PSYCHIATRIC COMORBIDITY IN PATIENTS WITH OPIOID USE DISORDER

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By

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LAY ABSTRACT

Background:

Opioid addiction has led to the deaths of tens of thousands of Canadians and many more people worldwide. Many individuals with opioid addiction also have other mental health problems that can be barriers to recovery from opioid use. Our current healthcare services are disconnected, and most people do not have access to treatments that can help with both addiction and other mental health problems at the same time. We conducted five studies looking at mental health problems within people who have opioid addiction. We focused on understanding risk factors, diagnoses, treatment, and use of mental healthcare services for individuals with opioid addiction and other mental health problems. Our findings provide new information on unmet mental health needs for people with opioid addiction. This information will help treatment programs, doctors, and policy makers better understand who needs more supports and consider how to improve services.

ABSTRACT

Objective: Opioid use disorder (OUD) remains a major public health problem within Canada and worldwide. Increasing our understanding of psychiatric comorbidity in this population is the focus of this thesis.

Methods: We used observational cohort data from two prospective studies of individuals with OUD receiving opioid agonist treatment (OAT). These data allowed us to examine risk factors for psychological symptoms and psychiatric comorbidities, to examine differences between youth and adults, and to assess the sensitivity and specificity of self-reported diagnoses against those made using a validated tool. We linked cohort data to Provincial health administrative data holdings to explore mental healthcare service use and associated costs.

Discoveries: This work provides new information on psychiatric comorbidity among individuals receiving treatment for OUD and carries implications that can inform future research to shape clinical care. The main conclusions drawn from this work were: 1) routine assessment of psychological symptoms, including suicidal ideation, in this population is warranted; 2) self-report of psychiatric disorders is not sufficiently sensitive to identify psychiatric comorbidity and other methods such as validated tools should be considered; 3) trauma and post-traumatic stress disorder are common in individuals with OUD and their impact may not be captured by solely measuring substance-related outcomes in treatment; 4) youth with OUD differ from adults in their health risk behaviours and psychiatric comorbidities and likely require distinct services and supports; and 5) outpatient non-substance-related mental healthcare for individuals with OUD is provided largely by primary care physicians for whom increased resources and training are needed, and emergency department visits and hospitalizations (which are costlier to the system) are not uncommon.

Conclusion: Psychiatric comorbidity is prevalent in OUD and integrated mental health and addictions treatment requires clinical and research attention. Future studies are needed to test interventions and build an evidence base to inform clinical management.

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LIST OF ABBREVIATIONS

OUD	Opioid use disorder
OAT	Opioid agonist treatment
MAT	Medication assisted treatment
MMT	Methadone maintenance treatment
GENOA	GENetics of Opioid Addiction
POST	Pharmacogenetics of Opioid Substitution Treatment
DSM	Diagnostic and Statistical Manual of Mental Disorders
CATC	Canadian Addiction Treatment Centers
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
MAP	Maudsley Addiction Profile
REDCap	Research Electronic Data Capture
IQR	Interquartile range
SD	Standard deviation
CI	Confidence interval
OR	Odds ratio
MINI	Mini International Neuropsychiatric Interview
SUD	Substance use disorder
SCID	Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders
CIDI	Composite International Diagnostic Interview
OCD	Obsessive compulsive disorder
PTSD	Post-traumatic stress disorder

ED	Emergency department
ICD-10-CA	International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Canada
ICES	Institute for Clinical Evaluative Sciences
RECORD	Reporting of studies Conducted using Observational Routinely-collected Data
NACRS	Canadian National Ambulatory Care Reporting System
DAD	Discharge Abstract Database
OMRS	Ontario Mental Health Reporting System
OHIP	Ontario Health Insurance Program
CRR	Cost rate ratio
MDD	Major depressive disorder
RR	Risk Ratio

DECLARATION OF ACADEMIC ACHIEVEMENT

I am the primary author of four of the five studies included in this thesis. I contributed substantially to each work by taking a lead role in conceiving the study question, writing the protocol, conducting the statistical analysis, interpreting findings, and drafting the manuscript. In the fourth study included in this Thesis, I supervised two medical students who are the primary authors of the work. In this supervisory role, I developed the study question, planned and performed the statistical analysis, and provided guidance to the students who drafted the manuscript. Detailed lists of author contributions are provided at the end of each study.

CHAPTER 1: Thesis Objectives

INTRODUCTION

The opioid crisis has been both a national and global experience: worldwide, an estimated 62 million people use medical or non-medical opioids, a prevalence that has doubled since 2010.[1] In North America, deaths related to opioids also doubled over the same time period.[1] Across Canada, 34,455 people died from opioid overdoses between January 2016 and September 2022, representing 20 deaths each day.[2] More than 26 million people in the world experience opioid use disorder (OUD),[3] a condition characterized by recurrent opioid use with increasing quantity or duration of use, inability to cut down or control use, interference with social obligations and activities, associated experiences of physical or psychological problems, or the development of tolerance and withdrawal.[4] OUD leads to a myriad of other harms beyond overdose and mortality, including increased transmission of communicable diseases[5], increased use of health care resources[6], economic burden and unemployment[7,8].

In response to the opioid crisis, public health efforts have focused on reducing opioid prescribing, addressing the toxic drug supply, and increasing available treatments and harm reduction strategies. Methadone, a full opioid agonist, and buprenorphine, a partial opioid agonist, are the two most commonly used medications in the management of OUD.[9] These medications are used to reduce opioid cravings and withdrawal to promote abstinence from ongoing opioid use. Opioid agonist treatments (OAT) have been shown to reduce medical and non-medical opioid use in systematic reviews of experimental studies.[10,11]. While benefits of these treatments undoubtedly exist, not all patients have favorable treatment trajectories and there are differences between individuals in course of illness and outcomes.[12,13] For the purpose of this thesis, the terms OAT and medication assisted treatment (MAT) are used interchangeably and refer to the same opioid agonist medications indicated in the treatment of OUD. This reflects shifts in the terminology used within the field over time. Methadone maintenance treatment (MMT) refers to OAT with methadone only.

Individuals with OUD have a high prevalence of comorbid mental health and substance use disorders.[14-16] In Canada, the presence of a co-occurring substance use disorder with another mental health disorder is commonly referred to as concurrent disorders. We have previously found that 80% of patients with OUD have at least one comorbid psychiatric disorder,[15] a figure cited similarly in other Canadian studies.[16] The most common psychiatric comorbidities include anxiety disorders and mood disorders.[14-16] Other substance use disorders occur in 80-90% of patients with heroin- and prescription-OUD.[17] Problematically, patients with psychiatric comorbidity are often excluded from experimental studies (i.e., randomized clinical trials) of OAT for OUD because of their comorbidity.[18] As a result, observational studies are relied upon to obtain information on these individuals, the course of their illness, and their outcomes in treatment. There exists little information on the mental healthcare needs of patients with OUD or evidence-informed guidance on their treatment. Clinically, there is a lack of integration between mental health and addictions services. Patients are often required to have one disorder treated before the other (sequential treatment), or treatment for substance use disorders takes place in a different setting with different treatment teams than treatment for other mental health disorders (parallel treatment). Sequential or parallel, rather than integrated, treatment continues to be the dominant approach to care.[19] In 2018, a Canadian national clinical practice guideline on the management of OUD was published.[9] This guideline provides direction on initiation and long-term management of OUD; there is little guidance provided on the management of psychiatric comorbidities in patients with OUD. Psychosocial treatments and support, in general, are recommended to be routinely offered, however the specifics are vague due to limited evidence for effective interventions in comorbid psychiatric disorders with OUD.[9] Despite their prevalence, there are knowledge gaps within the field of OUD regarding the management of comorbid psychiatric disorders from both clinical and health systems perspectives.

THESIS OBJECTIVES

The overarching objective of this thesis is to explore and understand psychiatric comorbidity in patients with OUD. This thesis is comprised of five papers examining different aspects of this issue including risk factors for psychiatric comorbidity, methods of diagnosis, management of comorbid disorders, association with OUD treatment outcomes, and healthcare service utilization patterns and costs. To accomplish this, we used data from two prospective observational cohort studies supplemented by routinely collected data from Provincial health administrative records.

The first paper, Chapter 2, explores psychological symptoms among patients enrolled in OAT as measured using a validated questionnaire. In this study, we aim to understand the relationship between psychological symptoms and patient sociodemographic and clinical characteristics. We also explore the association between psychological symptoms and opioid and non-opioid substance use during treatment. This paper is published in BJPsych Open.

In the second paper, Chapter, 3, we examine the issue of diagnosis of psychiatric comorbidities in this population. This study's primary questions were: 1) What is the validity of using self-reported psychiatric diagnoses for patients enrolled in OAT? and 2) Does patient self-report correctly identify the individual as having a psychiatric diagnosis or not having a psychiatric diagnosis? We determined the sensitivity and specificity of patient self-reported diagnoses compared to a validated, semi-structured, diagnostic interview. This paper has been published in BMC Psychiatry.

