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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

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.

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,
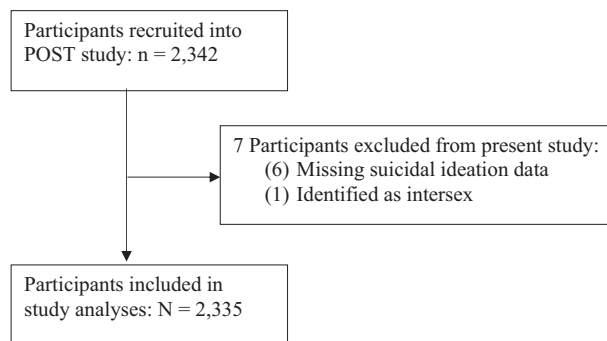

FIGURE 1. Flow chart of participant inclusion.

TABLE 1. Baseline Participant Characteristics (n = 2335)

Participant Characteristic	Total (n = 2335) Mean (SD)	Participants Reporting Suicidal Ideation in Past 30 d (n = 481) Mean (SD)	Participants Denying Suicidal Ideation in Past 30 d (n = 1854) 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,

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.

1.23, $P = 0.490$). This remained true when we analyzed men and women in our sample separately (data not shown).
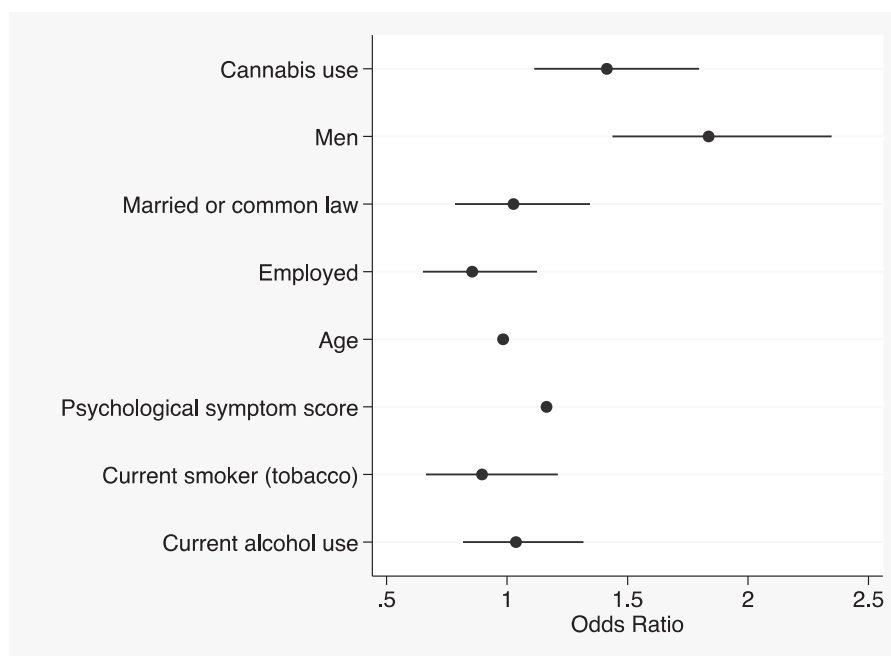
DISCUSSION

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 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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