomes for patients with OUD since the onset of the fentanyl era and subsequent legalization of cannabis in Canada, and to evaluate the potential association of cannabis use and treatment outcomes.

Methods: We used data from a large sample of patients receiving treatment (methadone or buprenorphine) for OUD from fifty-four clinical sites across Ontario, Canada between 2018 and 2023. We conducted three studies aimed at evaluating various aspects of treatment outcomes for patients with OUD. We specifically focused on the potential implications of cannabis use in these patients.

Results: The main conclusions of this work include: 1) although patients on methadone are more likely to stay in treatment than those on buprenorphine, the treatment type did not affect continued non-prescribed opioid use in patients who completed 12-months of follow-up; 2) approximately half of the patients with OUD used cannabis which did not improve treatment outcomes; 3) cannabis use was associated with a heightened propensity for suicidal ideation, irrespective of the frequency of use.

Conclusion: We identified several trends associated with response to treatment amongst

patients using opioids in the current fentanyl era, and since the legalization of cannabis in Canada. The findings of this thesis are highly generalizable to the typical patient with OUD, and help to identify potentially higher-risk individuals who may benefit from more intensive treatment programs. Future studies are needed to gain a deeper understanding of treatment outcomes for patients with OUD.

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LIST OF ABBREVIATIONS

OAT	Opioid agonist therapy
OUD	Opioid use disorder
MMT	Methadone maintenance therapy
Bup/nal	Buprenorphine/naloxone
POST	Pharmacogenetics of Opioid Substitution Treatment Response
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
SD	Standard deviation
PSM	Propensity score matched
IVDU	Intravenous drug use
MAP	Maudsley Addiction Profile
SMD	Standardized mean difference
OR	Odds ratio
CI	Confidence interval
CIHR	Canadian Institute for Health Research
VIF	Variance inflated factor
IQR	Interquartile range
HR	Hazard ratio
THC	Delta-9-tetrahydrocannabinol

DECLARATION OF ACADEMIC ACHIEVEMENT

I am primary author of the three manuscripts included in this thesis. I took a lead role generating the research question, developing a research plan, conducting statistical analyses, interpreting results, and drafting each manuscript. I was responsible for gathering input from all co-authors and incorporating edits and suggestions. Detailed contributions of each author are included at the end of each study.

CHAPTER 1: THESIS INTRODUCTION

Morbidity and mortality due to the opioid crisis have reached alarming rates. Over the past decade, rates of opioid overdose deaths have risen exponentially, having nearly quadrupled between 2010 and 2021 in the United States.[1] We have seen a similar rise of opioid-related deaths in Canada during this time period.[2,3] This has played a large role in the reversal of life expectancy trends since 2014, which had otherwise been upward trending since 1959.[4] A major contributor to this has been the increasing availability of synthetic opioids, namely fentanyl and its analogues, contaminating the street drug supply. For instance, Canadian national data revealed that over 80% of accidental opioid overdose deaths in 2023 involved fentanyl, which is 44% higher than in 2016.[5] The rates of opioid-related emergency department visits and hospitalizations that have involved fentanyl and its analogues have also risen by 100% and 120% between 2018 and 2023, respectively.[5]

Opioid agonist therapy (OAT) is the mainstay of treatment for patients with opioid use disorder (OUD). Specifically, methadone, and more recently, buprenorphine, are first-line agents recommended for the treatment of OUD in the majority of treatment guidelines.[6,7] Methadone is a full-opioid agonist which acts at the mu-opioid receptor to mimic the effects of other opioids, helping to mitigate cravings and symptoms of opioid withdrawal. Buprenorphine, on the other hand, is a partial opioid agonist, such that it only stimulates the mu-opioid receptor to a certain extent before plateauing, thus also mitigating the risk of overdose. Given the superior safety profile, the latter has increasingly been recommended and preferred in the treatment of OUD.[8]

However, many have called into question whether existing evidence and guidelines continue to hold true given the much more potent drug supply. Newer guidelines have been drafted to specifically address patients who use fentanyl.[9] Given the higher potency of methadone, it has been questioned whether methadone may be more effective than buprenorphine in the current fentanyl era. However, these recommendations were largely based on theoretical extrapolations and clinical experience.[9]

In addition to this, another major limitation of the current treatment guidelines is the fact that they are not truly representative of the patients we treat day to day, with multiple comorbidities and co-substance use. Our group has previously published about the limited external validity of current treatment guidelines.[10] This is largely because the trials cited impose very stringent eligibility criteria, such as the exclusion of patients with concurrent substance use or psychiatric comorbidity.[10] This is problematic given the high prevalence of polysubstance use as well as comorbid psychiatric and medical conditions within this population, rendering approximately 70% of patients in our observational clinical sample ineligible for inclusion.[10]

Another factor that may influence treatment outcomes for OUD is the increasing prevalence of cannabis use in Canada, and the federal legalization of recreational cannabis use in 2018.[11] There is emerging research that suggests cannabis may be an effective adjunct in the treatment of OUD, though results are still mixed.[12,13] Another major concern is the association between cannabis use and suicidal behavior in the general population, and the potential for this to negatively impact outcomes for patients with OUD.[14]

The limited applicability of current evidence and the worsening opioid epidemic, together, were the impetus of this thesis work. Using various statistical methods, we aimed to assess predictors of treatment outcomes in a pragmatic sample of patients with OUD. Through a series of three studies, we aimed to 1) compare the effectiveness of methadone to buprenorphine in the treatment of OUD using data since the fentanyl era; 2) identify the association between cannabis use and opioid relapse in patients with OUD; and 3) identify the association between cannabis use and suicidal ideation in patients with OUD. All studies included in this thesis used data collected for a prospective cohort study titled Pharmacogenetics of Opioid Substitution Treatment Response (POST). This is a prospective cohort study aimed at evaluating the association between biopsychosocial factors and treatment outcomes for patients with OUD. Data were collected from fifty-four sites across Ontario, Canada, between 2018 and 2023. All patients who were 16 years of age or older and receiving OAT for OUD were eligible for inclusion. Any additional eligibility criteria imposed for each analysis were outlined in the individual studies (Chapters 2-4).

The first study included in this thesis, Chapter 2, aimed to compare the effectiveness of methadone to buprenorphine in patients with OUD. We looked at continued non-prescribed opioid use during treatment as the primary outcome, as well as retention in treatment as a secondary outcome. We also assessed whether the effectiveness of these treatments were different amongst high risk opioid users, such as those who report intravenous drug use. This study is currently under review in Addiction.[15] The second study, Chapter 3, aimed to evaluate

the association between cannabis use and opioid relapse, as measured by urine drug screens positive for non-prescribed opioids. We also aimed to investigate other predictors of relapse for patients in treatment for OUD. This study was published in Frontiers in Psychiatry.[16] The final study of this thesis, Chapter 4, aimed to evaluate the association between cannabis use and suicidal ideation in patients with OUD. This study was published in the Journal of Addiction Medicine.[17] In both of the latter studies, we compared cannabis users versus non users, and then conducted secondary analyses comparing cannabis users by frequency of cannabis use (daily or non-daily users). In all studies, we adjust our statistical models by patients' sex. We would like to note that we use the terms 'sex', 'male', 'female', 'man' and 'woman' to refer to one's biological sex assigned at birth. The variation in terminology used in the various manuscripts is due to changes in accepted terminology over time.

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CHAPTER 2: Effectiveness of methadone versus buprenorphine in the treatment of opioid use disorder: A propensity score matched analysis

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ABSTRACT

Background and Aims: Opioid use disorder (OUD) remains a public health crisis in North America. Methadone maintenance therapy (MMT) and buprenorphine-naloxone (bup/nal) are considered first line treatments for OUD, but little is known about their comparative effectiveness on continued opioid use in real clinical settings. The purpose of our study is to compare the effectiveness of bup/nal and MMT in the treatment of OUD.

Design: Prospective cohort study.

Setting: Fifty-four outpatient substance use disorder clinics across Ontario, Canada

Participants: A total of 668 participants with OUD aged 16 years or older and followed for one year.

Intervention and Comparator: MMT versus bup/nal.

Measurements: Ongoing non-prescribed opioid use, as measured by routine urine drug screens.

Findings: Eight percent of patients on bup/nal were considered non-responders, compared to 11.9% of patients on MMT. We did not find a statistically significant association between treatment type and treatment response. However, we did find that patients on MMT were more likely to stay in treatment for 12 months (OR=1.79, 95% CI: 1.45, 2.22, p<0.001). We also found that, amongst patients without a history of intravenous drug use, those on MMT were more likely to continue using non-prescribed opioids, compared to those on bup/nal (OR=1.72, 95% CI: 1.07, 2.77, p=0.023).

Conclusion: Although we found that patients on MMT are more likely to stay in treatment, it is unclear whether this correlates with improvements in patient-centered outcomes. Amongst a

cohort of patients with OUD, we find that there is no statistically significant difference in ongoing non-prescribed opioid use between patients receiving MMT compared to bup/nal. Future studies should aim to further compare treatment effectiveness using patient-centered outcomes and pragmatic trial designs. The emphasis should be less on retention in treatment, and more focused on substance use patterns, high risk behaviors, and quality of life of measures.

INTRODUCTION

The prevalence of opioid use disorder (OUD) as well as its detrimental impact on individuals and society has reached an all-time-high. In the United States, the opioid crisis has been declared a Public Health Emergency since 2017, and rates of morbidity and mortality have continued to rise since.[1,2] This is largely due to the increasing prevalence of fentanyl and similar very potent synthetic opioids in the street supply, that substance users are sometimes inadvertently exposed to, leading to unintentional overdose and death.[3]

Methadone maintenance therapy (MMT) has traditionally been the first-line treatment for OUD. Methadone is a synthetic opioid with a long half-life which acts as a full agonist on the mu-opioid receptors to mitigate cravings and withdrawal symptoms, while minimizing the 'high' associated with short-acting opioids.[4] In 2002, buprenorphine-naloxone (bup/nal) was approved by the FDA for the treatment of OUD and, in more recent guidelines, has been considered to be first line treatment for OUD along with MMT.[5,6] Buprenorphine is a partial opioid agonist with very high affinity for the mu-opioid receptor.[4] This allows buprenorphine to displace other opioids, while also mitigating cravings and withdrawals through its agonistic properties at the receptor. The unique property of being a partial-agonist, however, makes it such that its effects plateau at higher levels – mitigating the risk of overdose and sedation that may occur with high doses of methadone.[4] This, amongst other properties, makes buprenorphine a popular treatment recommendation, and potentially safer treatment option for OUD.

The data comparing the effectiveness of MMT to bup/nal for OUD are mixed, however. While many studies have identified that MMT is superior for retention in treatment, a recent systematic review found no benefit between the two treatments on rates of concurrent substance use, among other outcomes.[7] A closer look at the individual studies, however, identifies many limitations that restrict the external validity of the findings.[7–9] Many of these trials have very stringent eligibility criteria, excluding patients with concurrent substance use or comorbidities, for instance, while other trials implement stringent fixed-dose protocols which are not representative of real clinical settings and patients' needs.[7–9] The varying protocols used may partly explain the mixed outcomes. Moreover, the majority of these studies have reported on retention in treatment as a primary outcome, though prior research suggested that this outcome is of limited importance to the patients seeking treatment.[10] These studies are also outdated as they had been conducted prior to the fentanyl era, and there is increasing concern that previously recommended treatment regimens and dosing schedules may no longer be as effective.[11] The purpose of our study is to assess the effectiveness of bup/nal compared to MMT in the treatment of patients with OUD using current data, as measured by continued non-prescribed opioid use.

METHODS

Study Design

We used data collected from a longitudinal study entitled Pharmacogenetics of Opioid Substitution Treatment Response (POST). This is a prospective cohort study aimed at assessing the association between biopsychosocial factors and opioid agonist therapy (OAT) outcomes.

Data for the study were collected from fifty-four clinical sites across Ontario, Canada, between May 2018 and January 2023. The protocol for this study has previously been described.[10] The study has been approved by the Hamilton Integrated Research Ethics Board (#4556) and funded by the Canadian Institute for Health Research (CIHR). The current study is reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.[12]

To be included in the present study, participants had to be at least 16 years of age, have provided written informed consent, and be receiving either MMT or bup/nal therapy for OUD. We defined OUD as per the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5).[13] All participants underwent a semi-structured baseline interview with trained research staff whereby demographic information, as well as past medical and substance use histories were obtained. As part of the usual treatment for OUD, participants underwent regular urine toxicology screens, typically on a weekly to bi-weekly basis. The FaStep Assay (Trimedic Supply Network Ltd, Concord, Ontario, Canada) was used to detect morphine, oxycodone, fentanyl, methadone metabolite, and buprenorphine, as well as other non-opioid substances. Participants were followed up for 12 months.

Statistical Methods

All analyses were conducted using STATA Version 13.0.[14] Descriptive statistics were used to summarize baseline participant demographics. We used means and standard deviations (SD) to

express continuous variables, as well as counts and percentages to summarize categorical variables.

Primary Analysis: Propensity Score Matching

We employed a propensity score matched (PSM) analysis to compare treatment outcomes amongst patients receiving MMT compared to bup/nal. Considering the observational nature of the study, we used a PSM analysis to minimize confounding and account for any potential systemic differences in baseline characteristics between treatment arms. We used ongoing non-prescribed opioid use as an indicator of treatment outcome, as one of the OAT objectives is to reduce non-prescribed opioid use. We considered participants with >50% UDS in the past 12 months positive for non-prescribed opioids to be "non-responders". Patients receiving MMT were matched in a 1:1 ratio with patients receiving bup/nal using a PSM analysis. The propensity score was generated using the following clinically important factors: age (years), sex, employment status, marital status, history of intravenous drug use in the past 30 days (IVDU; yes/no), concurrent non-prescribed benzodiazepine use (yes/no), cannabis use (yes/no), Maudsley Addiction Profile (MAP) score for psychological stress, and history of overdose (yes/no). We applied the nearest neighbor matching algorithm with a caliper width of 0.25 of the logit of the propensity score, as is the commonly recommended practice.[15] Balance after PSM was assessed by calculating the standardized mean difference (SMD), and we considered balance to have been achieved when SMD is less than 0.1.[16] We estimated and reported the average treatment effect on the treated (ATT).

Secondary Analysis: Multivariable Logistic Regression

We conducted subgroup analyses to identify whether the type of OAT was associated with ongoing non-prescribed opioid use amongst patients with and without a history of IVDU who remained in treatment for one year. Two identical multivariable logistic regression models were employed among patients with and without a history of IVDU, while adjusting the model for the same factors that were used in the PSM, namely: age (years), sex, employment status, marital status, history of opioid overdose (yes/no), concurrent non-prescribed benzodiazepine use (yes/no), cannabis use (yes/no), and MAP score for psychological stress. Another logistic regression was conducted using the entire dataset to assess whether treatment type for OUD is associated with retention in treatment. Once again, treatment retention at 12 months was regressed against treatment type (MMT vs bup/nal) while adjusting for the same clinically important variables.

RESULTS

Baseline Participant Demographics

This study include data from 2601 participants, of whom 2068 were receiving MMT and 533 were receiving bup/nal for OUD. The mean age of participants was 39.4 years (SD: 10.9), and 45% were female. The mean dose of MMT and bup/nal was 71.6mg (SD: 41.7) and 12.1mg (SD: 6.8) per day, respectively. Seventy-one percent (n=1850) remained in the study for the 12 months of follow-up. Over the one-year period, 13.1% of participants were considered non-responders. Please see Tables 1 and 2 for details regarding baseline participant demographics before and after the PSM.

Primary PSM Analysis: Ongoing Non-Prescribed Opioid Use Amongst Patients Receiving MMT Compared to Bup/nal.

Our PSM analysis included data from 668 participants (Figure 1). Eight percent (8.1%) of patients on bup/nal were considered non-responders, compared to 13.5% of patients on methadone. We did not find a statistically significant association between treatment type and treatment response in our propensity score matched analysis, adjusting for age, sex, employment status, marital status, IVDU history, opioid overdose history, non-prescribed benzodiazepine use, cannabis use, and MAP score for psychological stress (p=0.055).