In the third paper, Chapter 4, we focus on trauma and post-traumatic stress disorder within individuals with OUD, and investigate their prevalence, management, and association with OUD treatment outcomes. This paper is published in BJPsych Open.

In the fourth paper, Chapter 5, we study the differences between youth younger than 25 years and adults older than 25 in their sociodemographic characteristics, substance use, treatment outcomes, and psychiatric comorbidities.

The fifth and final paper in this thesis, Chapter 6, uses observational cohort data linked with Provincial health administrative data holdings at ICES. We examine mental healthcare service utilization including acute, hospital-based care (emergency department visits and hospitalizations) and outpatient care and explore individual-level factors associated with mental healthcare. We also examine costs of this care to the healthcare system.

Concluding remarks to summarize the work of this thesis, discuss strength and limitations, and propose future research in this area are included in Chapter 7.

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CHAPTER 2: Exploring psychological symptoms and associated factors in patients receiving medication-assisted treatment for opioid-use disorder

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ABSTRACT

Background: Patients receiving treatment for opioid use disorder (OUD) may experience psychological symptoms without meeting full criteria for psychiatric disorders. The impact of these symptoms on treatment outcomes is unclear.

Aims: To determine the prevalence of psychological symptoms in a cohort of individuals receiving medication assisted treatment for OUD and explore their association with patient characteristics and outcomes in treatment.

Method: Data were collected from 2,788 participants receiving ongoing treatment for OUD recruited in two Canadian prospective cohort studies. The Maudsley Addiction Profile psychological symptoms-subscale was administered to all participants via face-to-face interviews. A subset of participants (n=666) also received assessment for psychiatric disorders with the Mini International Neuropsychiatric Interview. We used linear regression analysis to explore factors associated with psychological symptom score.

Results: Mean psychological symptom score was 12.6/40 (Standard Deviation [SD]=9.2). Participants with psychiatric comorbidity had higher scores than those without (mean 16.8 versus 8.6, $p<0.001$) and 31% reported suicidal ideation. Higher psychological symptom score was associated with female sex (B=1.59, 95% Confidence Interval [CI] 0.92-2.25, $p<0.001$), antidepressant-prescription (B=4.35, 95% CI 3.61-5.09, $p<0.001$), percentage of opioid-positive urine screens (B=0.02, 95% CI 0.01-0.03, $p<0.001$), and use of non-opioid substances (B=1.92, 95% CI 0.89-2.95, $p<0.001$). Marriage and employment were associated with lower psychological symptoms.

Conclusions: Psychological symptoms are associated with treatment outcomes in this population and the prevalence of suicidal ideation is an area of concern. Our findings highlight the ongoing need to optimize integrated mental health and addictions services for patients with OUD.

BACKGROUND

In recent years, public and scientific attention surrounding addictions has been dominated by the 'opioid epidemic', which remains an ongoing public health crisis across North America and increasingly in Europe.[1] High rates of opioid use, opioid use disorder (OUD) and opioid-related deaths persist despite efforts to reduce prescribing of opioid medications and increase available treatments and harm reduction strategies. The rise in opioid-related deaths, increasing by more than 20% on average between 2011 and 2016, has been most pronounced in the US, Canada, Sweden, Norway, Ireland, and England and Wales.[1] Medication assisted treatment (MAT) for OUD, including methadone, a full opioid agonist, and buprenorphine, a partial opioid agonist, have demonstrated benefits in the reduction of prescription and non-prescription opioid use;[2,3] however, not all patients have favorable outcomes in treatment.[4] Individuals with OUD have a high prevalence of comorbid psychiatric disorders including depression and anxiety.[5,6] These comorbidities have been associated with worse retention in treatment[7], opioid use,[5,6] and mortality.[8] Many patients may also experience psychological symptoms that do not meet full diagnostic criteria for psychiatric disorders but may compromise wellbeing or impair function nonetheless.[7]

The problem of psychological symptoms in patients receiving treatment for substance use disorders is one of significant complexity. It has long been acknowledged that individuals with substance use disorders have a high prevalence of other comorbid psychiatric disorders.[9,10] Psychological symptoms may also be "substance-induced" and occur secondary to a primary substance use disorder, or in the context of intoxication or withdrawal.[11,12] Numerous theories exist to explain the high rate of comorbidity including common underlying genetic predisposition, common neurobiological pathways, and diagnostic confounding.[12,13] The natural history of psychological symptoms during MAT, and the implications for treatment outcomes, are not definitively understood. Unfortunately, patients with psychiatric comorbidity are often excluded from experimental studies of MAT for OUD on the basis of their comorbidity.[14] Therefore, observational studies must be relied upon to obtain information on these patients and their course in treatment. There is an enduring need to optimize the integration of mental health and addictions services; parallel, rather than integrated, treatment continues to be the dominant conceptual framework and therefore the dominant approach to care.[15] Resources available in addictions treatment to address psychological or psychiatric comorbidity are often limited.[15] A better understanding of the psychological symptoms experienced by patients with OUD has the potential to inform clinical assessments, management of underlying comorbidity, treatment decision-making, and resource allocation.

OBJECTIVES

The objectives of this study are as follows: (a) to determine the prevalence of psychological symptoms in a cohort of patients receiving MAT for OUD; (b) to determine the prevalence of psychological symptoms among patients in this cohort with known comorbid psychiatric disorders versus those without psychiatric comorbidity; and (c) to explore the association between psychological symptoms and demographic and clinical characteristics, including treatment outcomes such as ongoing opioid and non-opioid substance use.

METHOD

Data

We used data from two large, prospective, cohort studies: the GENetics of Opioid Addiction (GENOA) study and the Pharmacogenetics of Opioid Substitution Treatment Response (POST) study. Study methods for the GENOA project have been previously described.[5,16] Briefly, data collection for the GENOA cohort occurred between 2011 and 2017, and information is available on 1,390 individuals receiving treatment for OUD across 20 outpatient MAT clinics within Ontario, Canada. Participants were eligible for study inclusion if they were at least 18 years old, diagnosed with OUD as per the Diagnostic and Statistical Manual of Mental Disorders (DSM), Fourth Edition criteria,[17] and enrolled in MAT for their OUD. At study entry, participants provided information on demographic characteristics, medical history, medications, and clinical information on their MAT medication, dose and duration in treatment. The POST study began recruitment in May 2018 from outpatient MAT clinics within Ontario, Canada and 1,769 participants were recruited as of June 2019. Inclusion criteria for this study were similar to that of the GENOA study: individuals diagnosed with OUD as per the DSM, Fifth Edition criteria,[18] and receiving MAT. Participants completed a similar baseline assessment including demographic and clinical information. Participants recruited to both studies were enrolled in ongoing MAT, for varying lengths of time, at the time of study recruitment. In both studies, participants were followed for 12 months and urine drug screens to assess for ongoing opioid or other substance use were conducted as per clinical protocol. All clinical sites included in the studies are run centrally by the same management teams through the Canadian Addiction Treatment Centres (CATC) and all follow the same treatment protocols. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. Ethics approval was obtained from the Hamilton Integrated Research Ethics

Board (GENOA project ID 11-056; POST project ID 4556), and all participants provided verbal and written informed consent.

Records from these two cohort studies were merged and duplicate enrolment was identified using patient name and birthdate. In the event of duplicate enrolment, data collected in the GENOA study were retained and the duplicate case from the POST study was removed. Duplicate enrolment in both studies affected 339 participants (Figure 1, study flow diagram). Participants were excluded from this study's main analyses if they were missing baseline data on psychological symptoms (Figure 1). This study is reported in accordance with the *Strengthening the Reporting of Observational Studies in Epidemiology* (STROBE) guidelines.[19]

Study instruments and measures

The primary objective of this study was to determine the prevalence of psychological symptoms in patients receiving MAT for OUD. At study entry all participants were administered the Maudsley Addiction Profile (MAP),[20] a validated questionnaire examining individuals' self-reported substance use, physical and psychological symptoms, and social functioning in the last 30 days. Psychological symptoms of depression and anxiety are measured by 10 items rated on five-point Likert scales and participants are asked to report the frequency of symptoms including tension, fear, nervousness, panic, hopelessness, worthlessness, anhedonia, loneliness, and suicidal ideation they have experienced in the past month.[20] Each item is rated as occurring "never", "rarely", "sometimes", "often", or "always".[20] A total score for psychological symptoms is calculated by adding the item scores for a total symptom score that can range from 0 to 40.[20] The psychological symptoms subscale is derived from the Brief Symptom Inventory,[21] which is derived from the Symptom Check List 90.[22] All participants received face-to-face interviews with a research assistant and the data were entered into the Research Electronic Data Capture (REDCap) tool.[23,24] The first 666 participants consecutively recruited into the GENOA study received extensive assessment of psychiatric comorbidity using the MINI International Neuropsychiatric Interview version 6.0.[25] This allowed for identification of comorbid psychiatric disorders including mood disorders, anxiety disorders, psychotic disorders, substance use disorders, and eating disorders. The MINI was not administered to subsequently recruited participants due to the time burden of administration.

Assessment of treatment outcome was conducted using urine drug screen results to identify continued opioid use. An opioid-positive urine screen was defined as a non-methadone- or buprenorphine-positive opioid screen. We were therefore able to calculate the percentage of opioid-positive urine screens for each participant. As participants report on psychological symptoms in the past 30 days at time of study entry, we elected to examine urine drug screens also in the period prior to study entry. By doing so, the results of both psychological symptom assessment and urine drug screens were as close in time as possible. In the GENOA study, the results of urine drug screens were available for the 3-month interval prior to study entry and the mean number of urine drug screens was 16. In the POST study, the results of urine drug screens were available for up to 12 months prior to study entry and the mean number of urine drug screens was 45. To further assess treatment outcome, we examined also the percentage of non-opioid positive urine drug screens collected during the same period prior to study entry. This includes urine screens positive for amphetamines, benzodiazepines, and cocaine. Amphetamine- or benzodiazepine-positive urines were not counted for patients with confirmed amphetamine or benzodiazepine prescriptions in their medical chart. Urine drug screens were conducted as per routine clinical care at the CATC sites, typically at weekly or bi-weekly frequency, using the IMDx™ Prep assay[26] for morphine, oxycodone, fentanyl, cocaine, amphetamine, methamphetamine, diazepam, methadone metabolite and buprenorphine.

Analysis

Our first objective was to determine the prevalence of psychological symptoms in this study cohort. We used STATA version 15.1[27] (StataCorp LP, College Station, TX, USA) to conduct all statistical analyses. We present data on demographic characteristics and psychological symptoms using descriptive statistics with continuous variables summarized as means and standard deviations (SD) for normally distributed variables, and medians with interquartile range (IQR) for skewed data. Categorical variables were summarized as percentages. Our second objective was to assess the prevalence of psychological symptoms amongst patients with known comorbid psychiatric disorders identified using the MINI, who we compared to patients with no psychiatric comorbidity identified. Group differences were assessed using independent samples t-tests for continuous variables and chi-square tests for dichotomous variables.

Our third and final objective was to explore the association between participant characteristics and psychological symptoms. We constructed a linear regression model with total psychological symptom score (ranging from 0 to 40) as the dependent variable. Sociodemographic characteristics included as covariates in the regression analysis were selected based on previous research suggesting potential influence on psychological symptoms. These included: 1) age as older age has been associated with under-reporting of psychological symptoms;[28] 2) sex, due to known sex differences in mental health disorders and psychological patterns such as internalizing and externalizing;[29] 3) marital status, which has been demonstrated to confer mental health benefits for both men and women;[30] and 4) employment status, as unemployment has been established in numerous studies to impair mental health.[31] The clinical characteristics included as covariates in the regression model included: 1) type of MAT (i.e., methadone or buprenorphine), 2) duration in treatment, and 3) prescription of an antidepressant medication. Finally, we included the percentage of opioid-positive urine drug screens (continuous), and the presence of non-opioid substance use (dichotomous) as covariates in the model in order to assess the association between psychological symptoms and substance use during treatment, adjusting for the other aforementioned factors.

The linear regression model was constructed as described above. Model diagnostics were assessed to ensure that the assumptions for linear regression analysis were adequately met. This included testing for multicollinearity with variance inflation factor, testing for homoscedasticity by plotting residuals against fitted values, graphing residuals against a normal curve and assessing P-P and Q-Q plots for assessment of the normality of residuals. The level of significance for hypothesis testing was set at alpha = 0.05 for all analyses. Our sample size of 2,788 participants was sufficiently powered to conduct the analyses described above, such that there were at least 10 participants per covariate included in the model.[30] Finally, we conducted subgroup analysis by sex in light of increasing awareness that sex is associated with biological and social differences that contribute to differential health outcomes, which warrant understanding.

RESULTS

Demographic and clinical characteristics

Altogether, 2,788 participants met study inclusion criteria and were included in the analyses (Figure 1). Information on participant demographic and clinical characteristics is detailed in Table 1: males accounted for 57% of the cohort (n = 1,575), and participants' mean age was 38.5 years (SD = 11). The majority of participants held at least a high school diploma (n = 2,098; 75.3%) but were unemployed (n = 1,819; 65%). Methadone was the most commonly prescribed MAT (85%) and the median methadone dose was 65 mg per day (IQR = 60), while the median dose of buprenorphine was 12 mg per day (IQR = 8). In addition to their MAT medication, nearly 27% of participants were prescribed an antidepressant medication (n = 737). The median duration in treatment was 2 years (IQR = 4.42). In total, 37% of participants were abstinent from any ongoing opioid use, as measured by urine drug screens, for the 3 months prior to study entry. Individuals with ongoing opioid use had on average 30% of urine screens positive for opioids (SD = 29.3). Only 11% of participants were entirely abstinent from non-opioid substances (i.e., amphetamines, benzodiazepines, and cocaine).

Psychological symptoms

In the entire study sample of 2,788 participants, the mean total psychological symptoms score was 12.6 out of 40 (SD = 9.2; Table 2). Altogether, 92% of participants endorsed at least one psychological symptom present in the last 30 days (data not shown). The most commonly endorsed symptoms were feeling tense (80%), feeling no interest in things (70%), feeling lonely (66%), and feeling hopeless about the future (64%; Table 2). The mean total psychological symptoms score was lower in males compared to females (11.4, SD = 8.7 versus 14.1, SD = 9.5; $t = -7.5$, $p < 0.001$; data not shown).

Amongst the subset of 666 participants who received comprehensive assessment of psychiatric comorbidity using the MINI, 400 individuals (60%) were identified to have a comorbid mood, anxiety, psychotic, or eating disorder. We compared the prevalence of psychological symptoms in these participants, with the prevalence of psychological symptoms in participants identified not to have a psychiatric comorbidity (Table 2). The prevalence of every symptom was higher amongst those patients with psychiatric comorbidity (Table 2). The total psychological symptoms score was also significantly higher in patients with psychiatric comorbidity than those without (16.8 versus 8.6, $p < 0.001$; Cohen's d = -1.01, 95% CI -1.18 to -0.85). Notably, 31% of participants with psychiatric comorbidity endorsed thoughts of ending their life in the past 30 days, whereas 11% of participants who were not identified to have psychiatric comorbidity identified the same ($p < 0.001$). Overall, the prevalence of suicidal ideation was similar in males and females (22% versus 20%, $\chi^2 = 1.68$, $p = 0.195$; data not shown).

Factors associated with psychological symptom score

Higher psychological symptom score was associated with female sex, antidepressant prescription, ongoing opioid use, and use of non-opioid substances (Table 3). Female sex was associated with two points higher on the psychological symptom score, on average, adjusting for the other covariates ($B = 1.59$, 95% CI 0.92 to 2.25, $p < 0.001$). For each percentage point more of opioid-positive urine drug screens, psychological symptom score was associated with a 0.02 increase ($B = 0.02$, 95% CI 0.01 to 0.03, $p < 0.001$). Any use of non-opioid substances detected by urine drug screens was associated with about two points higher psychological symptom score, on average ($B = 1.92$, 95% CI 0.89 to 2.95, $p < 0.001$). Lower psychological symptom score was associated with younger age, ($B = -0.08$, 95% CI -0.11 to -0.05, $p < 0.001$), being married or in a common-law relationship ($B = -1.72$, 95% CI -2.43 to -1.02, $p < 0.001$), being employed ($B = -2.75$, 95% CI -3.45 to -2.05, $p < 0.001$), and treatment with buprenorphine ($B = -1.13$, 95% CI -2.06 to -0.02, $p = 0.017$; Table 3).

Subgroup analysis by sex resulted in similar findings to those of the primary analysis described above (Table 3). For both females and males, psychological symptom score was associated with age, marital status, employment, antidepressant prescription, and use of non-opioid substances (Table 4). The association between higher psychological symptom score and more ongoing opioid use appears to be present in females ($B = 0.04$, 95% CI 0.02 to 0.06, $p < 0.001$) but not in males ($B = 0.01$ 95% CI -0.003 to 0.03, $p = 0.134$; Table 3). Treatment with buprenorphine as compared to methadone was not associated with psychological symptom score in men ($B = -0.89$, 95% CI -2.08 to 0.30, $p = 0.141$), but showed a trend towards statistical significance in women ($B = -1.45$, 95% CI -2.93 to 0.03, $p = 0.054$; Table 3).

DISCUSSION

Main findings

In this large study involving two cohorts of patients receiving outpatient MAT for OUD, we found that the majority of participants reported psychological symptoms during treatment. Higher psychological symptoms were associated with worse treatment outcomes including more opioid use in women and use of non-opioid substances in both men and women. Our results highlight psychological symptoms as an area of need for patients enrolled in this treatment. These data contribute to a growing body of literature on the mental health of patients with OUD.