Secondary Analysis: Association Between Treatment Type and Retention in Treatment

Data from 2601 participants were included in this analysis. We find that patients who are on methadone are 1.8 times more likely to stay in treatment at 12 months of follow-up, compared to patients on bup/nal (Odds ratio [OR]=1.79, 95% confidence interval [CI]: 1.45, 2.22, p<0.001). Furthermore, patients with a history of IVDU or opioid overdose were 1.9 times (OR=1.89, 95% CI: 1.47, 2.39, p<0.001) and 1.5 times (OR=1.47, 95% CI: 1.22, 1.79, p<0.001) more likely to drop out of treatment prior to completion of the one-year follow-up, respectively. Patients who are currently employed are also 1.4 times more likely to stay in treatment, compared to those who are unemployed (OR=1.36, 95% CI: 1.11, 1.67, p=0.003). We also find that older age is a predictor of treatment retention (OR=1.03, 95% CI: 1.02, 1.04, p<0.001). Lastly, we find that women are more likely to stay in treatment compared to men (OR=1.36, 95% CI: 1.13, 1.63,

p=0.001). We found no association between retention in treatment and cannabis use, marital status, non-prescribed benzodiazepine use or MAP psychological symptoms score (Table 3).

Secondary Analysis: Association Between Treatment Type and Continued Non-Prescribed Opioid Use Stratified by History of IVDU

Among patients with a history of IVDU, we find that there is no difference in treatment outcomes by treatment type, after adjusting for clinically important variables (Table 4). Amongst those without a history of IVDU (n=1,619), however, we find that patients who are on methadone are 1.7 times more likely to be non-responders, compared to those on bup/nal (OR=1.72, 95% CI: 1.07, 2.77, p=0.023). Moreover, amongst those without a history of IVDU, we found that concurrent non-prescribed benzodiazepine use was associated with poor treatment response (OR=2.07, 95% CI: 1.19, 3.59, p=0.010).

DISCUSSION

The substance use crisis continues to dominate headlines as opioid overdose remains the leading cause of accidental death in the US.[2,17] OATs are the mainstay of treatment given their established superiority as a harm reduction approach. Novel OATs have been introduced to the market over the years, though little data exist to guide selection of the optimal OAT based on patient characteristics and circumstances. While many options exist, including slow release oral morphine and injectable diacetylmorphine, MMT and buprenorphine remain first line recommendations by most organizational guidelines.[5,6] Nonetheless, current evidence comparing MMT to bup/nal is mixed, and little is known about which patients will fare better

on MMT compared to bup/nal.[7,8] This is largely due limited applicability of the current evidence, such as due to the experimental trial designs, restrictive eligibility criteria, and fixed-dosed schedule commonly employed by trials.[7–9]

Amongst a pragmatic sample of patients with OUD, the present study identified that there is no statistically significant association between OAT treatment type and response to treatment, as measured by ongoing non-prescribed opioid use, amongst patients receiving MMT or bup/nal over a 12-month period. However, we did find that patients who were on MMT were almost twice as likely to remain in treatment at the 12 months follow-up. We also found that amongst lower risk substance users, particularly those without a history of IVDU, MMT was associated with improved treatment response compared to bup/nal. This association was not seen amongst patients with a history of IVDU.

A Cochrane review published in 2014 showed that there was no difference between MMT and bup/nal when looking at non-prescribed substance use.[8] They did, however, find that MMT was associated with better treatment retention compared to bup/nal.[8] This is consistent with our findings. However, there is an emerging trend to shift away from treatment retention as an outcome for OUD treatments, and rather focus on patient-centered measures.[18] A prior study of 2,301 patients on OAT found that the majority of patients prioritized coming off OAT completely as the primary treatment goal, which is in direct contrast to the primary outcome of treatment retention used in most studies.[10] While OAT has several reported benefits for OUD patients, little is known about the comparative effectiveness of these treatments on such

outcomes in real clinical settings. A recent systematic review aimed to evaluate the comparative effectiveness on patient centered outcomes including sleep quality, global functioning, and quality of life, but found that few to no studies examined these outcomes, making it difficult to draw any conclusions.[19] A more recent randomized controlled trial (RCT) analyzing data from 272 participants found that patients on flexible dose bup/nal reported less cravings intensity and frequency compared to patients on MMT over 22 weeks of follow-up.[20] Interestingly, they also found improved treatment retention among the MMT patients despite having more cravings.[20]

Given that MMT is a more potent opioid agonist without the ceiling effect associated with bup/nal, patients are more likely to experience a 'high' with methadone which they do not get with bup/nal. This may partly explain why MMT is associated with better treatment retention, without necessarily leading to improved treatment outcomes. More recent data are supporting rapid induction onto bup/nal and has been shown to lead to improved treatment retention. Further data stratifying patients by induction method would be helpful to add to the discussion. Additionally, it is difficult to determine whether this benefit is solely due to the OAT or skewed due to co-intervention bias secondary to the stringent treatment programs and dispensing practices surrounding MMT use. Nonetheless, while methadone may have clear superiority over bup/nal when it comes to retention in treatment, further studies are required to evaluate more patient-centered outcomes.[8,19,20]

We used ongoing non-prescribed use as an outcome, rather than focusing on relapse, as the purpose of OAT is harm reduction and patients do not necessarily consider complete abstinence to be goal of intervention.[21,22] Interestingly, we found that there was no difference between the two treatments, similar to prior studies. Given the higher potency of MMT at the mu-opioid receptor, it is sometimes preferred for patients with severe OUD, such as those with a history of IVDU, overdose, or fentanyl use.[11,23] However, while this is a general recommendation, it is not founded on evidence. As such, we conducted a secondary analysis evaluating predictors of treatment response among patients with and without a history of IVDU, as a surrogate for severe OUD. We found that there was no difference in treatment response by treatment type amongst patients with a history of IVDU, but that amongst those without a history of IVDU, being on MMT was associated with a higher likelihood of ongoing non-prescribed opioid use. This contrasts with what is often recommended, as our study found that there was no difference among high-risk users, and bup/nal may be superior among low-risk users. This may be due to the fact that patients with an IVDU history are at higher risk for continued opioid use at baseline, and therefore we are unable to detect a signal when comparing MMT to bup/nal. Given that the number of participants with a history of IVDU is also smaller, we may not be powered to detect this difference. That said, when we conducted the same analysis using overdose history as a surrogate for being a high-risk user, we once again found no difference in treatment response amongst those with a history of overdose (n=161), but that patients on bup/nal had superior treatment outcomes amongst those without a history of overdose (n=708, OR=0.55, 95% CI: 0.32, 0.94, p=0.028), as measured by ongoing non-

prescribed opioid use. Further studies addressing this in a larger sample to allow for adequate subgroups, while controlling for co-interventions would be valuable.

Strengths, Limitations, and Future Direction

A major strength of the study is that it included prospectively collected data that represents the current toxic drug supply. This is in contrast to the majority of literature on OUD, which was conducted prior to the fentanyl crisis. This is important as there is increasing concern that prior dosing guidelines and treatment regimens may no longer be as effective in treating patients who use fentanyl, given its exponentially stronger potency.[11] Our study is also strengthened by the large sample of patients and long follow-up period. We employed an objective primary outcome of ongoing non-prescribed opioid consumption, measured by urine drug screens, rather than relying self-report. Furthermore, we imposed very minimal eligibility criteria, rendering the sample representative of the true patient population. A major strength of PSM is that it allows us to balance known confounders between the two treatment groups. While there may be other unmeasured or unknown confounders that cannot be accounted for, one would need to conduct an RCT to account for these confounders. If this RCT would need to be done, it should follow a pragmatic trial design with flexible dosing schedules, large sample size, adequate follow-up, and realistic eligibility criteria.

Future studies should aim to further compare the effectiveness between MMT and bup/nal using patient-centered outcomes and pragmatic trial designs. The emphasis should be

less on retention in treatment, and more focused on substance use patterns, high risk behaviors (e.g., IVDU), quality of life of measures, and overdose risk.

CONCLUSION

Amongst a cohort of patients receiving OAT for OUD, we find that there is no statistically significant difference in ongoing non-prescribed opioid use between patients receiving MMT compared to bup/nal. Although we did find that patients on MMT are more likely to stay in treatment, it is unclear whether this correlates with improvements in patient centered outcomes. We also find no association between treatment type and high-risk opioid consumption patterns amongst patients with a history of IVDU or opioid overdose, which does not support the recommendation to use MMT for patients with severe OUD, although severity of OUD can be broadly interpreted. This study adds to the current data on the comparative effectiveness of MMT and bup/nal, identifying no differences in ongoing opioid consumption even within a high-risk population. Further research is required to specifically investigate other important treatment outcomes including patient-centered outcomes, such as substance use patterns and quality of life measures, within a realistic sample of patients to help generate treatment recommendations that are precise, and person centred.

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Author Contributions: LN and ZS conceived the research question and protocol. LN, TR, LT and ZS developed study design and statistical plan. LN conducted the statistical analyses and wrote the initial draft of the manuscript. All authors contributed equally to the writing and revision of the manuscript. All authors approved the final version of the manuscript.

TABLES AND FIGURES

Table 1: Baseline Demographics Table of All Participants (n=2601)

	Methadone (n=2068)	Buprenorphine/ Naloxone (n=533)
	Mean (SD)	
Age (years)	39.6 (10.8)	38.9 (11.1)
Average dose (mg/day)	71.6 (41.7)	12.1 (6.8)
Average psych sx score	12.6 (9.3)	12.0 (9.1)
	Count (%)	
Female sex	924 (44.7)	245 (46.0)
Currently working	626 (30.3)	213 (40.0)
Married	603 (29.2)	161 (30.2)
History of IVDU	346 (16.7)	61 (11.4)
History of opioid overdose	708 (34.2)	161 (30.2)
Non-responders*	770 (37.2)	226 (42.4)
Completed 12 months follow-up	1512 (73.1)	334 (62.7)
Cannabis user	1072 (51.8)	350 (65.7)

**- Defined as having >50% of UDS positive for opioids in the 12 months period*

Table 2: Baseline Demographics Table of Participants included in PSM Analysis (n=668)

	Methadone (n=334)	**Bup/Nal(n=334)**	**SMD**
	Mean (SD)		
Age (years)	41.7 (10.7)	40.6 (11.2)	0.007
Average psych sx score	10.7 (8.8)	10.5 (8.6)	0.003
	Count (%)		**SMD**
Female sex	924 (44.7)	245 (46.0)	0.023
Currently working	626 (30.3)	213 (40.0)	0.028
Married	603 (29.2)	161 (30.2)	0.062
History of IVDU	346 (16.7)	61 (11.4)	0.011
History of opioid overdose	708 (34.2)	161 (30.2)	0.048
Cannabis user	1072 (51.8)	350 (65.7)	<0.001

Table 3: Logistic regression: Predictors of retention in treatment at 12 months (n=2601)

	Odds Ratio	95% CI	P-Value
Methadone use*	1.79	1.45, 2.22	P<0.001
Female sex	1.36	1.13, 1.62	0.001
Cannabis user	0.91	0.76, 1.08	0.277
Currently working	1.36	1.11, 1.66	0.003
Age	1.03	1.02, 1.04	P<0.001
IVDU	0.53	0.42, 0.68	P<0.001
Married or common-law	1.09	0.89, 1.33	0.407
Non-prescribed benzodiazepine use	1.14	0.82, 1.57	0.438
Opioid overdose history	0.68	0.56, 0.82	P<0.001
MAP psychological stress score	1.00	0.98, 1.00	0.345

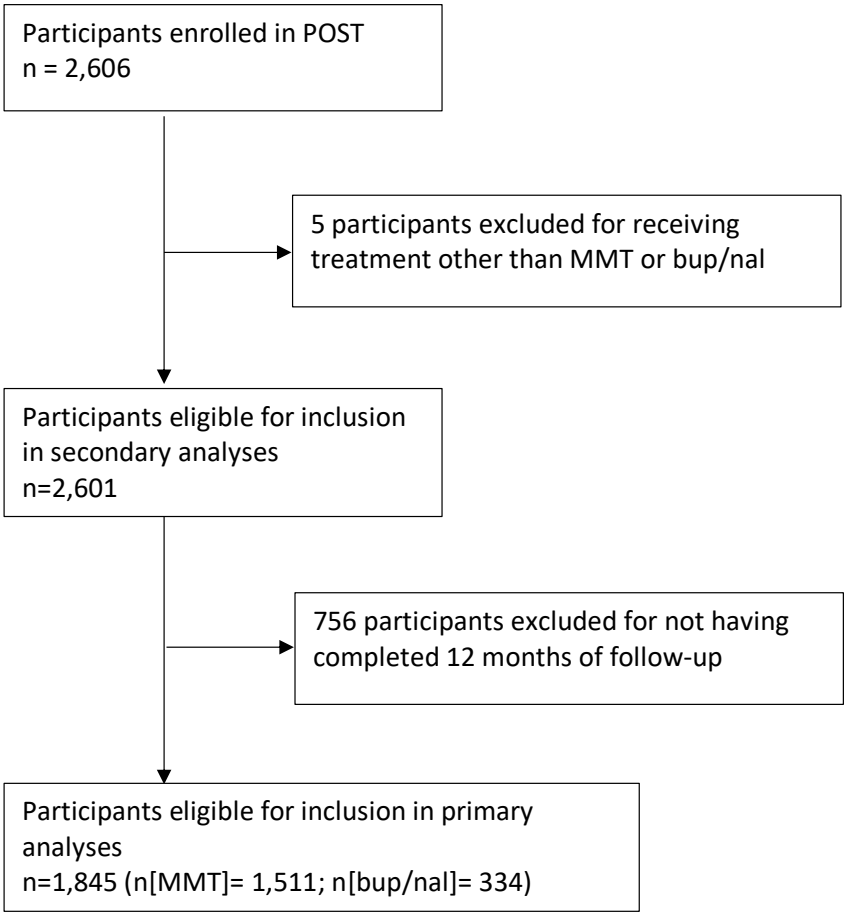
**- compared to bup/nal*

Table 4: Logistic regression: Predictors of continued non-prescribed opioid use by IVDU status

	No history of IVDU (n=1619)			History of IVDU (n=227)		
	Odds Ratio	95% CI	P-Value	Odds Ratio	95% CI	P-Value
Methadone use*	1.72	1.07, 2.77	0.023	1.59	0.55, 4.55	0.400
Female sex	0.78	0.56, 1.10	0.156	1.01	0.56, 1.85	0.962
Cannabis user	0.99	0.71, 1.37	0.932	1.01	0.55, 1.84	0.983
Currently working	1.28	0.91, 1.82	0.159	1.23	0.56, 2.69	0.604
Age	0.99	0.98, 1.01	0.222	0.99	0.97, 1.02	0.706
Married or common-law	0.97	0.68, 1.39	0.879	1.02	0.52, 2.01	0.947
Non-prescribed benzodiazepine use	2.07	1.19, 3.59	0.010	1.09	0.52, 2.31	0.819
Opioid overdose history	1.28	0.90, 1.82	0.176	1.35	0.76, 2.40	0.311
MAP psychological stress score	0.99	0.97, 1.01	0.342	1.01	0.98, 1.05	0.406

**- compared to bup/nal*

Figure 1: Participant Flow Diagram



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CHAPTER 3: Cannabis use and opioid relapse: An exploratory survival analysis of prospectively collected data

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ABSTRACT

Importance: It is known that only minority of patients with opioid use disorder (OUD) receive treatment, of which only a fraction successfully complete treatment as intended. Factors associated with poor treatment outcomes remain unclear, and there is emerging but conflicting evidence that cannabis use may mitigate opioid use.

Objective: To analyze predictors of relapse amongst patients receiving buprenorphine-naloxone for OUD and identify the association between cannabis use and time to relapse

Design: Data were prospectively collected between May 2018 and October 2020, and patients were followed for 12 months.

Setting: Thirty-one outpatient opioid agonist treatment clinics across Ontario, Canada

Participants: All patients 16 years of age or older receiving buprenorphine-naloxone for OUD who had a urine toxicology screen negative for opioids at baseline were eligible for inclusion. Of the 488 patients consecutively sampled, 466 were included.

Exposure: Cannabis use

Main Outcome and Measure: Relapse to opioid use assessed using urine toxicology screens. We employed a multivariable Cox-proportional hazard model for our analyses.