Comparison with findings from other studies

A challenge for situating our findings in the pre-existing literature is the considerable variation between studies in the measures used for the assessment of psychological symptoms. A systematic review by Fingleton et al. in 2015 examined changes in mental health during MAT and identified 19 different instruments used to measure psychological symptoms in the included studies.[33] This review concluded that mental health significantly improved in 14 out of 22 included studies though improvements were not always sustained.[31]

There are a handful of previous studies that examined psychological symptoms using the MAP with which our results can be compared.[34-37] In a small observational study of 15 patients beginning MAT for OUD, psychological symptoms were measured at baseline and following 8-weeks of treatment.[37] The authors found that the mean psychological symptoms score at baseline was 20.1, while at 8-week follow up this decreased to 13.[34] These findings are consistent with ours, seeing as patients in our study were enrolled in treatment for significantly longer than 8 weeks on average (and had a mean psychological symptom score of 12.6 out of 40). The most commonly reported symptoms were “feeling tense” and “feeling no interest in things”;[34] the same was the case in our study. We caution careful interpretation of specific items being more commonly reported as there is a possibility that the individual items reported more frequently reflect a property of the questionnaire itself, rather than symptoms experienced by patients, if these items are worded in a way that makes them more likely to be endorsed. Another observational study including 404 participants found a slightly lower prevalence of symptoms of anxiety and depression than those identified in our cohort.[35] For example, for the two most commonly reported symptoms, “feeling tense” and “feeling no interest in things”, rates in this study were 62-66% and 50-60% at study intake, respectively. Finally, two randomized controlled trials (RCT) also used the MAP to assess change in psychological symptoms during treatment.[36,37] The first study included 235 participants and found the mean psychological symptoms score at baseline to be 29.7 (SD = 7.7) with a reduction to 24 after 36 months of treatment.[37] The second RCT also identified “feeling tense” and “feeling no interest in things” as the most commonly reported psychological symptoms at baseline in a cohort of 45 patients receiving methadone treatment in a community setting.[36] This study also identified a slightly lower prevalence of these symptoms than that in our study: 58% and 56%, respectively, with decreases in prevalence to 53% and 54%, respectively, after 1 year of treatment.[36]

Interpretation of our findings

What level of psychological symptoms, as measured using the MAP, is clinically significant to impact functioning and require intervention is unknown. There are no defined standards for interpretation of the MAP or validation against clinical diagnosis of anxiety or depressive disorders. Our finding that individuals with confirmed psychiatric diagnoses had significantly higher psychological symptom scores than individuals without psychiatric comorbidity supports the suggestion that higher symptoms may have a clinical relevance. This finding suggests that intervention, whether psychological or pharmacological, may be warranted and raises questions about the services provided for managing psychological or psychiatric symptoms in MAT clinics. We also found an association between antidepressant prescription and increased psychological symptoms, suggesting that antidepressant treatment alone is insufficient to eliminate psychological symptoms, though it is certainly possible that without antidepressant treatment these individuals would have even higher psychological symptoms.

A troubling finding of this study was that 21% of participants reported suicidal thinking in the last 30 days. This rate was higher amongst participants with identified psychiatric comorbidity at 31%. Our findings are consistent with previous studies in patients with OUD that have documented suicidal ideation in about 20-25% of patients.[35, 36] In comparison, a study of substance-using patients in primary care (most with non-opioid substance use) found a 12.1% prevalence of past-month suicidal ideation.[38] Suicidal ideation is a significant concern in patients with OUD, a population in which rates of overdose and mortality are alarmingly high and increasing.[1] Recent US estimates indicate that more than 40% of suicide and overdose deaths in 2017 involved opioids[39] and rates of suicide by opioid overdose are likely under-estimated as it is difficult to assess intent in overdose deaths.[40] Opioids have high lethality in overdose, whether unintentional or intentional, and there is strong evidence that access to lethal means increases risk for suicide.[41] This points to a pressing need to identify and manage suicidal ideation in this high-risk population.

We found that treatment with buprenorphine was associated with lower psychological symptoms, as compared to treatment with methadone, though this finding did not hold in subgroup analysis by sex. There is no readily discernable biological explanation for this finding and its significance is unclear. Notably, Fingleton et al. identified tentative evidence to suggest methadone was less effective at improving mental health than other types of MAT.[33] It is possible that there are systematic differences between patients who end up on treatment with buprenorphine as compared to methadone that could explain the finding that they have less psychological symptoms. We examined differences in demographic characteristics in our participants with methadone compared to buprenorphine treatment and found no significant differences between in the groups in age (mean age 38.6 versus 37.7, $p = 0.133$), sex (57% versus 56%, $p = 0.876$), high school education (47% versus 44%, $p = 0.259$), or marital status (30% versus 32%, $p = 0.312$). In contrast, there was a significant difference between the two treatment groups in mean duration in treatment (methadone 4.2 years versus buprenorphine 1.8 years, $p < 0.001$) and ongoing opioid use (mean percentage of opioid-positive urine screens: methadone 20.1, buprenorphine 12.5, $p < 0.001$). Finally, the finding that employment and marital status was associated with a positive impact on psychological symptoms (i.e., lower symptoms) highlights the importance of supporting patients to achieve improvements in social functioning during treatment.

Strengths and limitations

This study is strengthened by its large sample size and multisite design which lends increased confidence in the results. The use of the MAP, a validated tool for assessment of symptoms in patients with substance use disorders, is an added strength. This study, like others, was susceptible to healthy user and volunteer biases, such that individuals with fewer psychological symptoms may have been more likely to participate. We have no way to explore this issue empirically. As is the case in all observational studies, we are unable to establish a causal relationship; whether a greater burden of psychological symptoms leads to increased substance use, or increased substance use causes a greater burden of psychological symptoms is unknown. The measurement of psychological symptoms in this study using the MAP[20] (derived from the Brief Symptom Inventory,[21] itself derived from the Symptom Check List 90[22]) does not capture the complete psychological profile of respondents, but rather focuses on anxiety and depression symptoms – a limitation of this study. However, the ability of the psychological symptoms subscale to discriminate between patients with psychiatric comorbidity as diagnosed by the MINI (higher psychological symptom scores) and those without psychiatric comorbidity (lower psychological symptom scores) as evidenced by a large effect size (Cohen's d = -1.01, 95% CI -1.18, -0.85) suggests that despite limitations, the measure discriminates between these groups of patients well.

This study is also limited by the assessment of psychological symptoms cross-sectionally. We note that the median duration in treatment was two years; whether these results generalize to patients newly starting MAT is unknown. We would hypothesize that patients newly starting MAT may be at greater risk of experiencing psychological symptoms in the context of possible opioid withdrawal, relapses to substance use, or under-treatment of comorbid psychiatric disorders in the initial stages of MAT. In contrast to this hypothesis, we found that longer time in treatment was associated with slightly higher report of psychological symptoms.

How well these results would generalize to settings outside of Ontario, Canada, to other settings in North America or to other areas of the world is unclear. In Canada, MAT primarily takes on a harm-reduction role, such that retention in treatment is not contingent on abstinence from opioid or other substance use. In this setting, concerns around patient factors that may be associated with ongoing opioid or polysubstance use is inherently heightened, particularly due to risks of opioid overdose and mortality.

This study focussed solely on one dimension of treatment outcome, namely substance use, as measured by urine drug screens. There are many other potentially important treatment outcomes that should be considered but fell outside of the scope of this study, including treatment retention, suicide-related behaviors, opioid overdose or death, and the use of psychiatric or emergency department services.

Directions for future study

Considering the notable prevalence and risks associated with suicidal ideation in this population, future research should explore the association between suicidal ideation and overdose, death and contact with psychiatric services. Whether different forms of MAT produce different outcomes with respect to psychological symptoms should also be investigated. Finally, future studies may wish to examine psychological symptoms over time and identify factors that influence their trajectory.

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Author Contribution

TR, AW, LT, DCM and ZS are responsible for the study concept and design. TR and ZS developed the methods and data analysis. TR wrote the first draft of the manuscript, and TR, AW, LT, DCM, and ZS contributed to writing and critically revising the final manuscript. All authors reviewed and approved the final manuscript.

FIGURES AND TABLES

Figure 1: Study flow diagram.

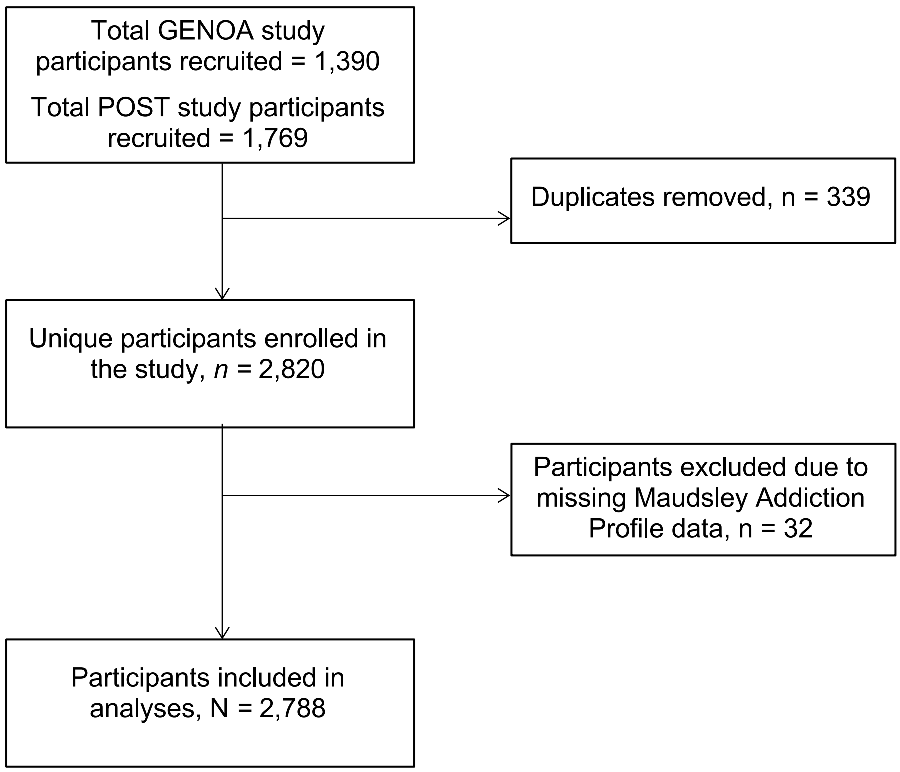

Table 1. Participant demographic and clinical characteristics (N = 2,788).

Characteristic	Statistics
Sociodemographic	
Age (years); mean (SD)	38.5 (11)
Male sex; *n* (%)	1575 (56.5%)
Caucasian ethnicity; *n* (%)	2207 (79.2%)
Married or common law; *n* (%)	840 (30.1%)
Education; *n* (%) Less than high school High school Post-secondary	 690 (24.8%) 1295 (46.5%) 803 (28.8%)
Unemployment; *n* (%)	1819 (65.2%)
Clinical	
Type of MAT Methadone Buprenorphine	 2369 (85%) 419 (15%)
Dose (mg / day); median (IQR) Methadone Buprenorphine	 65 (60) 12 (8)
Duration in treatment (years); median (IQR)	2 (4.42)
Number of opioid urine drug screens: mean (SD)	31.3 (24.2)
Opioid abstinence; *n* (%)	1031 (37%)
Percentage of opioid-positive urine drug screens amongst non-abstainers; mean (SD)	30.1 (29.3)
Abstinence from other substances; *n* (%)	317 (11.4%)
Percentage of positive urine drug screens amongst non-abstainers of other substances; mean (SD) Amphetamines (n = 229) Benzodiazepines (n = 559) Cocaine (n = 935)	 57.2 (35.4) 32.1 (29.6) 49.2 (34.7)
Antidepressant medication prescription; *n* (%)	737 (26.4%)

Table 2. Psychological symptoms (*N* = 2,788).

		Participants assessed for comorbid psychiatric disorders[a] (*n* = 666)			
Psychological Symptoms[b]	**Total sample** (*N* = 2,788)	**Psychiatric comorbidity**[c] (*n* = 400)	**No psychiatric comorbidity**[d] (*n* = 266)	**Test statistic**	***p***
Total score; mean (SD)	12.6 (SD = 9.2)	16.8 (8.9)	8.6 (6.9)	t = -12.79	< 0.001
Feeling tense; *n* (%)	2230 (80%)	372 (93%)	206 (77.4%)	χ^2 = 85.8	< 0.001
Suddenly scared for no reason; *n* (%)	1187 (42.6%)	230 (57.5%)	85 (32%)	χ^2 = 62.9	< 0.001
Feeling fearful; *n* (%)	1304 (46.8%)	252 (63%)	98 (36.8%)	χ^2 = 72.7	< 0.001
Nervousness or shakiness inside; *n* (%)	1741 (62.4%)	320 (80%)	139 (52.3%)	χ^2 = 92.5	< 0.001
Spells of terror or panic; *n* (%)	1224 (43.9%)	251 (62.8%)	78 (29.3%)	χ^2 = 84.9	< 0.001
Feeling hopeless about the future; *n* (%)	1795 (64.4%)	328 (82%)	148 (55.6%)	χ^2 = 85.4	< 0.001
Feelings of worthlessness; *n* (%)	1580 (56.7%)	292 (73%)	115 (43.2%)	χ^2 = 83	< 0.001
Feeling no interest in things; *n* (%)	1942 (69.7%)	332 (83%)	158 (59.4%)	χ^2 = 60.6	< 0.001
Feeling lonely; *n* (%)	1825 (65.5%)	323 (80.8%)	144 (54%)	χ^2 = 77.2	< 0.001
Thoughts of ending your life; *n* (%)	594 (21.3%)	123 (31%)	30 (11.3%)	χ^2 = 35.4	< 0.001

[a] A subset of participants received the MINI diagnostic interview to identify comorbid psychiatric disorders (*n* = 666).
[b] Each item in the MAP psychological symptoms subscale is assessed on a 5-point Likert scale ranging from "never" (score of 0) to "always" (score of 4) experiencing the symptom. In this table we present the frequency of scores of ≥1 for each symptom, indicating the presence of the symptom but not the intensity.
[c] Participants identified to meet criteria for a comorbid mood, anxiety, psychotic, or eating disorder using the MINI.
[d] Participants identified *not* to meet criteria for a comorbid mood, anxiety, psychotic, or eating disorder using the MINI.

Table 3. Multivariable model of demographic and clinical factors associated with psychological symptom score (N = 2,778).

	Primary analysis Total Sample			**Subgroup analysis Females**			**Males**		
Covariate	**Estimated Beta coefficient [B]**	**95% CI**	***p-value***	**B**	**95% CI**	***p-value***	**B**	**95% CI**	***p -value***
Age (years)	-0.08	-0.11, -0.05	<0.001	-0.08	-0.14, -0.03	0.002	-0.07	-0.11, -0.03	<0.001
Female Sex	1.59	0.92, 2.25	<0.001	-	-	-	-	-	-
Married	-1.72	-2.43, -1.02	<0.001	-2.84	-4.03, -1.65	<0.001	-1.25	-2.17, -0.34	<0.001
Employed	-2.75	-3.45, -2.05	<0.001	-2.24	-3.36, -1.13	<0.001	-2.72	-3.58, -1.86	<0.001
Buprenorphine	-1.13	-2.06, -0.02	0.017	-1.45	-2.93, 0.03	0.054	-0.89	-2.08, 0.30	0.141
Duration in treatment (years)	0.06	-0.02, 0.13	0.149	0.11	-0.01, 0.23	0.072	0.003	-0.10, 0.11	0.953
Antidepressant Prescription	4.35	3.61, 5.09	<0.001	4.08	2.98, 5.18	<0.001	4.61	3.60, 5.62	<0.001
Percentage of opioid-positive urine screens	0.02	0.01, 0.03	<0.001	0.04	0.02, 0.06	<0.001	0.01	-0.003, 0.03	0.134
Use of non-opioid substances	1.92	0.89, 2.95	<0.001	1.84	0.19, 3.49	0.029	1.98	0.67, 3.29	0.003

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CHAPTER 3: Sensitivity and specificity of self-reported psychiatric diagnoses amongst patients treated for opioid use disorder

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ABSTRACT

Background: Patients with opioid use disorder (OUD) frequently present with comorbid psychiatric illnesses which have significant implications for their treatment outcomes. Notably, these are often identified by self-report. Our study examined the sensitivity and specificity of self-reported psychiatric diagnoses against a structured diagnostic interview in a cohort of patients receiving outpatient pharmacological treatment for OUD.

Methods: Using cross-sectional data from adults receiving outpatient opioid agonist treatment for OUD in clinics across Ontario, Canada, we compared participants' self-reported psychiatric diagnoses with those identified by the Mini Neuropsychiatric Interview (MINI) Version 6.0 administered at the time of study entry. Sensitivity and specificity were calculated for self-report of psychiatric diagnoses.

Results: Amongst a sample of 683 participants, 24% (n = 162) reported having a comorbid psychiatric disorder. Only 104 of these 162 individuals (64%) reporting a comorbidity met criteria for a psychiatric disorder as per the MINI; meanwhile, 304 (75%) participants who self-reported no psychiatric comorbidity were in fact identified to meet MINI criteria for a psychiatric disorder. The sensitivity and specificity for any self-reported psychiatric diagnoses were 25.5% (95% CI 21.3, 30.0) and 78.9% (95% CI 73.6, 83.6), respectively.