Results: We found that cannabis use was not protective against relapse (hazard ratio [HR]=1.03, 95% confidence interval [CI]: 0.78, 1.36, p=0.84). We found that participants who have been in treatment for at least two years had a 44% decrease in the hazard of relapse compared to those in treatment for less than a year (HR=0.56, 95% CI: 0.34, 0.92, p=0.021). We also found that the hazard of relapse was 2.6 times higher for participants who were intravenous drug users (HR=2.61, 95% CI: 1.74, 3.91, p<0.001), and that for every 1mg increase in the participants'

buprenorphine-naloxone dose, the hazard of relapse is 2% greater (HR=1.02, 95% CI: 1.01, 1.03, p<0.001).

Conclusion: Our analysis failed to show cannabis to be protective against relapse to opioid use in patients receiving buprenorphine-naloxone for OUD. We identified that individuals who inject drugs, are on higher doses of buprenorphine-naloxone, or have been in treatment for less than two years have a higher hazard for relapse. The presence of such factors may thus warrant closer patient follow-up and more stringent treatment protocols to mitigate risk of relapse and potential overdose.

INTRODUCTION

Opioid use disorder (OUD) has led to a serious public health crisis and epidemic. In the United States, drug overdoses remain the leading cause of death in those under 45 years of age,[1] with opioid overdoses being the main driver of fatalities.[2,3] Unfortunately, studies have shown that more than 90% of opioid overdose-related deaths are unintentional.[4] Opioid agonist therapy (OAT), by means of methadone and buprenorphine-naloxone, are the mainstay for pharmacological treatment of OUD.[5,6] The latter has become increasingly favored due to its comparable effectiveness but safer side effect profile and much lower risk of misuse and overdose.[5] Despite the magnitude of the opioid crisis, less than 35% of patients with OUD seek treatment, of whom less than one third actually remain in treatment as intended due to high rates of relapse and loss to follow-up.[7–9]

Few studies have aimed to identify predictors of relapse amongst patients receiving buprenorphine-naloxone therapy as a primary outcome. These studies have been limited by their retrospective design, smaller sample sizes, and statistical methods challenges.[8,10–12] We aim to conduct a survival analysis, using time-to-event data, to analyze predictors of relapse amongst patients receiving buprenorphine-naloxone for OUD. Although clinical data are still lacking, there is emerging but conflicting evidence that cannabis use may mitigate opioid use, possibly through triggering endogenous opioid release and amplifying the analgesic effect of opioids.[13–17] We are, therefore, particularly interested in identifying the association between cannabis use and time to relapse amongst this population. Our group recently published a manuscript identifying that daily cannabis use is associated with a lower likelihood of continued

opioid use during OAT treatment, amongst patients on both methadone and buprenorphine-naloxone.[18] This study focuses on identifying predictors of relapse amongst patients who are abstinent at study onset, and focuses on the subpopulation of patients receiving buprenorphine-naloxone. We hypothesize that cannabis use is protective for relapse into opioid use in patients using cannabis during OAT treatment, due to emerging evidence about its potential benefits at mitigating withdrawal amongst patients with OUD.[14,15,18,19]

Research Question: What is the association between cannabis use and relapse amongst patients receiving buprenorphine-naloxone for OUD?

METHODS:

Study Design

We conducted our analyses using data collected from an ongoing longitudinal study entitled Pharmacogenetics of Opioid Substitution Treatment Response (POST).[20] This is a prospective cohort study aimed at assessing the association between biopsychosocial factors and opioid agonist therapy (OAT) outcomes. Data for the study were collected from 31 clinical sites across Ontario, Canada, between May 2018 and October 2020. The protocol for this study has previously been described.[20] The study has been approved by the Hamilton Integrated Research Ethics Board (#4556) and funded by the Canadian Institute for Health Research (CIHR). The current study is reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.[21]

In order to be included into the present study, participants had to be at least 16 years of age or older, have provided written informed consent, be receiving buprenorphine-naloxone therapy for OUD, and have a urine toxicology screen negative for illicit opioids at the time of study entry. OUD is defined as per the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5).[22] All participants underwent a semi-structured baseline interview with trained research staff whereby baseline demographic information, past medical and substance use histories were obtained by self-report. Frequency, compound of choice, amount, and route of cannabis and illicit benzodiazepine use in the past 30 days were ascertained by self-report using the Maudsley Addiction Profile.[23] We included illicit benzodiazepines use as have previously shown it to be a predictor of accelerated relapse amongst patients with OUD on methadone maintenance therapy.[24] As part of the usual treatment for OUD, participants underwent regular urine toxicology screens, typically on a weekly to bi-weekly basis. The FaStep Assay (Trimedic Supply Network Ltd, Concord, Ontario, Canada) was used to detect morphine, oxycodone, fentanyl, methadone metabolite, and buprenorphine, as well as other non-opioid substances.[20] Participants were followed at three months intervals, for up to 12 months. At study entry and each follow-up, the following data were obtained from participants' electronic medical records: current buprenorphine-naloxone dose, length of time on treatment, date of last dose taken, and results of all urine toxicology screens within the preceding three months period.

Statistical Analysis

Analyses were conducted using STATA version 13.0.[25] We used descriptive statistics to summarize participants' baseline characteristics. Continuous variables were expressed using

mean and standard deviation, whereas categorical variables were expressed using percentages. We employed two-sample t-tests (for continuous variables) and Pearson's chi-square tests (for categorical variables) to compare baseline participants' characteristics between relapsing and non-relapsing participants. We used Kaplan Meier curves to estimate time to relapse for cannabis users and non-users. We compared the survival times between by cannabis use using the log-rank method. We then employed a multivariable Cox-proportional hazard model to assess the association between time to relapse and cannabis use, while adjusting for clinically important variables that may impact treatment outcomes. Specifically, we adjusted our model for age (continuous variable), duration of time in treatment (categorical variable), current dose (continuous variable), marital status (dichotomous variable), employment status (dichotomous variable), illicit benzodiazepine use (dichotomous variable) and history of injection drug use (dichotomous variable). Given that the continuous variable time in treatment violated the proportional hazard assumption, it was converted to a categorical variable which satisfied the assumption. We chose cut-off points of less than or equal to 12 months (n=87), 12 to 24 months (n=146), 24 to 36 months (n=90), and greater than 36 months (n=143). The cut-off points were chosen based on clinically important time points, while also ensuring that a sufficient number of participants remained in each of the categories. The minimum recommended treatment duration is 12 months, and this was used as the initial cut-off, followed by each additional year, as longer duration in treatment is an indicator of stability.[5] We used time of entry into the study as the time origin, and time in study (days) as the time scale. We defined time to relapse as the time from study enrolment to the time of first urine toxicology screen positive for a non-prescribed opioid. We conducted identical analyses within

the cannabis users, assessing the association between daily cannabis use and time to relapse, compared to non-daily use. We assessed for multi-collinearity by calculating the variance inflated factor (VIF), and considered a VIF of greater or equal to five or ten to suggest moderate or severe multi-collinearity, respectively. We followed the general rule of thumb of 10 events per variable for achieving adequate power in a cox model.[26]

Handling of Censored Data

At each follow-up, data regarding the reason censored participants may no longer be in treatment were recorded, as well as the date of their last urine toxicology screen and date of the last buprenorphine-naloxone dose consumed. If censored data were deemed to be random, independent and non-informative based on our assessment, then basic Kaplan Meier plots and Cox-proportional hazard functions were used to handle censored data.[27,28] If, based on the reason for censoring, it was deemed that censoring may have been informative, then a worst-case imputation approach was used as a sensitivity analysis to assess the robustness of the findings.[27,28]

RESULTS:

Participant Characteristics

Data from 466 participants receiving buprenorphine-naloxone therapy were available for analysis. Please see Figure 2 for participant flow diagram. Participants were followed between May 2018 and October 2020, for a median 165 days (interquartile range [IQR]: 37, 357), and a total of 85,451 person-years of follow-up. Forty-six percent of participants relapsed during the

one year study period, constituting an event rate of 0.25 events per 100 person-years. Of the 254 participants with no documented relapse episodes, 148 participants completed 12-month follow-up without a relapse (31.8% of the total study sample).

The mean age of participants was 39 years, and approximately half (46%) were female. The average dose of buprenorphine-naloxone was 16.7 mg (standard deviation [SD] 16.8) in the group that relapsed, compared to 10.8 mg (SD 8.70) in the group that did not relapse ($p<0.001$). A larger proportion of those who relapsed (17%) endorsed injection drug use, compared to those who did not relapse (5%) during follow-up ($p<0.001$). Please see Table 5 for complete baseline patient characteristics.

Primary Analyses:

1) Multivariable-adjusted Cox Regression: predictors of relapse and the association with cannabis use

In the multivariable-adjusted Cox regression, we found that cannabis use was not protective against relapse (hazard ratio [HR]=1.03, 95% confidence interval [CI]: 0.78, 1.36, p=0.84). We found that participants who have been in treatment between two and three years had a 44% decrease in the hazard of relapse compared to those in treatment for less than a year (HR=0.56, 95% CI: 0.34, 0.92, p=0.021). Similarly, those in treatment for three or more years had a 37% reduction in the hazard of relapse compared to those in treatment for less than a year (HR=0.63, 95% CI: 0.40, 0.98, p=0.041). We also found that the hazard of relapse was 2.6 times higher for participants who injected drugs compared to those who did not (HR=2.61, 95% CI:

1.74, 3.91, p<0.01). Finally, we find that for every 1mg or 10mg increase in the participants' buprenorphine-naloxone dose, the hazard of relapse is 2% or 22% greater, respectively (HR=1.02 per 1mg increase in dose, 95% CI: 1.01, 1.03, p<0.001). The VIF of included variables ranged between 1.02 to 2.04, thus ruling out multi-collinearity. See Table 6. The results were unchanged in a sensitivity analysis conducted within cannabis users, assessing the association between daily cannabis use and time to relapse, compared to non-daily use, while adjusting for the same covariates [data not shown].

2) Kaplan-Meier Estimates: association between cannabis use and relapse

Unadjusted Kaplan-Meier curves reveal that cannabis users have a trend towards shorter time to relapse, but that this association is not statistically significant (p=0.380). Please see Figure 3. The log-rank test remained statistically non-significant in a sensitivity analysis amongst cannabis users, assessing association between daily cannabis use and relapse, compared to non-daily cannabis use [data not shown]. This is consistent with the findings of the multivariable-adjusted Cox model above.

Sensitivity Analysis: Handling of Censored Data

Of the 254 (55%) with no documented relapse episodes, 245 were right censored and 9 were interval censored. Of the 245 participants who were right censored, 148 were censored due to completing the 12 months follow-up (study end), 18 were transferred to another provider, 11 completed treatment and were discharged from the clinic, and 8 were incarcerated. We consider these participants to be censored for non-informative reasons. The remaining 60

participants who were right censored, and 9 who were interval censored, were lost to follow-up as they stopped attending their clinic appointments. It may be argued that these participants who are lost to follow-up have relapsed, and as such, we conducted a sensitivity analysis whereby we assumed that all 69 participants who were censored for having withdrawn from treatment had relapsed at the time of censoring. The association between cannabis use and time to relapse remained non-significant in this multivariable-adjusted Cox regression analysis (HR=0.96, 95% CI: 0.76, 1.22, p=0.755). The log-rank test comparing unadjusted survival times stratified by sex also indicated no statistically significant difference in the time to relapse between cannabis users and non-users (p=0.557). The association between time-to-relapse and the remainder of the predictors assessed remained unchanged from the primary analysis, with the exception of employment status whereby those who were employed had a 25% reduction in the hazard of relapse compared to those who were unemployed (HR=0.76, 95% CI 0.58, 0.98, p=0.031).

DISCUSSION

Our study identifies several predictors of opioid relapse for patients receiving buprenorphine-naloxone therapy, one of the first-line agents for OUD. While relapse in any substance use disorder is an important outcome, it is particularly relevant in OUD wherein patients lose tolerance to opioids within days of stopping use and are at significantly heightened risk of overdose with relapse to smaller amounts of opioids. Although buprenorphine is known to have affinity for the mu-opioid receptors and therefore helps maintain one's tolerance to opioids, the level of tolerance depends on the plasma concentration level and it is not known how this

equates to tolerance to fentanyl – a synthetic opioid with much higher potency.[29] Identifying patients at higher risk of relapse is therefore an integral aspect of harm reduction for managing patients with OUD, as we know that over 90% of opioid overdose deaths are unintentional.[4,30] In our study, we find that participants who inject drugs or are on a higher dose of buprenorphine-naloxone have a significantly higher hazard of relapse at any point in time, whereas being in treatment for more than two years is associated with a lower hazard of relapse. Our findings also indicate that cannabis use does not have a significant association with relapse to opioid use and we could not show protective effect of cannabis in this study amongst participants receiving buprenorphine-naloxone for OUD, even after adjusting for other clinically important variables.

We find that participants who inject drugs and those who are in treatment for a shorter period of time have a higher hazard of relapse at any point in time. This is likely explained by the fact that opioids have higher bioavailability when injected intravenously and intravenous use is typically an indicator of more severe OUD as well as poorer outcome.[24] Similarly, the longer one is in treatment, the more stable they are likely to be. Thus it is expected that individuals who are in treatment for a shorter period of time would be more likely to relapse.[5,10] Lastly, individuals with more severe OUD, including those who inject drugs, often require higher doses of buprenorphine-naloxone. As such, it once again seems plausible that the individuals with higher doses had a higher hazard of relapse due to them having a more severe OUD, necessitating the higher dose of treatment in the first place. This is consistent with prior research.[5,10]

Our findings add to the available literature investigating the association between cannabis use and OUD. Emerging evidence suggests that cannabis may serve as a harm reduction strategy to mitigate opioid consumption, as the active component delta-9-tetrahydocannabinol (THC) may amplify the analgesic effects of consumed opioids as well as trigger endogenous opioid release.[31–34] However, there is substantial heterogeneity in the evidence to support this association or mechanism of action.[14,15,19] Similar to our findings, a cross-sectional analysis of 777 patients receiving methadone maintenance therapy for OUD found that cannabis use was not associated with illicit opioid use during treatment.[14]

The study results may be impacted by the missing data on a number of individuals. As discussed above, 254 individuals were censored, of which 69 could have been informative censoring as they dropped out of treatment at some point during follow-up. In order to address this, we used the worst-case scenario imputation method, whereby we assumed that these 69 individuals relapsed at the time of drop out. This analysis yielded a similar finding, that cannabis use is not protective against relapse to opioids, highlighting the robustness of our findings.

Our findings are strengthened by the fact that all individuals who were censored were followed up and the timing as well as reason for censoring were documented. This allowed us to more reliably make a judgement regarding informative censoring, so as to conduct the appropriate analyses discussed above. Another strength of our study is that our outcome, time to relapse, is objective on the basis of a positive urine toxicology screen, and that it is collected on a weekly to biweekly basis, providing a relatively accurate timing of relapse. One limitation

of this study is that it is certainly possible for an individual to have relapsed prior to enrolment into the study. These individuals are not necessarily excluded, or left truncated, however, as long as their urine toxicology screen at study enrollment was negative for illicit opioids. Given we are interested in time-to-relapse, individuals who are actively using illicit opioids while on OAT are not part of our study population. It is not possible for us to know whether these individuals had ever achieved a period of sobriety and then relapsed (thus left truncated), or never achieved a period of sobriety to begin with (thus not part of our target study population). Nonetheless, only 22 participants had a urine toxicology screen that was positive for illicit opioids at baseline, of which only a fraction represent true relapses, thus would be unlikely to have biased our results (see Figure 2). Lastly, another limitation is the fact that time origin for this study is time of study enrolment, whereas patients could have been receiving treatment for varying periods of time. We have attempted to mitigate this by adjusting our model for length of time on treatment.