Conclusions: Our findings raise questions about the utility of self-reported psychiatric comorbidity in patients with OUD, particularly in the context of low sensitivity of self-reported diagnoses. Several factors may contribute to this including remittance and relapse of some

psychiatric illnesses, underdiagnosis, and the challenge of differentiating psychiatric and substance-induced disorders. These findings highlight that other methods should be considered in order to identify comorbid psychiatric disorders in patients with OUD.

BACKGROUND

The opioid crisis continues to be a major public health problem worldwide.[1-4] In 2017, it was estimated that 40.5 million people globally were dependent on opioids, although trends varied between countries.[1] The burden of opioid use and dependence is significantly more prevalent in North America compared to other parts of the world.[1] In Canada, overdose deaths and hospitalizations related to opioid use disorder (OUD) have remained high despite increasing awareness and intervention.[5,6] In the United States, opioids are involved in the majority of deaths related to drug overdose, which rose to an all-time high in 2019 with 49,860 overdose deaths involving opioids.[7-9] The impacts of the COVID-19 pandemic have additionally exacerbated pre-existing issues relating to access to appropriate treatment and interventions, ensuring that the opioid crisis will remain an ongoing concern for patients and families, healthcare workers, and policymakers alike.[9]

Patients with substance use disorders (SUD) experience comorbid psychiatric disorders, such as depression and anxiety, at rates higher than the general population.[10] Canadian data suggest that the 12-month prevalence of psychiatric comorbidity is 5 to 6 times higher among individuals with substance dependence compared to the general population (OR 5.29, 95% CI 3.90, 7.17).[10] Additionally, patients with psychiatric disorders report higher rates of substance use problems and are approximately twice as likely to have SUDs.[10,11] This comorbidity is exacerbated in patients with OUD who appear to have even higher lifetime prevalence of psychiatric disorders compared to those with other SUDs and the general population; lifetime rates are generally greater than 40%, although there is considerable variability in reported rates across studies.[12] We have previously found that among patients receiving methadone maintenance treatment for

OUD, approximately 80% of participants had a comorbid psychiatric disorder, with 43% having an anxiety disorder, and 41% having a mood disorder.[11] Psychiatric disorders are similarly associated with an increased risk of developing OUD in individuals who are prescribed opioids for pain (OR 1.46, 95% CI 1.12, 1.91).[13]

The importance of understanding a patient's psychiatric comorbidities in the context of their OUD should not be understated. When assessing patients, it may be challenging to determine whether their symptoms are due to a psychiatric comorbidity, or secondary to substance use.[14] These comorbidities also must be considered in the context of treatment. For patients with OUD, psychiatric comorbidities have been associated with worse clinical outcomes. A study examining retention in buprenorphine treatment found the presence of any comorbid mental illness to have a hazard ratio of 1.05 (95% CI 1.01, 1.10) for treatment discontinuation at three years[15] while inpatient mental health treatment was associated with a hazard ratio of 1.2 (95% CI 1.19, 1.30) for treatment discontinuation.[16] Similarly, psychiatric comorbidity conferred higher hazard for attrition from methadone treatment (hazard ratio 1.20, 95% CI 1.06, 1.35).(15) In studying the impact of psychological symptoms in OUD treatment outcomes, we have previously found that psychological symptoms were associated with higher percentages of opioid-positive drug screens (B = 0.02, 95% CI 0.01-0.02=3) and non-opioid-positive drug screens (B = 1.92, 95% CI 0.89, 2.95).[14] The prevalence of depression and anxiety disorders in opioid-related overdoses reaches rates greater than 30%,[17] and severe depression (OR 2.46, 95% CI 1.24, 4.89), post-traumatic stress disorder (PTSD) (OR 2.77, 95% CI 1.37, 5.60), and psychosis (OR 2.39, 95% CI 1.10, 5.15) are significantly associated with opioid overdoses.[18] In a study looking at factors associated with mortality among heroin users, a history of psychiatric treatment was associated with a hazard ratio of 6.21 (95% CI 2.52, 15.33) for all-cause mortality.[19]

Psychiatric comorbidity is also associated with lower reported quality of life for patients with OUD.[20] Epidemiological data on patient outcomes, in addition to other clinical and systems-level research, have reinforced the need for concurrent disorders treatment that integrates treatment for psychiatric disorders and addictions.[10,21]

Most commonly in substance use treatment programs, the record of historical mental health diagnoses is based on patient self-report.[22] The utility of self-reported psychiatric diagnoses within patients with SUDs was examined by Neumann and colleagues[22] who found self-reported diagnoses of bipolar disorder and depression were often not confirmed by current clinical measures, and many participants had undiagnosed psychiatric disorders. In light of these findings and a clinical reliance on patient self-report, the objective of this study was to examine the sensitivity and specificity of patient-reported psychiatric diagnoses in a cohort of patients receiving outpatient pharmacological treatment for OUD.

METHODS

Data were collected in the GENetics of Opioid Addiction (GENOA) prospective cohort study conducted in Ontario, Canada. The objective of the GENOA study was to examine biological and social factors affecting treatment outcome and course for patients with OUD.[23] Participants were recruited from 20 outpatient opioid agonist treatment clinics between 2011 and 2017. All clinics were run by the same management teams and followed the same treatment protocols.

Inclusion criteria required participants to be a minimum of 18 years of age, to meet diagnostic criteria for OUD as per DSM-IV criteria,[24] and to be enrolled in opioid agonist therapy (primarily methadone). At the time that this study was conducted, buprenorphine-naloxone was not covered through the Ontario provincial drug plan, thus greatly limiting its access, and making methadone primary opioid substitution treatment available. No restrictions were placed on participants' duration in treatment; therefore, individuals were enrolled in treatment for different lengths of time at the time of study entry. Ethics approval was obtained from the Hamilton Integrated Research Ethics Board (project ID 11-056) and all participants provided informed consent. We report the present study following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[25]

At study intake, all participants completed extensive baseline assessments performed by trained interviewers, including assessment of sociodemographic and clinical information (including opioid agonist treatment history). All participants were asked to self-report their medical history, with the open-ended question: "Do you have any medical conditions or health problems?" Responses to this question were recorded in an open-ended text field and later summarized into diagnostic categories by two study authors (KL and EX) in duplicate for consistency and accuracy.

Self-reported psychiatric diagnoses were compared against a diagnostic interview using the Mini Neuropsychiatric Interview (MINI) version 6.0[26] a standardized and structured tool widely used in research and clinical settings.[24] The MINI has been validated against the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders (SCID) and the Composite

International Diagnostic Interview (CIDI).[26] In comparison to the SCID, the sensitivity of the MINI was 70% or greater for 19 out of 22 diagnoses evaluated by the SCID while the specificity was 85% or higher for all diagnoses. When compared to the CIDI, the MINI had a sensitivity of 70% or greater for 7 out of 11 diagnoses captured by the CIDI and had a specificity of 70% or greater for all diagnoses. The MINI had excellent interrater reliability with 70% of interrater kappa values 0.90 or above. The retest reliability of the MINI was good with 61% of the retest kappa values being above 0.75. Additionally, the agreement between diagnoses made by general practitioners using the MINI and diagnoses from psychiatrists was 85%.[26]

The first 690 participants consecutively recruited into the study were administered the MINI version 6.0.[26] Use of the MINI was subsequently discontinued due to time burden of administration. The MINI interview encompasses assessments of mood disorders (major depression and bipolar disorder), anxiety disorders (panic disorder, agoraphobia, social anxiety disorder, generalized anxiety disorder), obsessive-compulsive disorder (OCD), PTSD, psychotic disorders (schizophrenia, schizoaffective disorder, schizophreniform disorder, brief psychotic disorder, substance induced psychotic disorder, and psychotic disorder not otherwise specified), and eating disorders (anorexia nervosa and bulimia nervosa). In order to reasonably compare self-reported psychiatric diagnoses with diagnoses identified by structured diagnostic interview, we only considered relevant the diagnoses assessed for in the MINI (for example, attention deficit hyperactivity disorder is not included in the MINI and was therefore excluded from self-report). Antisocial personality disorder is examined in the MINI, however this diagnosis was not self-reported by any of the study participants and was therefore excluded from the present analyses. No other personality disorders are identified using the MINI.

We used descriptive statistics to summarize participant demographic and clinical characteristics, using mean values with standard deviation (SD) or median values with interquartile range (IQR) for continuous variables, and frequencies for categorical variables. Sensitivity and specificity values were calculated for each of the following disorders: any psychiatric disorder, depression, bipolar disorder, anxiety disorder, OCD, PTSD, psychotic disorder, and eating disorder. All analyses were conducted using Stata version 15.1.

RESULTS

Altogether, 1,390 participants were recruited into the GENOA study, and upon exclusion of participants recruited in duplicate (n = 30) and participants who did not receive the MINI diagnostic interview (n = 677), our final study sample consisted of 683 participants (Figure 2. Study flow diagram). We summarize participant characteristics in Table 4: the mean age was 39.1 years (SD = 11.4) and men composed 58% of the cohort (n = 395).

The unemployment rate was 66% (n = 450). The reported mean age at first opioid use was 25.5 years (SD = 8.8) and the median years spent in treatment was 3 (Q1, Q3 = 1, 6). The mean methadone dose for the participants was 77 mg/day (SD = 46.5). Three participants in this study sample were prescribed buprenorphine-naloxone (0.4%) at the time of recruitment. At study entry, the percentage of participants that reported being abstinent from opioids was 49% (n = 335). The median percentage of opioid-positive drug screens in participants who reported being non-abstinent at the beginning of the study was 25% (Q1, Q3 = 10, 58.2).

Amongst all study participants, 104 (15.2%) reported a diagnosis of depression, 15 (2.2%) reported a diagnosis of bipolar disorder, 102 (14.9%) reported a diagnosis of an anxiety disorder, and 27 (4.0%) reported a diagnosis of PTSD. Less frequently reported diagnoses were OCD, psychotic disorders, and eating disorders. In total, 162 (23.7%) participants self-reported a history of psychiatric comorbidity (Table 5).

The sensitivity and specificity of self-reported psychiatric diagnoses are reported in Table 6.

Of the 162 participants who self-reported any psychiatric comorbidity, 104 met criteria for a comorbidity as per the MINI and 58 did not. Furthermore, 304 participants who reported no psychiatric comorbidity were identified to meet MINI criteria for a psychiatric disorder. The sensitivity and specificity for any self-reported psychiatric diagnoses was 25.5% (95% CI 21.3, 30.0) and 78.9% (95% CI 73.6, 83.6), respectively.

The sensitivity and specificity for self-reported depression was 17.9% (95% CI 12.7, 24.1) and 85.8% (95% CI 82.4, 88.8), respectively; meanwhile the sensitivity and specificity for self-reported anxiety disorders was 14.8% (95% CI 10.5, 20.1) and 85% (95% CI 81.4, 88.2), respectively; and the sensitivity and specificity for self-reported PTSD was 4.2% (95% CI 0.8, 11.7) and 96.1% (95% CI 94.2, 97.5), respectively. The sensitivity for each of self-reported bipolar disorder, OCD, psychotic disorder, and eating disorders was 0% (95% CI for bipolar disorder 0, 4.0; 95% CI for OCD 0, 4.7; 95% CI for psychotic disorder 0, 13.7; 95% CI for eating disorder 0, 36.9). The specificity was 97.5% for self-reported bipolar disorder (95% CI 95.9, 98.6), 99.3% for OCD (95% CI 98.3, 99.8), 99.4% for psychotic disorder (95% CI 98.5, 99.8), and 99.9% for eating disorders (95% CI 99.2, 99.996). There were many new diagnoses identified using the MINI including 156 diagnoses of depression, 195 diagnoses of anxiety, 69 diagnoses of PTSD, 90 diagnoses of bipolar disorder, 76 diagnoses of OCD, 25 diagnoses of psychotic disorders, and 8 diagnoses of eating disorders.

DISCUSSION

Overall, we found that the sensitivity of self-reported psychiatric comorbidity was low, when compared to the MINI, particularly for self-reported depression, anxiety disorder, PTSD, and overall psychiatric diagnoses. In addition, none of the patients with a self-reported history of bipolar disorder, OCD, psychotic disorder, or eating disorder met the criteria for a current diagnosis of each disorder. Many new diagnoses were made in participants who did not report a history of these disorders - including but not limited to depression, anxiety, PTSD, and bipolar disorder. Although the specificity of self-report was higher for certain diagnoses (including anxiety disorder and PTSD), the overall low sensitivity illustrates that self-report did not accurately capture the patients' present clinical picture. Thus, the utility of self-reported psychiatric comorbidity is in question.

There are several potential explanations for the low sensitivity of self-reported psychiatric disorders. Psychiatric disorders can be episodic in nature, with recurrent symptoms that cycle through relapsing-remitting courses. Participants who reported a historical diagnosis may no longer be experiencing symptoms and no longer meet the criteria for that disorder at the time of assessment. Similarly, participants for whom new psychiatric diagnoses were made may not have previously met criteria for the respective diagnoses. In addition, psychiatric disorders are likely under-diagnosed in the OUD population as evidenced by the under-diagnosis of concurrent disorders as a whole.[27] There may be poor health literacy within the OUD population which can negatively impact an individual's ability to recognize symptoms of a mental disorder and then communicate these issues to a healthcare provider, contributing to underdiagnosis.[28] Furthermore, treatment for mental health and substance abuse disorders continues to be offered separately, despite the evidence supporting concurrent treatment, and between navigating both systems diagnoses may be missed.

Most studies examining the sensitivity and specificity of self-reported psychiatric diagnoses do not include participants with SUDs. For instance, studies have found moderate to high agreement between self-reported and clinically-diagnosed depression in groups of university graduates and adults being followed for osteoporosis.[29,30] Conversely, a self-report tool used to screen members of the United States Armed Forces for deployment was found to have low validity in identifying individuals with diagnosed mental health disorders.[31] Much of the related literature in the patients with SUDs examines self-reported substance use, rather than psychiatric comorbidity.[32] Neumann et al. compared self-reported historical psychiatric diagnoses with current clinical diagnoses assessed using the MINI screen, MINI Plus 500 structured interview, and Personality Diagnostics Questionnaire-4th edition. They found that self-reported diagnoses such as bipolar disorder and depression were often not verified by current clinical measures.[22] In addition, many patients had undiagnosed personality disorders, depression, and anxiety disorders.[22] To our knowledge, no other studies have examined the sensitivity and specificity of self-reported psychiatric diagnoses in SUD or OUD populations.

As discussed, individuals with OUD have higher rates of co-occurring psychiatric comorbidities compared to the general population, with rates reaching greater than 40% across their lifetime,[12] and these comorbidities are associated with increased psychiatric distress, rates of SUD, and poorer response to substance use treatment.[10,11,33] Despite this, the evidence surrounding the efficacy of psychiatric treatment in these individuals remains equivocal. Literature on pharmacotherapy (mostly consisting of placebo-controlled medication trials) has shown mixed results, with many studies showing no difference from placebo in reducing psychiatric symptoms or substance use.[33] With respect to psychosocial interventions, a Cochrane review found that patients receiving psychosocial interventions in addition to OAT did not show improved outcomes compared to individuals receiving OAT alone; whereas another systematic review did support their efficacy to improve clinical outcomes.[34] There is emerging evidence that some of these inconsistent findings may be indicative of other variables impacting patient responses to psychiatric treatment, including ongoing substance use and complex psychosocial such as housing and employment.[9,33,35]

The varied, interlinked, and complex needs of individuals with OUD (and other SUDs) have led to a movement towards concurrent treatment.[10,21] While the evidence for how psychiatric treatment impacts outcomes for patients with SUDs is conflicting, there have been encouraging results from literature evaluating integrated care for both psychiatric and SUDs. In patients receiving both OAT and psychiatric care, those who received on-site and integrated care of both had improved psychiatric outcomes compared to those who received their psychiatric care off-site and non-integrated with their substance use treatment; however, no difference was found in outcomes related to substance use.[36] This remains an area requiring further research to elucidate how to best support these clinically complex patients and improve their outcomes.

For patients experiencing SUDs, clinicians also face challenges differentiating between psychiatric disorders and substance-induced disorders as both intoxication and withdrawal from opioids can mimic the symptomatology seen in mood, anxiety, and psychotic disorders.[12,37,38] The difficulty in delineating between psychological symptoms as a result of a primary psychiatric disorder versus secondary to SUD (including OUD) makes diagnosing mental illness in this population a complex challenge.[12,37] In fact, due to the overlap in symptoms between symptom intoxication/withdrawal and affective disorders, Quello et al. advise that definitive assessments of psychiatric diagnoses should be postponed until individuals have achieved a reasonable period of abstinence, although the length of this period varies.[39] Instead they suggest using screening methods to identify possible mood disorders, with associated follow-up after abstinence for definitive diagnosis.[39] Furthermore, individuals may not recall, choose not to disclose, or disagree with a previous psychiatric diagnosis; in addition to self-diagnosing themselves incorrectly. This could occur for various reasons relating to the social stigma of substance use, the impacts of chronic substance use or untreated psychiatric disorders on memory, lack of access to healthcare for appropriate psychiatric assessment, among others.