Taken together, our study identifies that there is neither a positive nor protective association between cannabis use and time-to-relapse among patients receiving buprenorphine-naloxone for OUD. The majority of research evaluating cannabis use and outcomes of patients receiving opioid agonist therapy has focused on illicit opioid use and retention in treatment as study outcomes. This is the first study, to our knowledge, to investigate its impact on time-to-relapse. Relapse is an important outcome due to the serious implications associated with loss of tolerance and risk of overdose, as well as the fact that abstinence from opioid use is what patients consider to be the most important outcome of

treatment for OUD.[35] Our study calls upon further research to investigate the association between cannabis use and opioid use so as to optimize treatment outcomes, especially as the prevalence of cannabis use continues to rise.[36] Moreover, we identified that patients who inject drugs, are on higher doses of buprenorphine-naloxone, or have been in treatment for less time have a higher hazard of relapse. More stringent monitoring during treatment may be warranted to mitigate relapse risk amongst these patients, and future research is needed to further investigate these associations and replicate our findings.

CONCLUSION

We found that cannabis use was not protective against relapse to opioid use in patients receiving buprenorphine-naloxone for OUD. We identified that individuals who inject drugs drug users, are on higher doses of buprenorphine-naloxone, or have been in treatment for less than two years have a higher hazard for relapse. The presence of such factors may thus warrant closer patient follow-up and more stringent treatment protocols to mitigate risk of relapse and potential overdose. Future research aimed at delineating the potential protective or negative consequences cannabis use may have on treatment outcomes for patients with OUD is recommended.

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Author contributions: LN and ZS conceived the research question and protocol. NS, AH, JH collected participant data for the study. LN, NS and JH formatted and extracted the relevant data for the study. LN, LT, ZS conducted the study analyses. All authors contributed equally to the writing and revision of the manuscript. All authors approved the final version of the manuscript.

TABLES AND FIGURES

Table 5: Baseline Participant Characteristics

Participant Characteristic	**Total (n=466)**	**Relapsed (n=212)**	**Not Relapsed (i.e., censored, n=254)**	**P-Value**
	Mean (SD)			
Age (years)	38.59 (10.73)	38.32 (10.44)	38.82 (10.99)	0.620
Time on treatment (months)	34.94 (33.32)	34.76 (37.22)	35.10 (31.77)	0.916
Buprenorphine dose (milligrams)	13.48 (13.35)	16.71 (16.80)	10.79 (8.71)	<0.001
	N (%)			
Female	215 (46.14)	98 (46.23)	117 (46.06)	0.972
Cannabis user	225 (48.28)	107 (50.47)	118 (46.47)	0.388
Married	144 (30.90)	65 (30.66)	79 (31.10)	0.918
Employed	185 (39.70)	74 (34.91)	111 (43.70)	0.053
Injection drug use	49 (10.52)	37 (17.45)	12 (4.72)	<0.001
Illicit benzodiazepine use	29 (6.22)	17 (8.01)	12 (4.72)	0.143

Table 6: Multivariable Cox Regression Analysis: Predictors of Relapse Amongst Patients Receiving Buprenorphine-Naloxone for OUD (N=466)

Variable	Hazard Ratio	95% CI	P-Value
Cannabis use	1.03	0.78, 1.36	0.835
Female	0.89	0.67, 1.19	0.431
Age (years)	1.00[†]	0.98, 1.01	0.697
Currently employed	0.76	0.57, 1.02	0.069
Married	1.01	092, 1.10	0.896
Injection drug use	2.61	1.74, 3.91	<0.001
Amt. of last buprenorphine-naloxone dose (milligrams)	1.02[†‡]	1.01, 1.03	<0.001
Illicit benzodiazepine use	1.42	0.83, 2.41	0.200
Time on treatment* - >12 months and ≤24 months	1.04	0.69, 1.58	0.837
Time on treatment* - >24 months and ≤36months	0.56	0.34, 0.92	0.021
Time on treatment* - >36 months	0.63	0.40, 0.98	0.041

[†] Hazard ratio calculated per one unit change of independent variable

[‡] HR=1.22 per 10mg increase in buprenorphine-naloxone dose

*Compared to ≤12 months

Figure 2: Participant-Flow Diagram

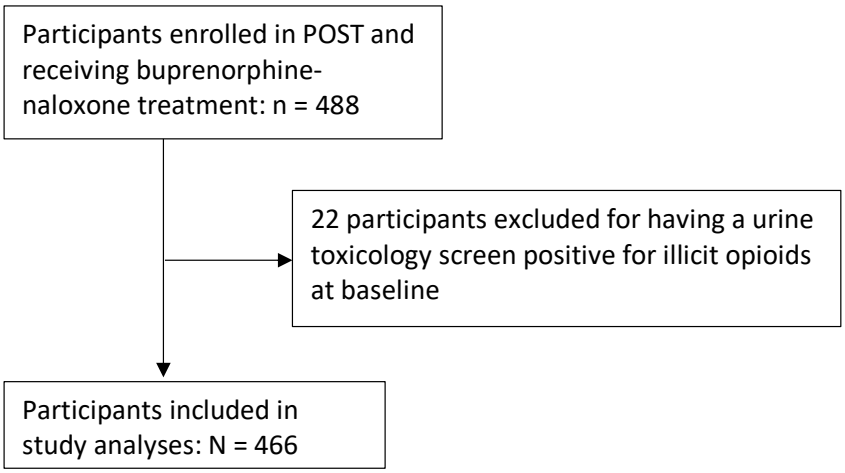
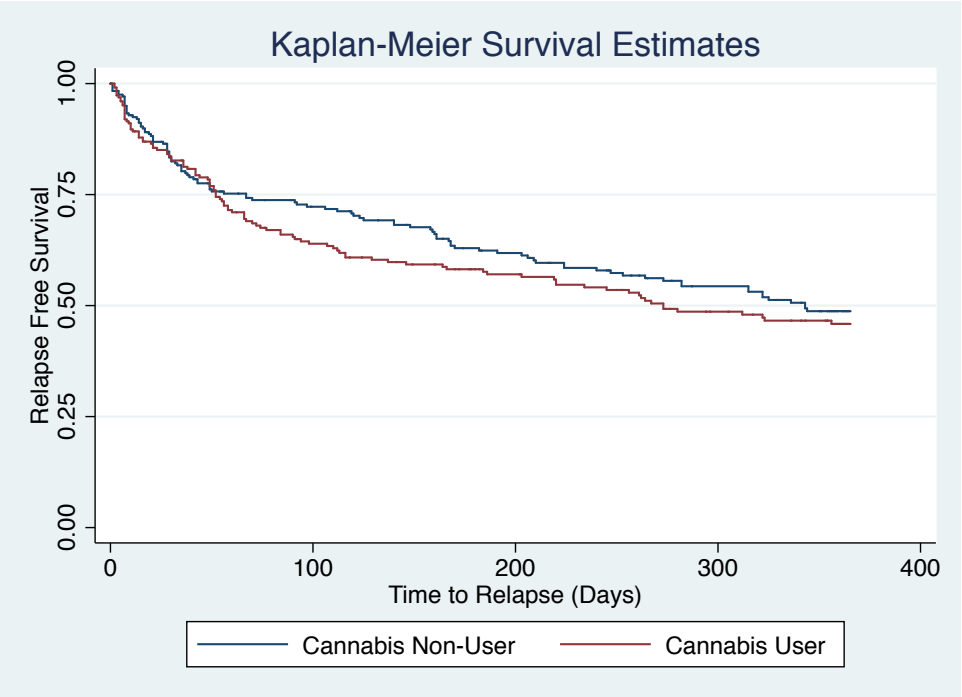


Figure 3: Kaplan-Meier Curves by Current Cannabis Use



Caption: The y-axis and x-axis labels are probability of survival and time until relapse (days), respectively. The log-rank test reveals that the survival distribution between those who currently use cannabis and those who do not is not statistically different (chi-square: 0.77, p=0.3804)

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CHAPTER 4: The role of cannabis use in suicidal ideation among patients with opioid use disorder

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ABSTRACT

Objectives: Cannabis use is associated with suicide risk in the general population; however, it is unknown if this association is also present in patients with opioid use disorder (OUD). The purpose of this study is to investigate the association between cannabis use and suicidal ideation in patients with OUD.

Methods: We conducted a multivariable logistic regression analysis to assess the association between cannabis use and suicidal ideation, amongst a large cohort of patients with OUD. Current cannabis use and suicidal ideation over the past 30 days were obtained by self-report.

Results: Cross-sectional data from 2,335 participants with OUD were included in the analysis, of whom 51% report current cannabis use. We found a positive association between cannabis use and suicidal ideation (OR=1.41, 95% CI 1.11, 1.80, p=0.005). We found that men (OR=1.84, 95% CI 1.44, 2.35, p<0.001), younger individuals (OR=1.02, 95% CI 1.01, 1.03), p=0.004), and that those with more symptoms of anxiety or depression (OR=1.16, 95% CI 1.15, 1.18, p<0.001) were more likely to report suicidal ideation.

Conclusion: Cannabis use is associated with a heightened propensity for suicidal ideation amongst patients with OUD, who are already a high-risk population. Further research into the potential harms of cannabis use in this population is required given the prevalence of its use and potential benefits in mitigating opioid withdrawal.

INTRODUCTION

The life expectancy amongst Canadians did not rise between 2016 to 2017 for the first time in over three decades.[1] This is despite the fact that Canadians aged 55 to 89 are living longer.[1] Statistics Canada reports reveal that advancements in healthcare, contributing to the observed longevity of older Canadians, have been offset by the increased rate of death amongst young adults, especially men, between the ages of 20 to 44.[1] This alarming rise was linked to the opioid crisis, and the increased rate of both accidental and intentional opioid overdose within this age group. [1]

Cannabis use has repeatedly been shown to be associated with a heightened propensity for suicidal behavior in the general population.[2–4] In fact, studies have found that those who use cannabis are more than twice as likely to attempt suicide compared to those who do not use cannabis.[2–4] Amongst those with opioid use disorder (OUD), a population already at a heightened risk for suicidal behavior, concurrent cannabis use is reported by 11.2% to 78.6% of individuals.[5] Given the recent legalization of cannabis in Canada, in the midst of the opioid crisis, we are interested in exploring the association between cannabis use and suicidal ideation amongst patients with OUD. This is especially important given emerging evidence that cannabis use may serve as a harm reduction strategy in the management of OUD and opioid withdrawal, though this approach is based on conflicting findings.[5–7] Proposed mechanisms include the synergistic effect of delta-9-tetrahydrocannabinol (THC), the psychoactive component of cannabis, on amplifying the analgesic effect of opioids, as well as the ability of cannabinoids to

increase endogenous opioid release [8–10]. We hypothesize that cannabis use would be associated with an increased risk of suicidal ideation in this population.

METHODS

Study Design

We conducted a cross-sectional analysis of data obtained from an ongoing prospective cohort study, titled Pharmacogenetics of Opioid Substitution Treatment Response (POST). Data for this study were collected from 30 clinical sites across the province of Ontario, Canada between May 2018 and February 2020. The protocol for this study has previously been described.[11] In summary, it is a prospective investigation aimed to delineate the association between genetic variants and concurrent substance use with opioid agonist therapy (OAT) outcomes. This study has been approved by the Hamilton Integrated Research Ethics Board (#4556) and funded by the Canadian Institutes for Health Research (CIHR). In order to be included in the present study, participants had to be at least 16 years of age, able to provide written informed consent and be receiving OAT for OUD. All participants underwent a baseline interview with trained research personnel whereby baseline demographic, medical and treatment information were obtained.

OUD was diagnosed as per the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5). Suicidal ideation was obtained through self-report as part of the Maudsley Addiction Profile (MAP) at the baseline interviews, whereby participants were asked to rate how often they experienced suicidal ideation over the past 30 days, on the following 5-point scale: never, rarely, sometimes, often and always.[12] Given that any suicidal ideation is

problematic, we dichotomized the presence of suicidal ideation into no (never) or yes (encompassing all other responses). Current cannabis use (yes/no) was also obtained by self-report at the baseline interview. We have previously validated this to be a reliable measure, with 80% sensitivity and specificity compared to THC detection in urine toxicology screens.[6] Participants who reported current cannabis use were then asked how often they used cannabis: "everyday", "every other day", "once a week", "2-3 times a month". Total psychological health symptom score was measured based on the 10-item psychological health scale in MAP, which was originally derived from the anxiety and depression subscales of the Brief Symptom Inventory.[12] Our scale included 9 items, as we excluded suicidal ideation due to collinearity with our outcome.

Statistical Analysis

We used descriptive statistics to summarize participant demographic and baseline characteristics. Means and standard deviation were used for continuous variables, whereas counts and percentages were used for categorical variables. A multivariable logistic regression was used to assess the association between suicidal ideation and self-reported cannabis use (yes/no). The model was adjusted for the following clinically important covariates: age, sex, marital status, employment status, smoking status (tobacco), current alcohol use and total psychological health symptom score. These characteristics are commonly adjusted for in the literature, and were chosen due to their clinical relevance or possible confounding.[13–16] Goodness of fit was assessed using the Hosmer-Lemeshow test and McFadden's pseudo R^2.[17,18]

A secondary analysis was also conducted evaluating whether frequency of cannabis use was associated suicidal ideation. Our team has previously shown that amongst a different sample of patients with psychiatric comorbidities, more frequent cannabis use was associated with a higher risk of suicide attempt in men, but not women.[13] We measured frequency of cannabis use as a binary variable, categorized into daily use or less than daily use. All analyses were performed using STATA version 13.0.[19]

We followed the Strengthening the Reporting of Observation Studies in Epidemiology (STROBE) checklist for reporting the study findings.[20]

RESULTS

Participant Characteristics

Amongst the 2,342 participants eligible for our study, six were excluded for having missing values in one or more of the variables analyzed, and one was excluded for being the only intersex participant. Please see Figure 4 for participant inclusion diagram. The average age of participants was 39.3 years (SD=10.9), and 56% were male. Approximately half the participants reported current cannabis use, 68% of whom reported daily use. Twenty-four percent of participants who use cannabis endorsed suicidal ideations in the past 30 days, compared to 17% of those who do not use cannabis. Overall, 216, 178, 56 and 31 participants reported experiencing suicidal ideation rarely, sometimes, often, and always, respectively. Please see Table 7 for additional participant characteristics.

Primary Analysis: The association between cannabis use and suicidal ideas

Factors significantly associated with suicidal ideation in this sample included cannabis use (odds ratio [OR]=1.41, 95% confidence interval [CI] 1.11, 1.80, p=0.005) and male sex (OR=1.84, 95% CI 1.44, 2.35, p<.001). Furthermore, we found that those who endorsed more symptoms of anxiety and depression were at higher risk of reporting suicidal ideation, such that every point increase in their psychological symptom score was associated with a 16% increase in the likelihood of reporting suicidal ideation (OR=1.16, 95% CI 1.15, 1.18, p<.001). We also found that for every year increase in age, the odds of reporting suicidal ideation in the past 30 years dropped by 2% (OR=0.98, 95% CI 0.97, 0.99, p=.004). Please see Table 8 and Figure 5 for the full results. Both the Hosmer-Lemeshow test (p=0.0691) and McFadden's pseudo R^2 (pseudo R^2=0.2283) revealed adequate model fit.

Secondary Analysis

We assessed the association between daily cannabis use and suicidal ideation, compared to less than daily cannabis use. Participants who denied current cannabis use were excluded from this analysis (n=1,145), and one participant was excluded from this analysis for not reporting frequency of use, rendering 1189 participants eligible for this analysis.We found that there is no association between frequency of cannabis use and suicidal ideation (OR=0.89, 95% CI 0.64, 1.23, p=0.490). This remained true when we analyzed men and women in our sample separately (data not shown).

DISCUSSION

Our study reveals that amongst a large cohort of participants with OUD on OAT, any cannabis use, regardless of frequency of use, is associated with a heightened propensity for endorsing suicidal ideation in the past month. We also find an increased risk for reporting suicidal ideation among men, younger individuals, and those who endorse more symptoms of anxiety and depression.

The rate of suicidal ideation in the past 3 months (20.6%) in our study sample is ten times the yearly rate of suicidal ideation amongst adults in developed countries such as the United States and Germany according to data from the World Health Organization.[14] This is an anticipated finding given the established increased risk of suicidal behavior, including ideations, attempts and completed suicide, associated with substance use disorders.[2,21,22] A systematic review of 12 studies on this topic found similar results, whereby those with OUD were 14 times more likely to die by suicide compared to the general population.[21] Given the high risk of suicide in the context of OUD, we investigated whether cannabis use influences the risk of suicidal ideation in patients with OUD. We identified that in addition to the baseline risk that is expected in this population, cannabis use contributes to an increased risk of suicidal ideation, consistent with what is typically seen in the general population. We also find that men, younger individuals and those with a higher psychological symptoms score are at higher risk for suicidal ideation. These are important findings, and ones that may help in managing this patient population by providing more comprehensive assessments and psychiatric interventions to reduce the risk of suicide in this already high-risk population. Patients with OUD are at high risk

for morbidity and mortality, and must therefore be monitored more closely. Studies have previously focused on identifying predictors of high-risk behaviors among patients with OUD, such as intravenous drug use and concurrent substance use, to allow healthcare workers to more closely monitor these individuals.[23–25] Our study finds that patients who use cannabis may be amongst this high-risk group. With the recent legalization of cannabis use in Canada, we anticipate cannabis use rates may increase thus potentially leading to adverse outcomes in the growing opioid crisis, such as increased suicidal behaviour.

Our findings also provide a different profile of risk factors for suicidal ideation in patients with OUD compared to the general population or those with other psychiatric disorders, calling upon a paradigm shift in thinking about these risk factors, and how they may not be homogenous across all settings. We find that men report a higher rate of suicidal ideation compared to women. This is contradictory to what is reported in the general population.[14,15] While among the general population, as well as those with OUD, men die by suicide at higher rates than women, women typically have higher rates of suicidal ideation.[14,15,21] Although men in our sample reported cannabis use at significantly higher rates than women (55% and 46%, respectively), rerunning our analysis amongst those who denied cannabis use rendered our results unchanged (data not shown). However, women did score significantly higher on the psychological symptom score, and it is only after adjusting for this that men were found to be at significantly higher risk of suicidal ideation (data not shown). Therefore, while women generally endorse more suicidal ideation and are at higher risk for mood disorders, both of which are likely interrelated, we found that after adjusting for

depressive and anxiety symptoms, men with OUD were at higher risk of suicidal ideation regardless of cannabis use.[14,15,21] Identifying drivers for this difference is beyond the scope of this study, but one that should be further explored.

We find that frequency of cannabis use is not associated with suicidal ideation. We hypothesize two possible reasons. Firstly, it is possible that the previously shown detrimental consequences of heavier cannabis use on suicidal behavior is counterbalanced by the possible perceived effects of cannabis in managing withdrawal symptoms and augmenting the effects of opioids, as is seen in some studies.[2,7,26] Management of these uncomfortable symptoms may be associated with a sense of improvement quality of life, thus compensating for the heightened risk of suicide ideation that has otherwise been seen with heavier cannabis use.[2,7,13,26] Second, we note that our study sample is already at a ten-fold increased risk of endorsing suicidal ideation, when we compare the point prevalence in our sample (3 months) compared to the general population point prevalence (one year). Therefore, it may be that the added risk of more frequent suicide ideation associated with heavier cannabis use that is seen in other populations is not large enough to reach statistical significance in this population, where the baseline risk or event rate (suicidal ideations) is already much higher.[14]

Our current study findings are strengthened by our large cohort of participants with OUD, a significant proportion of which report concurrent cannabis use and suicidal ideations. Our analyses were adjusted for known risk factors of suicidal ideation, including age, sex and the presence of depressive and anxiety symptoms. While this study's main limitation is the

cross-sectional design of the analysis, prohibiting us from establishing causality, we attempted to minimize this limitation by identifying current cannabis use, suicidal ideation and psychological symptoms in the same, recent time frame (past 30 days). Additionally, although suicidal ideation may be considered a risk factor for suicide attempt, which in turn increases the risk of dying by suicide, studying death by suicide in our study sample would provide superior evidence.[27–29]. However, in order to address the association between cannabis use and death by suicide, we would require an even larger sample given the small event rate and additional data sources to adjudicate the cause of death as suicide versus unintentional opioid overdose, for example. A retrospective analysis of 6,800 adults revealed that suicidal ideation is associated with a 123 times increase in the odds of attempting suicide within one year (OR=123.1, 95% CI 92.9, 162.9), rendering suicidal ideation a suitable surrogate outcome.[27] Nonetheless, suicidal ideation itself poses significant harms to mental and physical well-being, aside from completed suicide, making it an important outcome. Furthermore, we defined cannabis use based on self-report for past 30 days. We have previously shown that self-reported cannabis use highly correlates with urine drug screen, with 80% sensitivity and specificity.[6] It is also a commonly used modality to assess for cannabis use, given that THC may be detected in urine as late as 30 days after last use and therefore may not reflect current use.[30,31] Lastly, participants had not undergone formal psychiatric interviews to ascertain a diagnosis of depression and anxiety. However, we used data collected through the psychological health component of the MAP, which is a validated tool to assess for symptoms of anxiety and depression that is derived from the Brief Symptom Inventory, and has previously been used for this purpose.[12,32]

Future research on individuals with OUD followed longitudinally through health administrative databases would be ideal in overcoming these limitations, and identifying a possible causal association between cannabis use and suicidal behaviour (ideas, attempts and death by suicide). Additionally, exploring whether this association varies by the severity of opioid use and the opioid of choice may further help delineate the effects of cannabis use on patients with OUD. As further research aims to delineate the potential therapeutic benefits of cannabis in managing opioid withdrawal and its synergistic effects with opioids, it is important we gain a clearer understanding of its potential risks in this patient population. Additionally, with recent legalization and potential increase in recreational cannabis use in Canada, among other countries where legalization has been instated or considered, this is an especially important topic that requires ongoing assessment.

CONCLUSION

Amongst a large cohort of participants with OUD, we find that cannabis use, regardless of frequency of use, is associated with a 40% increase in the odds of endorsing suicidal ideation. Unlike the general population, we find that men with OUD are at higher risk of endorsing suicidal ideation compared to women. Our data highlight a high-risk population within an already at-risk group. Our results should be used to inform potential recommendations in the use of cannabis as a harm reduction strategy for OUD, as well as guide healthcare providers in risk assessment of patients for psychiatric assessment and follow-up if indicated.

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Author Contributions: LN and ZS conceived the research question and protocol. LN, TR, NS, LT and ZS developed study design and statistical plan. LN conducted the statistical analyses and wrote the initial draft of the manuscript. All authors contributed equally to the writing and revision of the manuscript. All authors approved the final version of the manuscript.

TABLES AND FIGURES

Table 7: Baseline participant characteristics (n=2335)

Participant Characteristic		Total (n=2335)	Participants reporting suicidal ideation in past 30 days (n=481)	Participants denying suicidal ideation in past 30 days (n=1,854)
		Mean (SD)	Mean (SD)	Mean (SD)
Current age (years)		39.3 (10.9)	37.6 (10.6)	39.7 (10.9)
		N (% of total)	N (% of participants reporting suicidal ideation)	N (% of participants denying suicidal ideation)
Sex	Male	1300 (55.7)	276 (57.4)	1024 (55.2)
	Female	1035 (44.3)	205 (42.6)	830 (44.8)
Employed	No	1566 (67.1)	367 (76.3)	1199 (64.7)
	Yes	769 (32.9)	114 (23.7)	655 (35.3)
Marital status	Married or living with partner	680 (29.1)	117 (24.3)	563 (30.4)
	Other	1655 (70.9)	364 (75.7)	1291 (69.6)
Cannabis use	No	1145 (49.0)	196 (40.8)	949 (51.2)
	Yes	1190 (51.0)	285 (59.3)	905 (48.8)
Frequency of cannabis use	Daily use	805 (34.5)	185 (64.9)	620 (68.6)
	Less than daily use	384 (16.4)	100 (35.1)	284 (31.4)
Current smoker (tobacco)	Yes	1870 (80.1)	396 (82.3)	1474 (79.5)
	No	465 (19.9)	85 (17.7)	380 (20.5)
Current alcohol use	Yes	1470 (63.0)	195 (40.5)	670 (36.1)
	No	865 (37.0)	286 (59.5)	1184 (63.9)
OAT	Methadone	1848 (79.1)	375 (78.0)	1473 (79.4)
	Suboxone	484 (20.7)	103 (21.4)	381 (20.6)
	Other	3 (0.13)	2 (0.42)	1 (0.05)

Table 8: Multivariable logistic regression analysis: The risk of suicidal ideation in patients with OUD (n=2335)

Covariates	Odds Ratio (95% CI)	P-Value
Cannabis use[1]	1.41 (1.11, 1.80)	0.005
Men	1.84 (1.44, 2.35)	<0.001
Married or common law	1.03 (0.78, 1.34)	0.849
Employed	0.87 (0.66, 1.14)	0.297
Age	0.98 (0.97, 0.99)	0.004
Psychological symptom score	1.16 (1.15, 1.18)	<0.001
Current smoker (tobacco)	0.90 (0.66, 1.21)	0.476
Current alcohol use	1.04 (0.82, 1.32)	0.765

[1]Cannabis use here is measured as dichotomous variable (yes/no) based on self-report

Figure 4: Flow chart of participant inclusion

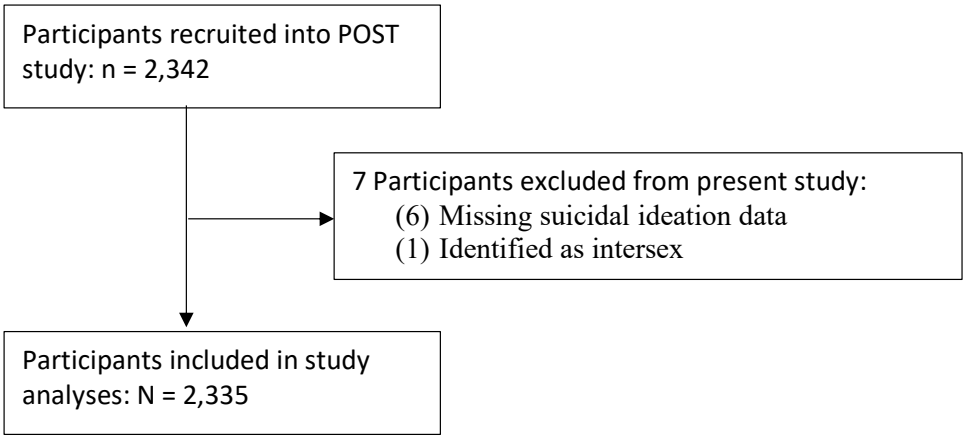
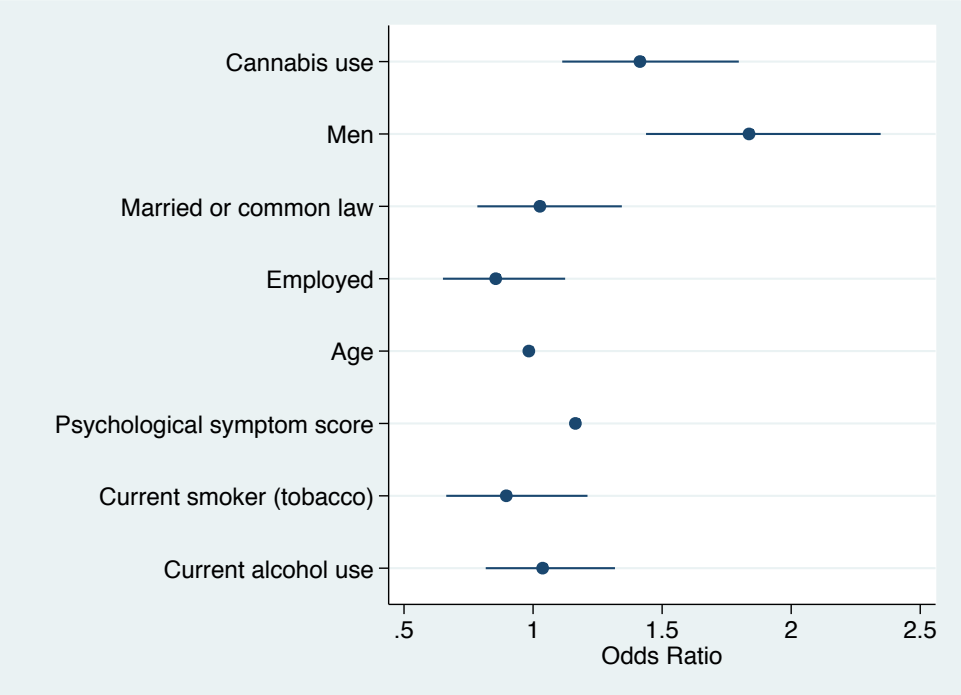


Figure 5: Forest plot of multivariable regression analysis: The risk of suicidal ideation in patients with OUD (n=2335)



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CHAPTER 5: THESIS DISCUSSION

OUD is a multifaceted, multimorbid, relapsing and remitting disorder. Identifying the best treatment and predicting which patients will benefit from treatment is therefore an extremely complex task that is dependent on the interplay of a variety factors. The introduction of highly potent synthetic opioids as well as the high rate of polysubstance use further contributes to the difficulties we face in treating patients with OUD. Through a series of studies on a large cohort of patients with OUD, we identify several factors that may assist in understanding treatment outcomes for patients with OUD, and stratifying high risk patients that may require additional supports through their treatment programs.

In the first study, Chapter 2, we conducted a propensity score matched (PSM) analysis to evaluate for differences in continued illicit opioid use between patients receiving methadone maintenance therapy (MMT) compared to buprenorphine.[1] We identified no difference in opioid consumption patterns between the two groups. Interestingly, however, we found that patients who are on MMT are more likely to remain in treatment for 12 months of follow-up, compared to those on buprenorphine. These findings highlight the complexity of treatment for OUD and the various aspects of treatment outcomes that need to be considered when gauging effectiveness, including the non-linear and multilayered outcomes to be considered. Future studies, ideally randomized controlled trials, would be valuable to replicate these findings and to further elicit effectiveness in wide range of treatment outcomes. Taken together, these findings suggest that MMT may not be superior to buprenorphine for the treatment of patients

during the fentanyl era, specifically when assessing its harm reduction potential through the mitigation of opioid use.[1]

In the second study, Chapter 3, we conducted a survival analysis to assess the association between cannabis use and opioid relapse.[2] We found no association been cannabis use and relapse to opioid use. Amongst cannabis users, we also did not find an association between frequency of cannabis use and opioid relapse. We did, however, find that patients who were in treatment for a shorter period of time, and those who report a history of intravenous drug use were more likely to relapse over the 12 months period.[2] These findings call upon further research to assess whether the theoretical benefits of tetrahydrocannobinol (THC) in mitigating ongoing opioid consumption hold true in practice.

In the third study, Chapter 4, we find that cannabis use is associated with an almost two fold increase in the rate of suicidal ideation.[3] We also find that males are more likely to report suicidal ideation, which is contrast to the general population – where females are more likely to endorse suicidal behaviors. These findings suggest that additional supports, including counselling and closer follow-up, may be important considerations in the treatment of men with OUD and patients with concurrent cannabis use.[3]

Together, data from Chapter 3 and Chapter 4 suggest that while cannabis use may not be directly associated with relapse, it may be associated with an increased propensity for suicidal ideation. This is still problematic given evidence that patients with suicidal ideation are

much more likely more likely to attempt suicide, and patients with OUD have access to highly lethal substances putting them at an even higher risk of completing suicide. Future studies looking at the association between cannabis use and emergency department visits, overdose, and mortality may help to further elucidate this potential link. Elucidating this association is particularly important to gain a holistic understanding of the impact of cannabis use on patients with OUD, as emerging evidence on cannabis use have primarily focused on assessing whether THC may mitigate ongoing opioid use through the endogenous release of opioids.[4,5]

Overall, we identified that continued opioid use during the current fentanyl crisis is independent of OAT treatment type.[1] We do find, however, that patients on MMT are more likely to remain in treatment. We find that cannabis use is highly prevalent amongst patients with OUD, and no benefit was demonstrated in this clinical sample to reduce opioid use contrary to what was suggested in the literature.[2] In addition, we reported that cannabis use, irrespective of frequency of use, is associated with an increased propensity for suicidal ideation, adding to the risks associated with OUD in this population.[3]

Our findings suggest that MMT may not be more effective in the treatment of patients with OUD during the fentanyl era, despite the theoretical rationale, given the complexity of the disease, mechanism of action of the different OATs, and interplay of other personal factors. Cannabis use may also have an impact on patients with OUD beyond just mitigating ongoing opioid use, and it is still uncertain whether the overall risks outweigh any potential benefits. Further studies assessing these outcomes using pragmatic patient samples followed over long

periods of time, or using administrative databases, are required to ensure that we provide the most optimal and evidence-based care for patients with this highly prevalent and lethal disorder.

STRENGTHS AND LIMITATIONS

There are several factors that strengthen our findings, and more importantly, sets this work apart from the majority of the published research on OUD. Firstly, we used prospectively collected data from a large cohort of patients with OUD receiving treatment in a clinical setting. Patients were not excluded from participation in this cohort based on comorbidities or polysubstance use, thus representing the 'real life' patient and rendering our findings more generalizable. Additionally, the data were collected between 2018 and 2023, thus representing contemporary trends in opioid and cannabis use since the fentanyl crisis, as well as the legalization of cannabis – both of which render our findings more generalizable in today's crisis. This is extremely important given the high potency of fentanyl and its analogues, causing opioid-related mortality rates to increase in recent years.[6] Therefore, gaining an understanding of treatment outcomes amongst patients using fentanyl, rather than basing it on theoretical and practical experience, is highly important. Lastly, the fact that patients were followed over 12 months and provided urine drug screens at the usual clinical intervals meant that we were able to evaluate these outcomes over a relatively long period of time, and employ robust statistical methods, namely propensity score matching, survival analyses, and adjusted multivariable logistic regressions to explore the studies' aims. Another strength is the use of objective data to measure our outcomes of relapse and continued non-prescribed opioid use.

A limitation of this work is the use of cohort data of participants in different stages of OUD and treatment course, allowing us to only draw associations rather than make any implications on causality. We attempted to mitigate the risk of cofounding through adjusting our models for known cofounders and conducting propensity score matched analyses where possible. However, large randomized controlled trials are needed to confirm and build upon these findings. Additionally, cannabis use was obtained by self-report of cannabis use in the past 30 days. However, our group has previously validated this measure against urine drug screens with 80% sensitivity and specificity.[4] Another major limitation, inherent to the field of OUD, is the limited knowledge we have on what patients consider to be important outcomes and relevant milestones in their recovery. Interestingly, the majority of the research focuses on retention in treatment, yet we have previously shown that this is not an important outcome for patients.[7,8] Rather, patients would like to focus on cessation of opioid use and ultimately weaning off of OAT.[7,8] We attempted to address these outcomes by looking at continued non-prescribed opioid use and relapse as primary outcomes. That being said, we were not able to address other aspects of illness recovery and social factors that patients may consider to be important, such as maintaining a job or relationships. Future research should specifically aim to elucidate these patient important outcomes, generate validated means of measuring them, and then assessing them through trials.

This study was also conducted throughout the COVID-19 pandemic, rendering our data representative of all the stressors patients endured and continue to face since the pandemic. While we have previously shown there to be an increased proportion of urine drug screens

positive for opioids after the onset of pandemic, we did not collect data to specifically assess changes in provisions of care due to the pandemic and their potential impact on treatment outcomes.[9] This is valuable information to not only understand the impact of the pandemic itself, but also indirectly assess the potential benefits or consequences of less stringent treatment requirements, such as less frequent visits, telemedicine visits, and more take-home doses that became inevitable due to pandemic restrictions.

FUTURE DIRECTIONS

The work summarized in this thesis provides valuable insights into aspects of patient treatment outcomes during the fentanyl era, and the potential implications of concurrent cannabis use among patients with OUD. Future studies are needed to confirm and add to these findings. A major drawback to the existing evidence base in OUD is the limited generalizability of the data available, and therefore of the clinical treatment guidelines. Our group has previously shown that the stringent eligibility criteria employed by trials actually excluded the majority of patients with OUD, thus rendering their findings of limited value.[10] We urge trialists moving forward to remove these criteria, so as to capture the true patients we are trying to treat. Moreover, the increasing prevalence of fentanyl and its analogues within the current drug supply has called into question the effectiveness of current treatment recommendations, which had been generated prior to the fentanyl crisis. Novel studies using data collected after 2016, when the fentanyl crisis seemed to have emerged, are needed to evaluate these theories and generate a body of evidence to inform current best practice guidelines. Moreover, given the increasing prevalence of cannabis use, as well as the potential risks and benefits it may have on patients

with OUD, further research aimed at evaluating the impact it has on patients with OUD is necessary. This includes research that assesses its impact holistically, including its effects on psychiatric comorbidities and suicidal behaviors, in addition to continued illicit opioid use. Lastly, further research is needed to gain a better understanding of patient important outcomes and ensure that these are being addressed in clinical trials. The primary purpose of OAT for OUD is harm-reduction, and abstinence from opioid use, albeit an important marker of recovery and overdose risk, may not be the goal patients have when entering treatment.[7,8] Addressing these gaps in knowledge will allow for advancements in the field of addiction and public health needs in light of the ongoing opioid crisis, to hopefully halt and eventually reverse opioid related mortality trends.

CONCLUDING REMARKS

OUD is a complex, multifaceted disorder that continues to evolve as the types of opioids comprising the street drug supply are changing. Over the past decade, we have witnessed a significant rise in the use of much more potent and lethal synthetic opioids. This has led to a significant worsening in opioid related overdose deaths, most of which are accidental. The majority of research on OUD is of limited generalizability given that it had been conducted prior to the introduction of these potent drugs in the street supply, as well as due to the unrealistic stringent eligibility criteria that are imposed by the trials. Our work provides valuable information on the current state of OUD and treatment outcomes for patients with OUD who are representative of the patients we treat day-to-day. We identified that the rate of continued non-prescribed opioid use is not associated with OAT type. We also found that there is no

association between cannabis use and continued opioid use. However, we did find that patients who are on MMT are almost twice as likely to remain in treatment for 12 months, and that those who remain in treatment for over 2 years are much less likely to relapse to opioid use. Lastly, we found that patients who use cannabis are more likely to report suicidal ideation, and thus may benefit from closer follow-up and suicide prevention measures. Future randomized controlled trials encompassing data from pragmatic patient populations and assessing patient-important outcomes are necessary to gain a better understanding of the current crisis.

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Cannabis use and opioid relapse: An exploratory survival analysis of prospectively collected data

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Importance: It is known that only minority of patients with opioid use disorder (OUD) receive treatment, of which only a fraction successfully complete treatment as intended. Factors associated with poor treatment outcomes remain unclear, and there is emerging but conflicting evidence that cannabis use may mitigate opioid use.

Objective: To analyze predictors of relapse amongst patients receiving buprenorphine-naloxone for OUD and identify the association between cannabis use and time to relapse.

Design: Data were prospectively collected between May 2018 and October 2020, and patients were followed for 12 months.

Setting: Thirty-one outpatient opioid agonist treatment clinics across Ontario, Canada.

Participants: All patients 16 years of age or older receiving buprenorphine-naloxone for OUD who had a urine toxicology screen negative for opioids at baseline were eligible for inclusion. Of the 488 patients consecutively sampled, 466 were included.

Exposure: Cannabis use.

Main outcome and measure: Relapse to opioid use assessed using urine toxicology screens. We employed a multivariable Cox-proportional hazard model for our analyses.

Results: We found that cannabis use was not protective against relapse [hazard ratio (HR) = 1.03, 95% confidence interval (CI): 0.78, 1.36, p = 0.84]. We found that participants who have been in treatment for at least two years had a 44% decrease in the hazard of relapse compared to those in treatment for less than a year (HR = 0.56, 95% CI: 0.34, 0.92, p = 0.021). We also found that the hazard of relapse was 2.6 times higher for participants who were intravenous drug users (HR = 2.61, 95% CI: 1.74, 3.91, $p < 0.001$), and that for every 1mg increase in the participants' buprenorphine-naloxone dose, the hazard of relapse is 2% greater (HR = 1.02, 95% CI: 1.01, 1.03, $p < 0.001$).

Conclusion: Our analysis failed to show cannabis to be protective against relapse to opioid use in patients receiving buprenorphine-naloxone for OUD. We identified that individuals who inject drugs, are on higher doses of buprenorphine-naloxone, or have been in treatment for less than two years have a higher hazard for relapse. The presence of such factors may thus warrant closer patient follow-up and more stringent treatment protocols to mitigate risk of relapse and potential overdose.

KEYWORDS

cannabis use, opioid use disorder, relapse, buprenorphine, opioid agonist therapy

Introduction

Opioid use disorder (OUD) has led to a serious public health crisis and epidemic. In the United States, drug overdoses remain the leading cause of death in those under 45 years of age (1), with opioid overdoses being the main driver of fatalities (2, 3). Unfortunately, studies have shown that more than 90% of opioid overdose-related deaths are unintentional (4). Opioid agonist therapy (OAT), by means of methadone and buprenorphine-naloxone, are the mainstay for pharmacological treatment of OUD (5, 6). The latter has become increasingly favored due to its comparable effectiveness but safer side effect profile and much lower risk of misuse and overdose (5). Despite the magnitude of the opioid crisis, less than 35% of patients with OUD seek treatment, of whom less than one third actually remain in treatment as intended due to high rates of relapse and loss to follow-up (7–9).

Few studies have aimed to identify predictors of relapse amongst patients receiving buprenorphine-naloxone therapy as a primary outcome. These studies have been limited by their retrospective design, smaller sample sizes, and statistical methods challenges (8, 10–12). We aim to conduct a survival analysis, using time-to-event data, to analyze predictors of relapse amongst patients receiving buprenorphine-naloxone for OUD. Although clinical data are still lacking, there is emerging but conflicting evidence that cannabis use may mitigate opioid use, possibly through triggering endogenous opioid release and amplifying the analgesic effect of opioids (13–17). We are, therefore, particularly interested in identifying the association between cannabis use and time to relapse amongst this population. Our group recently published a manuscript identifying that daily cannabis use is associated with a lower likelihood of continued opioid use during OAT treatment, amongst patients on both methadone and buprenorphine-naloxone (18). This study focuses on identifying predictors of relapse amongst patients who are abstinent at study onset, and focuses on the subpopulation of patients receiving buprenorphine-naloxone. We hypothesize that cannabis use is protective for relapse into opioid use in patients using cannabis during OAT treatment, due to emerging evidence about its potential benefits at mitigating withdrawal amongst patients with OUD (13–15, 18).

Research question

What is the association between cannabis use and relapse amongst patients receiving buprenorphine-naloxone for OUD?

Materials and methods

Study design

We conducted our analyses using data collected from an ongoing longitudinal study entitled Pharmacogenetics of Opioid Substitution Treatment Response (POST) (19). This is a prospective cohort study aimed at assessing the association between biopsychosocial factors and opioid agonist therapy (OAT) outcomes. Data for the study were collected from

31 clinical sites across Ontario, Canada, between May 2018 and October 2020. The protocol for this study has previously been described (19). The study has been approved by the Hamilton Integrated Research Ethics Board (#4556) and funded by the Canadian Institute for Health Research (CIHR). The current study is reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (20).

In order to be included into the present study, participants had to be at least 16 years of age or older, have provided written informed consent, be receiving buprenorphine-naloxone therapy for OUD, and have a urine toxicology screen negative for illicit opioids at the time of study entry. OUD is defined as per the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) (21). All participants underwent a semi-structured baseline interview with trained research staff whereby baseline demographic information, past medical and substance use histories were obtained by self-report. Frequency, compound of choice, amount, and route of cannabis and illicit benzodiazepine use in the past 30 days were ascertained by self-report using the Maudsley Addiction Profile (22). We included illicit benzodiazepines use as have previously shown it to be a predictor of accelerated relapse amongst patients with OUD on methadone maintenance therapy (23). As part of the usual treatment for OUD, participants underwent regular urine toxicology screens, typically on a weekly to bi-weekly basis. The FaStep Assay (Trimedic Supply Network Ltd, Concord, ON, Canada) was used to detect morphine, oxycodone, fentanyl, methadone metabolite, and buprenorphine, as well as other non-opioid substances (19). Participants were followed at 3 months intervals, for up to 12 months. At study entry and each follow-up, the following data were obtained from participants' electronic medical records: current buprenorphine-naloxone dose, length of time on treatment, date of last dose taken, and results of all urine toxicology screens within the preceding three months period.

Statistical analysis

Analyses were conducted using STATA version 13.0 (24). We used descriptive statistics to summarize participants' baseline characteristics. Continuous variables were expressed using mean and standard deviation, whereas categorical variables were expressed using percentages. We employed two-sample *t*-tests (for continuous variables) and Pearson's chi-square tests (for categorical variables) to compare baseline participants' characteristics between relapsing and non-relapsing participants. We used Kaplan–Meier curves to estimate time to relapse for cannabis users and non-users. We compared the survival times between by cannabis use using the log-rank method. We then employed a multivariable Cox-proportional hazard model to assess the association between time to relapse and cannabis use, while adjusting for clinically important variables that may impact treatment outcomes. Specifically, we adjusted our model for age (continuous variable), duration of time in treatment (categorical variable), current dose (continuous variable), marital status (dichotomous variable), employment status (dichotomous variable), illicit benzodiazepine use (dichotomous variable), and history of injection drug use (dichotomous variable). Given that the continuous variable time in treatment violated the proportional hazard assumption, it was converted to a categorical variable which satisfied the assumption. We chose cut-off points of less than or equal to 12 months (n = 87), 12–24 months (n = 146), 24–36 months (n = 90), and greater than 36 months (n = 143). The cut-off points were chosen based on clinically important time points, while also ensuring that a sufficient number of participants remained in each of the categories. The minimum recommended treatment duration is 12 months, and this was used as the initial cut-off, followed by each additional year, as longer duration in treatment is an indicator of stability (5). We used time of entry into the study as the time origin, and time in study (days) as the time scale. We defined time to relapse as the time from study enrolment to the time of first urine toxicology screen positive for a non-prescribed opioid. We conducted identical analyses within the cannabis users, assessing the association between daily cannabis use and time to relapse, compared to non-daily use. We assessed for multi-collinearity by calculating the variance inflated factor (VIF), and considered a VIF of greater or equal to five or ten to suggest moderate or severe multi-collinearity, respectively. We followed the general rule of thumb of 10 events per variable for achieving adequate power in a cox model (25).

Handling of censored data

At each follow-up, data regarding the reason censored participants may no longer be in treatment were recorded, as well as the date of their last urine toxicology screen and date of the last buprenorphine-naloxone dose consumed. If censored data were deemed to be random, independent and non-informative based on our assessment, then basic Kaplan–Meier plots and Cox-proportional hazard functions were used to handle censored data (26, 27). If, based on the reason for censoring, it was deemed that censoring may have been informative, then a worst-case imputation approach was used as a sensitivity analysis to assess the robustness of the findings (26, 27).

Results

Participant characteristics

Data from 466 participants receiving buprenorphine-naloxone therapy were available for analysis. Please see **Figure 1**

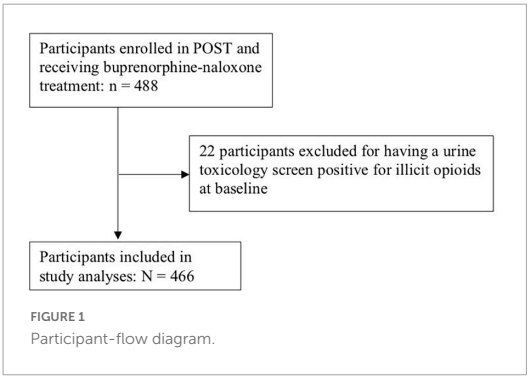

FIGURE 1
Participant-flow diagram.

for participant flow diagram. Participants were followed between May 2018 and October 2020, for a median 165 days [interquartile range (IQR): 37, 357], and a total of 85,451 person-years of follow-up. Forty-six percent of participants relapsed during the one year study period, constituting an event rate of 0.25 events per 100 person-years. Of the 254 participants with no documented relapse episodes, 148 participants completed 12-month follow-up without a relapse (31.8% of the total study sample).

The mean age of participants was 39 years, and approximately half (46%) were female. The average dose of buprenorphine-naloxone was 16.7 mg [standard deviation (SD) 16.8] in the group that relapsed, compared to 10.8 mg (SD 8.70) in the group that did not relapse ($p < 0.001$). A larger proportion of those who relapsed (17%) endorsed injection drug use, compared to those who did not relapse (5%) during follow-up ($p < 0.001$). Please see **Table 1** for complete baseline patient characteristics.

Primary analyses

Multivariable-adjusted Cox regression: Predictors of relapse and the association with cannabis use

In the multivariable-adjusted Cox regression, we found that cannabis use was not protective against relapse [hazard ratio (HR) = 1.03, 95% confidence interval (CI): 0.78, 1.36, $p = 0.84$]. We found that participants who have been in treatment between two and three years had a 44% decrease in the hazard of relapse compared to those in treatment for less than a year (HR = 0.56, 95% CI: 0.34, 0.92, $p = 0.021$). Similarly, those in treatment for three or more years had a 37% reduction in the hazard of relapse compared to those in treatment for less than a year (HR = 0.63, 95% CI: 0.40, 0.98, $p = 0.041$). We also found that the hazard of relapse was 2.6 times higher for participants who injected drugs compared to those who did not (HR = 2.61, 95% CI: 1.74, 3.91, $p < 0.01$). Finally, we find that for every 1 or 10 mg increase in the participants' buprenorphine-naloxone dose, the hazard of relapse is 2 or 22% greater, respectively (HR = 1.02 per 1 mg increase in dose, 95% CI: 1.01, 1.03, $p < 0.001$). The VIF of included variables ranged between 1.02 and 2.04, thus ruling out multi-collinearity. See **Table 2**. The results were unchanged in a sensitivity analysis conducted within cannabis users, assessing the association between daily cannabis use and time to relapse, compared to non-daily use, while adjusting for the same covariates [data not shown].

Kaplan–Meier estimates: Association between cannabis use and relapse

Unadjusted Kaplan–Meier curves reveal that cannabis users have a trend towards shorter time to relapse, but that this association is not statistically significant ($p = 0.380$). Please see **Figure 2**. The log-rank test remained statistically non-significant in a sensitivity analysis amongst cannabis users, assessing association between daily cannabis use and relapse, compared to non-daily cannabis use [data not shown]. This is consistent with the findings of the multivariable-adjusted Cox model above.

Sensitivity analysis: Handling of censored data

Of the 254 (55%) with no documented relapse episodes, 245 were right censored and 9 were interval censored. Of the 245 participants who were right censored, 148 were censored due to completing the 12 months follow-up (study end), 18 were transferred to another provider, 11 completed treatment and were discharged from the clinic, and 8 were incarcerated. We consider these participants to be censored for non-informative reasons. The remaining 60 participants who were right censored, and 9 who were interval censored, were lost to follow-up as they stopped attending their clinic appointments. It may be argued that these participants who are lost to follow-up have relapsed, and as such, we conducted a sensitivity analysis whereby we assumed that all 69 participants who were censored for having withdrawn from treatment had relapsed at the time of censoring. The association between cannabis use and time to relapse remained non-significant in this multivariable-adjusted Cox regression analysis (HR = 0.96, 95% CI: 0.76, 1.22, $p = 0.755$). The log-rank test comparing unadjusted survival times stratified by sex also indicated no statistically significant difference in the time to relapse between cannabis users and non-users ($p = 0.557$). The association between time-to-relapse and the remainder of the predictors assessed remained unchanged from the primary analysis, with the exception of employment status whereby those who were employed had a 25% reduction in the hazard of relapse compared to those who were unemployed (HR = 0.76, 95% CI 0.58, 0.98, $p = 0.031$).

TABLE 1 Baseline participant characteristics.

Participant characteristic	Total (n = 466)	Relapsed (n = 212)	Not relapsed (i.e., censored, n = 254)	P-value
Mean (SD)				
Age (years)	38.59 (10.73)	38.32 (10.44)	38.82 (10.99)	0.620
Time on treatment (months)	34.94 (33.32)	34.76 (37.22)	35.10 (31.77)	0.916
Buprenorphine dose (milligrams)	13.48 (13.35)	16.71 (16.80)	10.79 (8.71)	<0.001
***N* (%)**				
Female	215 (46.14)	98 (46.23)	117 (46.06)	0.972
Cannabis user	225 (48.28)	107 (50.47)	118 (46.47)	0.388
Married	144 (30.90)	65 (30.66)	79 (31.10)	0.918
Employed	185 (39.70)	74 (34.91)	111 (43.70)	0.053
Injection drug use	49 (10.52)	37 (17.45)	12 (4.72)	<0.001
Illicit benzodiazepine use	29 (6.22)	17 (8.01)	12 (4.72)	0.143

Discussion

Our study identifies several predictors of opioid relapse for patients receiving buprenorphine-naloxone therapy, one of the first-line agents for OUD. While relapse in any substance use disorder is an important outcome, it is particularly relevant in OUD wherein patients lose tolerance to opioids within days of stopping use and are at significantly heightened risk of overdose with relapse to smaller amounts of opioids. Although buprenorphine is known to have affinity for the mu-opioid receptors and therefore helps maintain one's tolerance to opioids, the level of tolerance depends on the plasma concentration level and it is not known how this equates to tolerance to fentanyl—a synthetic opioid with much higher potency (28). Identifying patients at higher risk of relapse is therefore an integral aspect of harm reduction for managing patients with OUD, as we know that over 90% of opioid overdose deaths are unintentional (4, 29). In our study, we find that participants who inject drugs or are on a higher dose of buprenorphine-naloxone have a significantly higher hazard of relapse at any point in time, whereas being in treatment for more than two years is associated with a lower hazard of relapse. Our findings also indicate that cannabis use does not have a significant association with relapse to opioid use and we could not show protective effect of cannabis in this study amongst participants receiving buprenorphine-naloxone for OUD, even after adjusting for other clinically important variables.

We find that participants who inject drugs and those who are in treatment for a shorter period of time have a higher hazard of relapse at any point in time. This is likely explained by the fact that opioids have higher bioavailability when injected intravenously and intravenous use is typically an indicator of more severe OUD as well as poorer outcome (23). Similarly, the longer one is in treatment, the more stable they are likely to be. Thus it is expected that individuals who are in treatment for a shorter period of time would be more likely to relapse (5, 10). Lastly, individuals with more severe OUD, including those who inject drugs, often require higher doses of buprenorphine-naloxone. As such, it once again seems plausible that the individuals with higher doses had a higher hazard of relapse due to them having a more severe OUD, necessitating the higher dose of treatment in the first place. This is consistent with prior research (5, 10).

Our findings add to the available literature investigating the association between cannabis use and OUD. Emerging evidence suggests that cannabis may serve as a harm

TABLE 2 Multivariable Cox regression analysis: Predictors of relapse amongst patients receiving buprenorphine-naloxone for OUD (N = 466).

Variable	Hazard ratio	95% CI	P-value
Cannabis use	1.03	0.78, 1.36	0.835
Female	0.89	0.67, 1.19	0.431
Age (years)	1.00†	0.98, 1.01	0.697
Currently employed	0.76	0.57, 1.02	0.069
Married	1.01	092, 1.10	0.896
Injection drug use	2.61	1.74, 3.91	<0.001
Amt. of last buprenorphine-naloxone dose (milligrams)	1.02†‡	1.01, 1.03	<0.001
Illicit benzodiazepine use	1.42	0.83, 2.41	0.200
Time on treatment*			
- > 12 months and ≤ 24 months	1.04	0.69, 1.58	0.837
- > 24 months and ≤ 36 months	0.56	0.34, 0.92	0.021
- > 36 months	0.63	0.40, 0.98	0.041

†Hazard ratio calculated per one unit change of independent variable.
‡HR = 1.22 per 10 mg increase in buprenorphine-naloxone dose.
*Compared to ≤12 months.

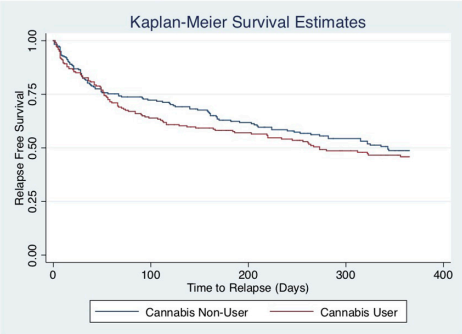

FIGURE 2
Kaplan–Meier curves by current cannabis use. The y-axis and x-axis labels are probability of survival and time until relapse (days), respectively. The log-rank test reveals that the survival distribution between those who currently use cannabis and those who do not is not statistically different (chi-square: 0.77, p = 0.3804).

reduction strategy to mitigate opioid consumption, as the active component delta-9-tetrahydocannabinol (THC) may amplify the analgesic effects of consumed opioids as well as trigger endogenous opioid release (30–33). However, there is substantial heterogeneity in the evidence to support this association or mechanism of action (13–15). Similar to our findings, a cross-sectional analysis of 777 patients receiving methadone maintenance therapy for OUD found that cannabis use was not associated with illicit opioid use during treatment (14).

The study results may be impacted by the missing data on a number of individuals. As discussed above, 254 individuals were censored, of which 69 could have been informative censoring as they dropped out of treatment at some point during follow-up. In order to address this, we used the worst-case scenario imputation method, whereby we assumed that these 69 individuals relapsed at the time of drop out. This analysis yielded a similar finding, that cannabis use is not protective against relapse to opioids, highlighting the robustness of our findings.

Our findings are strengthened by the fact that all individuals who were censored were followed up and the timing as well as reason for censoring were documented. This allowed us to more reliably make a judgment regarding informative censoring, so as to conduct the appropriate analyses discussed above. Another strength of our study is that our outcome, time to relapse, is objective on the basis of a positive urine toxicology screen, and that it is collected on a weekly to biweekly basis, providing a relatively accurate timing of relapse. One limitation of this study is that it is certainly possible for an individual to have relapsed prior to enrolment into the study. These individuals are not necessarily excluded, or left truncated, however, as long as their urine toxicology screen at study enrollment was negative for illicit opioids. Given we are interested in time-to-relapse, individuals who are actively using illicit opioids while on OAT are not part of our study population. It is not possible for us to know whether these individuals had ever achieved a period of sobriety and then relapsed (thus left truncated), or never achieved a period of sobriety to begin with (thus not part of our target study population). Nonetheless, only 22 participants had a urine toxicology screen that was positive for illicit opioids at baseline, of which only a fraction represent true relapses, thus would be unlikely to have biased our results (see **Figure 1**). Lastly, another limitation is the fact that time origin for this study is time of study enrolment, whereas patients could have been receiving treatment for varying periods of time. We have attempted to mitigate this by adjusting our model for length of time on treatment.

Taken together, our study identifies that there is neither a positive nor protective association between cannabis use and time-to-relapse among patients receiving buprenorphine-naloxone for OUD. The majority of research evaluating cannabis use and outcomes of patients receiving opioid agonist therapy has focused on illicit opioid use and retention in treatment as study outcomes. This is the first study, to our knowledge, to investigate its impact on time-to-relapse. Relapse is an important outcome due to the serious implications associated with loss of tolerance and risk of overdose, as well as the fact that abstinence from opioid use is what patients consider to be the most important outcome of treatment for OUD (34). Our study calls upon further research to investigate the association between cannabis use and opioid use so as to optimize treatment outcomes, especially as the prevalence of cannabis use continues to rise (35). Moreover, we identified that patients who inject drugs, are on higher doses of buprenorphine-naloxone, or have been in treatment for less time have a higher hazard of relapse. More stringent monitoring during treatment may be warranted to mitigate relapse risk amongst these patients, and future research is needed to further investigate these associations and replicate our findings.

Conclusion

We found that cannabis use was not protective against relapse to opioid use in patients receiving buprenorphine-naloxone for OUD. We identified that individuals who inject drugs drug users, are on higher doses of buprenorphine-naloxone, or have been in treatment for less than 2 years have a higher hazard for relapse. The presence of such factors may thus warrant closer patient follow-up and more stringent treatment protocols to mitigate risk of relapse and potential overdose. Future research aimed at delineating the potential protective

or negative consequences cannabis use may have on treatment outcomes for patients with OUD is recommended.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Hamilton Integrated Research Ethics Board. The participants provided their written informed consent to participate in this study.

Author contributions

LN and ZS conceived the research question and protocol. NS, AH, and JH collected participant data for the study. LN, NS, and JH formatted and extracted the relevant data for the study. LN, LT, and ZS conducted the study analyses. All authors contributed equally to the writing and revision of the manuscript and approved the final version of the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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OPEN

The Role of Cannabis Use in Suicidal Ideation Among Patients With Opioid Use Disorder

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Objectives: Cannabis use is associated with suicide risk in the general population; however, it is unknown if this association is also present in patients with opioid use disorder (OUD). The purpose of this study is to investigate the association between cannabis use and suicidal ideation in patients with OUD.

Methods: We conducted a multivariable logistic regression analysis to assess the association between cannabis use and suicidal ideation, amongst a large cohort of patients with OUD. Current cannabis use and suicidal ideation over the past 30 days were obtained by self-report.

Results: Cross-sectional data from 2335 participants with OUD were included in the analysis, of whom 51% report current cannabis use. We found a positive association between cannabis use and suicidal ideation (OR = 1.41, 95% CI 1.11, 1.80, $P = 0.005$). We found that men (OR = 1.84, 95% CI 1.44, 2.35, $P < 0.001$), younger individuals (OR = 1.02, 95% CI 1.01, 1.03), $P = 0.004$), and that those with more symptoms of anxiety or depression (OR = 1.16, 95% CI 1.15, 1.18, $P < 0.001$) were more likely to report suicidal ideation.

Conclusions: Cannabis use is associated with a heightened propensity for suicidal ideation amongst patients with OUD, who are already a high-risk population. Further research into the potential harms of cannabis use in this population is required given the prevalence of its use and potential benefits in mitigating opioid withdrawal.

Key Words: cannabis, opioid use disorder, suicide

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The life expectancy amongst Canadians did not rise between 2016 to 2017 for the first time in over 3 decades.[1] This is despite the fact that Canadians aged 55 to 89 are living longer.[1] Statistics Canada reports reveal that advancements in healthcare, contributing to the observed longevity of older Canadians, have been offset by the increased rate of death amongst young adults, especially men, between the ages of 20 to 44.[1] This alarming rise was linked to the opioid crisis, and the increased rate of both accidental and intentional opioid overdose within this age group.[1]

Cannabis use has repeatedly been shown to be associated with a heightened propensity for suicidal behavior in the general population.[2–4] In fact, studies have found that those who use cannabis are more than twice as likely to attempt suicide compared to those who do not use cannabis.[2–4] Amongst those with opioid use disorder (OUD), a population already at a heightened risk for suicidal behavior, concurrent cannabis use is reported by 11.2% to 78.6% of individuals.[5] Given the recent legalization of cannabis in Canada, amid the opioid crisis, we are interested in exploring the association between cannabis use and suicidal ideation amongst patients with OUD. This is especially important given emerging evidence that cannabis use may serve as a harm reduction strategy in the management of OUD and opioid withdrawal, though this approach is based on conflicting findings.[5–7] Proposed mechanisms include the synergistic effect of delta-9-tetrahydrocannabinol (THC), the psychoactive component of cannabis, on amplifying the analgesic effect of opioids, and the ability of cannabinoids to increase endogenous opioid release.[8–10] We hypothesize that cannabis use would be associated with an increased risk of suicidal ideation in this population.

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METHODS

Study Design

We conducted a cross-sectional analysis of data obtained from an ongoing prospective cohort study, titled Pharmacogenetics of Opioid Substitution Treatment Response (POST). Data for this study were collected from 30 clinical sites across the province of Ontario, Canada between May 2018 and February 2020. The protocol for this study has previously been described.[11] In summary, it is a prospective investigation aimed to delineate the association between genetic variants and concurrent substance use with opioid agonist therapy (OAT) outcomes. This study has been approved by the Hamilton Integrated Research Ethics Board (#4556) and funded by the Canadian Institutes for Health Research (CIHR). To be included in the present study, participants had to be at least 16 years of age, able to provide written informed consent, and be receiving OAT for OUD. All participants underwent a baseline interview with trained research personnel whereby baseline demographic, medical and treatment information were obtained.

OUD was diagnosed as per the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). Suicidal ideation was obtained through self-report as part of the Maudsley Addiction Profile (MAP) at the baseline interviews, whereby participants were asked to rate how often they experienced suicidal ideation over the past 30 days, on the following 5-point scale: never, rarely, sometimes, often, and always.[12] Given that any suicidal ideation is problematic, we dichotomized the presence of suicidal ideation into no (never) or yes (encompassing all other responses). Current cannabis use (yes/no) was also obtained by self-report at the baseline interview. We have previously validated this to be a reliable measure, with 80% sensitivity and specificity compared to THC detection in urine toxicology screens.[6] Participants who reported current cannabis use were then asked how often they used cannabis: "everyday," "every other day," "once a week," "2 to 3 times a month." Total psychological health symptom score was measured based on the 10-item psychological health scale in MAP, which was originally derived from the anxiety and depression subscales of the Brief Symptom Inventory.[12] Our scale included 9 items, as we excluded suicidal ideation due to collinearity with our outcome.

Statistical Analysis

We used descriptive statistics to summarize participant demographic and baseline characteristics. Means and standard deviation were used for continuous variables, whereas counts and percentages were used for categorical variables. A multivariable logistic regression was used to assess the association between suicidal ideation and self-reported cannabis use (yes/no). The model was adjusted for the following clinically important covariates: age, sex, marital status, employment status, smoking status (tobacco), current alcohol use, and total psychological health symptom score. These characteristics are commonly adjusted for in the literature, and were chosen due to their clinical relevance or possible confounding.[13–16] Goodness of fit was assessed using the Hosmer-Lemeshow test and McFadden's pseudo R^2.[17,18]

A secondary analysis was also conducted evaluating whether frequency of cannabis use was associated suicidal ideation. Our team has previously shown that amongst a different sample of patients with psychiatric comorbidities, more frequent cannabis use was associated with a higher risk of suicide attempt in men, but not women.[13] We measured frequency of cannabis use as a binary variable, categorized into daily use or less than daily use. All analyses were performed using STATA version 13.0.[19]

We followed the Strengthening the Reporting of Observation Studies in Epidemiology (STROBE) checklist for reporting the study findings.[20]

RESULTS

Participant Characteristics

Amongst the 2342 participants eligible for our study, 6 were excluded for having missing values in one or more of the variables analyzed, and one was excluded for being the only intersex participant. Please see Figure 1 for participant inclusion diagram. The average age of participants was 39.3 years (SD = 10.9), and 56% were male. Approximately half the participants reported current cannabis use, 68% of whom reported daily use. Twenty-four percent of participants who use cannabis endorsed suicidal ideations in the past 30 days, compared to 17% of those who do not use cannabis. Overall, 216, 178, 56, and 31 participants reported experiencing suicidal ideation rarely, sometimes, often, and always, respectively. Please see Table 1 for additional participant characteristics.

Primary Analysis: the Association Between Cannabis Use and Suicidal Ideas

Factors significantly associated with suicidal ideation in this sample included cannabis use (odds ratio [OR] = 1.41, 95% confidence interval [CI] 1.11, 1.80, $P = 0.005$) and male sex (OR = 1.84, 95% CI 1.44, 2.35, $P < 0.001$). Furthermore, we found that those who endorsed more symptoms of anxiety and depression were at higher risk of reporting suicidal ideation, such that every point increase in their psychological symptom score was associated with a 16% increase in the likelihood of reporting suicidal ideation (OR = 1.16, 95% CI 1.15, 1.18, $P < 0.001$). We also found that for every year increase in age, the odds of reporting suicidal ideation in the past 30 years dropped by 2% (OR = 0.98, 95% CI 0.97, 0.99,

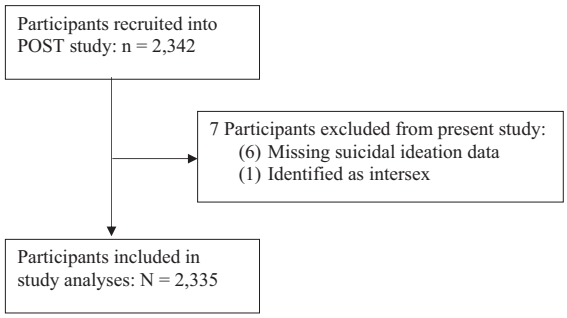

FIGURE 1. Flow chart of participant inclusion.

TABLE 1. Baseline Participant Characteristics (n = 2335)

	Total (n = 2335)	Participants Reporting Suicidal Ideation in Past 30 d (n = 481)	Participants Denying Suicidal Ideation in Past 30 d (n = 1854)
Participant Characteristic	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**
Current age (yrs)	39.3 (10.9)	37.6 (10.6)	39.7 (10.9)
	N (% of total)	**N (% of Participants Reporting Suicidal Ideation)**	**N (% of Participants Denying Suicidal Ideation)**
Sex			
Male	1300 (55.7)	276 (57.4)	1024 (55.2)
Female	1035 (44.3)	205 (42.6)	830 (44.8)
Employed			
No	1566 (67.1)	367 (76.3)	1199 (64.7)
Yes	769 (32.9)	114 (23.7)	655 (35.3)
Marital status			
Married or living with partner	680 (29.1)	117 (24.3)	563 (30.4)
Other	1655 (70.9)	364 (75.7)	1291 (69.6)
Cannabis use			
No	1145 (49.0)	196 (40.8)	949 (51.2)
Yes	1190 (51.0)	285 (59.3)	905 (48.8)
Frequency of cannabis use			
Daily use	805 (34.5)	185 (64.9)	620 (68.6)
Less than daily use	384 (16.4)	100 (35.1)	284 (31.4)
Current smoker (tobacco)			
Yes	1870 (80.1)	396 (82.3)	1474 (79.5)
No	465 (19.9)	85 (17.7)	380 (20.5)
Current alcohol use			
Yes	1470 (63.0)	195 (40.5)	670 (36.1)
No	865 (37.0)	286 (59.5)	1184 (63.9)
OAT			
Methadone	1848 (79.1)	375 (78.0)	1473 (79.4)
Suboxone	484 (20.7)	103 (21.4)	381 (20.6)
Other	3 (0.13)	2 (0.42)	1 (0.05)

$P = 0.004$). Please see Table 2 and Figure 2 for the full results. Both the Hosmer-Lemeshow test ($P = 0.0691$) and McFadden pseudo R^2 (pseudo $R^2 = 0.2283$) revealed adequate model fit.

Secondary Analysis

We assessed the association between daily cannabis use and suicidal ideation, compared to less than daily cannabis use. Participants who denied current cannabis use were excluded from this analysis (n = 1145), and 1 participant was excluded from this analysis for not reporting frequency of use, rendering 1189 participants eligible for this analysis. We found that there is no association between frequency of cannabis use and suicidal ideation (OR = 0.89, 95% CI 0.64, 1.23, $P = 0.490$). This remained true when we analyzed men and women in our sample separately (data not shown).

TABLE 2. Multivariable Logistic Regression Analysis: The Risk of Suicidal Ideation in Patients With OUD (n = 2335)

Covariates	Odds Ratio (95% CI)	P
Cannabis use*	1.41 (1.11, 1.80)	0.005
Men	1.84 (1.44, 2.35)	<0.001
Married or common law	1.03 (0.78, 1.34)	0.849
Employed	0.87 (0.66, 1.14)	0.297
Age	0.98 (0.97, 0.99)	0.004
Psychological symptom score	1.16 (1.15, 1.18)	<0.001
Current smoker (tobacco)	0.90 (0.66, 1.21)	0.476
Current alcohol use	1.04 (0.82, 1.32)	0.765

*Cannabis use here is measured as dichotomous variable (yes/no) based on self-report.

DISCUSSION

Our study reveals that amongst a large cohort of participants with OUD on OAT, any cannabis use, regardless of frequency of use, is associated with a heightened propensity for endorsing suicidal ideation in the past month. We also find an increased risk for reporting suicidal ideation among men, younger individuals, and those who endorse more symptoms of anxiety and depression.

The rate of suicidal ideation in the past 3 months (20.6%) in our study sample is 10 times the yearly rate of suicidal ideation amongst adults in developed countries such as the United States and Germany according to data from the World Health Organization.[14] This is an anticipated finding given the established increased risk of suicidal behavior, including ideations, attempts, and completed suicide, associated with substance use disorders.[2,21,22] A systematic review of 12 studies on this topic found similar results, whereby those with OUD were 14 times more likely to die by suicide compared to the general population.[21] Given the high risk of suicide in the context of OUD, we investigated whether cannabis use influences the risk of suicidal ideation in patients with OUD. We identified that in addition to the baseline risk that is expected in this population, cannabis use contributes to an increased risk of suicidal ideation, consistent with what is typically seen in the general population. We also find that

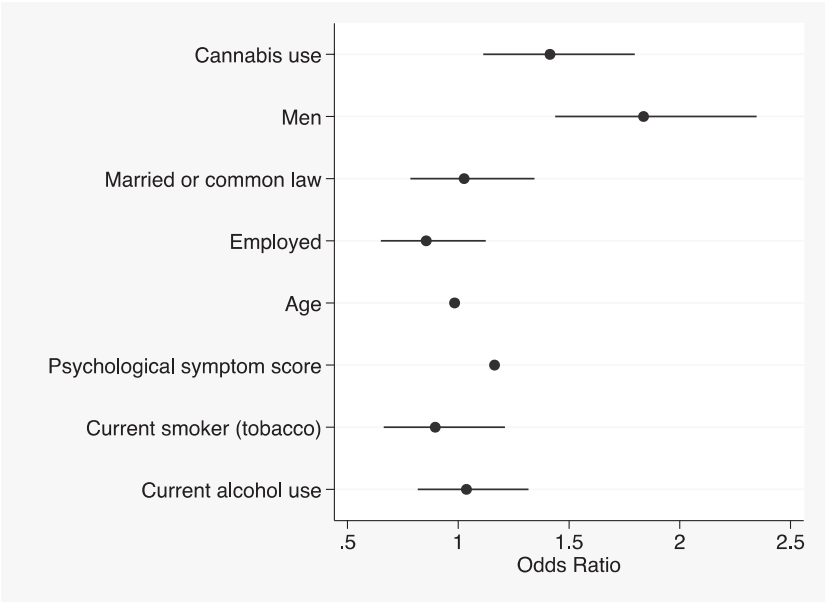

FIGURE 2. Forest plot of multivariable regression analysis: The risk of suicidal ideation in patients with opioid use disorder (n = 2335).

men, younger individuals, and those with a higher psychological symptoms score are at higher risk for suicidal ideation. These are important findings, and ones that may help in managing this patient population by providing more comprehensive assessments and psychiatric interventions to reduce the risk of suicide in this already high-risk population. Patients with OUD are at high risk for morbidity and mortality, and must therefore be monitored more closely. Studies have previously focused on identifying predictors of high-risk behaviors among patients with OUD, such as intravenous drug use and concurrent substance use, to allow healthcare workers to more closely monitor these individuals.[23–25] Our study finds that patients who use cannabis may be amongst this high-risk group. With the recent legalization of cannabis use in Canada, we anticipate cannabis use rates may increase thus potentially leading to adverse outcomes in the growing opioid crisis, such as increased suicidal behavior.

Our findings also provide a different profile of risk factors for suicidal ideation in patients with OUD compared to the general population or those with other psychiatric disorders, calling upon a paradigm shift in thinking about these risk factors, and how they may not be homogenous across all settings. We find that men report a higher rate of suicidal ideation compared to women. This is contradictory to what is reported in the general population.[14,15] Whereas among the general population, as well as those with OUD, men die by suicide at higher rates than women, women typically have higher rates of suicidal ideation.[14,15,21] Although men in our sample reported cannabis use at significantly higher rates than women (55% and 46%, respectively), rerunning our analysis amongst those who denied cannabis use rendered our results unchanged (data not shown). However, women did score significantly higher on the psychological symptom score, and it is only after adjusting for this that men were found to be at significantly higher risk of suicidal ideation (data not shown). Therefore, while women generally endorse more suicidal ideation and are at higher risk for mood disorders, both of which are likely interrelated, we found that after adjusting for depressive and anxiety symptoms, men with OUD were at higher risk of suicidal ideation regardless of cannabis use.[14,15,21] Identifying drivers for this difference is beyond the scope of this study, but one that should be further explored.

We find that frequency of cannabis use is not associated with suicidal ideation. We hypothesize 2 possible reasons. Firstly, it is possible that the previously shown detrimental consequences of heavier cannabis use on suicidal behavior is counterbalanced by the possible perceived effects of cannabis in managing withdrawal symptoms and augmenting the effects of opioids, as is seen in some studies.[2,7,26] Management of these uncomfortable symptoms may be associated with a sense of improving quality of life, thus compensating for the heightened risk of suicide ideation that has otherwise been seen with heavier cannabis use.[2,7,13,26] Second, we note that our study sample is already at a 10-fold increased risk of endorsing suicidal ideation when we compare the point prevalence in our sample (3 months) compared to the general population point prevalence (1 year). Therefore, it may be that the added risk of more frequent suicide ideation associated with heavier cannabis use that is seen in other populations is not large enough to reach statistical significance in this population, where the baseline risk or event rate (suicidal ideations) is already much higher.[14]

Our current study findings are strengthened by our large cohort of participants with OUD, a significant proportion of

which report concurrent cannabis use and suicidal ideations. Our analyses were adjusted for known risk factors of suicidal ideation, including age, sex, and the presence of depressive and anxiety symptoms. Although this study's main limitation is the cross-sectional design of the analysis, prohibiting us from establishing causality, we attempted to minimize this limitation by identifying current cannabis use, suicidal ideation, and psychological symptoms in the same, recent time frame (past 30 days). Additionally, although suicidal ideation may be considered a risk factor for suicide attempt, which in turn increases the risk of dying by suicide, studying death by suicide in our study sample would provide superior evidence.[27–29]. However, to address the association between cannabis use and death by suicide, we would require an even larger sample given the small event rate and additional data sources to adjudicate the cause of death as suicide versus unintentional opioid overdose, for example. A retrospective analysis of 6800 adults revealed that suicidal ideation is associated with a 123 times increase in the odds of attempting suicide within 1 year (OR = 123.1, 95% CI 92.9, 162.9), rendering suicidal ideation a suitable surrogate outcome.[27] Nonetheless, suicidal ideation itself poses significant harms to mental and physical well-being, aside from completed suicide, making it an important outcome. Furthermore, we defined cannabis use based on self-report for past 30 days. We have previously shown that self-reported cannabis use highly correlates with urine drug screen, with 80% sensitivity and specificity.[6] It is also a commonly used modality to assess for cannabis use, given that THC may be detected in urine as late as 30 days after last use and therefore may not reflect current use.[30,31] Lastly, participants had not undergone formal psychiatric interviews to ascertain a diagnosis of depression and anxiety. However, we used data collected through the psychological health component of the MAP, which is a validated tool to assess for symptoms of anxiety and depression that is derived from the Brief Symptom Inventory, and has previously been used for this purpose.[12,32]

Future research on individuals with OUD followed longitudinally through health administrative databases would be ideal in overcoming these limitations, and identifying a possible causal association between cannabis use and suicidal behavior (ideas, attempts, and death by suicide). Additionally, exploring whether this association varies by the severity of opioid use and the opioid of choice may further help delineate the effects of cannabis use on patients with OUD. As further research aims to delineate the potential therapeutic benefits of cannabis in managing opioid withdrawal and its synergistic effects with opioids, it is important we gain a clearer understanding of its potential risks in this patient population. Additionally, with recent legalization and potential increase in recreational cannabis use in Canada, among other countries where legalization has been instated or considered, this is an especially important topic that requires ongoing assessment.

CONCLUSIONS

Amongst a large cohort of participants with OUD, we find that cannabis use, regardless of frequency of use, is associated with a 40% increase in the odds of endorsing suicidal ideation. Unlike the general population, we find that men with OUD are at higher risk of endorsing suicidal ideation compared to women. Our data highlight a high-risk population within an already at-risk group. Our results should be used to inform potential recommendations in the use of cannabis as a harm reduction strategy for OUD, as well as guide healthcare providers in risk assessment of patients for psychiatric assessment and follow-up if indicated.

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