Our results highlight the need for improved methods to ascertain comorbid psychiatric disorders in the OUD population during treatment. While the specificities of many psychiatric disorders were high, the sensitivities remained poor. That several patients in this study received new diagnoses additionally highlights the issue of under-diagnosis of psychiatric comorbidities in this population, and the need for better ways to identify them.[27] Potential alternatives to patient self-report of psychiatric diagnoses may include structured interviews or questionnaires. In the setting of an addiction treatment clinic, time and resource limitations, and clinical expertise influence the ability to conduct diagnostic interviews and comprehensively assess psychiatric symptomatology. The GENOA study, from which our data were obtained, initially used the MINI structured diagnostic interview, which takes approximately 20 minutes to administer and use of this tool was later discontinued due to the time burden of administration on participants who did not like the additional 20 minutes it took to complete the interview. However, the MINI is one of the quickest diagnostic tools used to assess for psychiatric disorder, and other standardized assessments such as the CIDI[40] or the SCID[41] both require more time to administer compared to the MINI.[42]

Since diagnostic tools require significant time resources, an alternative option would be to administer screening tools that take less time to complete in order to identify the patients who may benefit from a more detailed diagnostic interview. This would be particularly pertinent in relation to the low sensitivities of our results as a way to provide diagnostic clarification when patients self-report psychiatric concerns. Examples of screening tools which require less than 10 minutes to complete include the Brief Symptom Inventory,[43] Modified MINI screen,[44] and the General Health Questionnaire.[45] The Dual Diagnosis Screening Instrument[46] and Mental Health Screening Form-III[47] are both screening tools that have been developed specifically for the detection of psychiatric comorbidity in patients with SUDs. Another potential solution would be to have a psychiatrist on-site who would be able to administer assessments for psychiatric disorders, which has also been shown to increase patient engagement with psychiatric services.[48]

A limitation of this study was the way self-reported psychiatric disorders were elicited, with an open-ended question inquiring about any medical or health problems. This question may have been understood as asking for solely non-psychiatric medical problems or only for current issues that the patient is experiencing, not past diagnoses that are now in remittance. A question that explicitly asks around a history of mental health disorders both past and present would be less susceptible to misinterpretation. Additionally, the MINI does not assess for personality disorders, which are heavily implicated in SUD,[49] or attention deficit hyperactivity disorder. Thus, analysis regarding the sensitivity and specificity of self-report for these disorders is unavailable. Importantly, there is an under-reporting and under-recognition of psychiatric comorbidities in the context of OUD despite the demonstrated impact of such comorbidity on treatment outcomes. Health care providers need to be aware of the prevalence of such disorders in this population and policies regarding systematic screening of patients attending treatment for SUDs for comorbid psychiatric conditions are needed. The choice of a screening tool or clinical assessment that is feasible to use must balance accuracy, effort, and scalability. It is also possible that for some patients, poor mental health literacy in the SUD population likely further exacerbates the issue of self-recognition of psychiatric symptoms and subsequently seeking help with diagnosis.

CONCLUSION

The sensitivity and specificity of self-reported psychiatric comorbidity in patients with OUD was found to be low when compared to standardized, structured, diagnostic interviews. The remitting-relapsing nature of psychiatric disorders, under-diagnosis, the difficulty in differentiating independent psychiatric disorders from substance-induced disorders, and patient factors likely contributed to these findings. These findings highlight that other methods should implemented in order to identify comorbid psychiatric disorders in patients with OUD.

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Authors' contributions

TR, and ZS are responsible for the study concept and design. KL and EX cleaned and prepared the data for analysis and TR conducted statistical analyses. KL and EX wrote the first draft of the manuscript, and TR, AW, LT, and ZS contributed to writing and critically revising the final manuscript. All authors reviewed and approved the final manuscript.

FIGURES AND TABLES

Figure 2. Study flow diagram

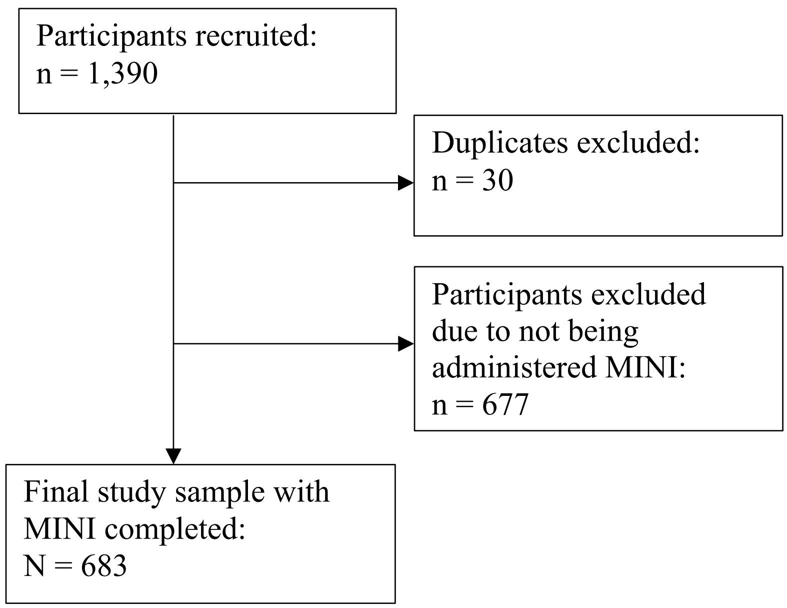

Table 4. Participant characteristics at study entry (N = 683)

Characteristic	**Total sample** N = 683	**Self-reported psychiatric comorbidity** n = 162 (23.7%)	**No self-reported psychiatric comorbidity** n = 521 (76.3%)
Age (years); mean (SD)	39.1 (11.4)	37.8 (11.6)	39.4 (11.3)
Sex; n (%) Males Females	 395 (57.8%) 288 (42.2%)	 94 (58.0%) 68 (42.0%)	 301 (57.8%) 220 (42.2%)
Unemployment; *n* (%)	450 (65.9%)	108 (66.7%)	342 (65.5%)
Age at first opioid use (years); mean (SD)	25.5 (8.8)	25.2 (8.7)	25.6 (8.8)
Years in treatment; median (Q1, Q3)	3 (1, 6)	2 (1, 5)	3 (1, 7)
Methadone dose (mg/d); mean (SD)	77.0 (46.5)	71.8 (39.8)	78.7 (48.3)
Opioid abstinence at study entry; *n* (%)	335 (49.1)	71 (43.8)	264 (50.7)
Percentage (%) of opioid-positive drug screens at study entry if non-abstinent; median (Q1, Q3)	25 (10, 58.2)	29.6 (12, 64.3)	23.5 (9.1, 55.6)
SD = Standard Deviation, Q1 = Quartile 1, Q3 = Quartile 3			

Table 5. Psychiatric comorbidity identified within the study sample (N = 683)

Psychiatric comorbidity	Self-reported	MINI-Diagnosed
Any psychiatric disorder; *n* (%)	162 (23.7%)	408 (59.7%)
Depression; *n* (%)	104 (15.2%)	190 (27.8%)
Bipolar disorder; *n* (%)	15 (2.2%)	90 (13.2%)
Anxiety disorder; *n* (%)	102 (14.9%)	229 (33.5%)
PTSD; *n* (%)	27 (4.0%)	72 (10.5%)
OCD; *n* (%)	4 (0.6%)	76 (11.1%)
Psychotic disorder; *n* (%)	4 (0.6%)	25 (3.7%)
Eating disorder; *n* (%)	1 (0.2%)	8 (1.2%)
MINI = Mini-International Neuropsychiatric Interview, PTSD = Post-traumatic Stress Disorder, OCD = Obsessive Compulsive Disorder		

Table 6. Sensitivity and specificity of self-reported psychiatric disorders (N = 683)

	Sensitivity (95% CI)	Specificity (95% CI)
Any psychiatric disorder	25.5% (21.3, 30.0)	78.9% (73.6, 83.6)
Any depressive disorder	17.9% (12.7, 24.1)	85.8% (82.4, 88.8)
Bipolar disorder	0% (0, 4.0)	97.5% (95.9, 98.6)
Any anxiety disorder	14.8% (10.5, 20.1)	85% (81,4, 88.2)
PTSD	4.2% (0.8, 11.7)	96.1% (94.2, 97.5)
OCD	0% (0, 4.7)	99.3% (98.3, 99.8)
Psychotic disorder	0% (0, 13.7)	99.4% (98.5, 99.8)
Any eating disorder	0% (0, 36.9)	99.9% (99.2, 99.996)
CI = Confidence Interval, PTSD = Post-traumatic Stress Disorder, OCD = Obsessive Compulsive Disorder		

Figure 3. Paired contingency tables comparing results of self-reported diagnosis to Mini International Neuropsychiatric Interview diagnosis.

Any psychiatric disorder		**MINI Interview**	
		Positive	Negative
Self-report	Positive	104	58
	Negative	304	217

Any depressive disorder		**MINI Interview**	
		Positive	Negative
Self-report	Positive	34	70
	Negative	156	423

Bipolar disorder		**MINI Interview**	
		Positive	Negative
Self-report	Positive	0	15
	Negative	90	578

Any anxiety disorder		**MINI Interview**	
		Positive	Negative
Self-report	Positive	34	68
	Negative	195	386

Post-traumatic stress disorder		**MINI Interview**	
		Positive	Negative
Self-report	Positive	3	24
	Negative	69	587

Obsessive compulsive disorder		**MINI Interview**	
		Positive	Negative
Self-report	Positive	0	4
	Negative	76	603

Any psychotic disorder		**MINI Interview**	
		Positive	Negative
Self-report	Positive	0	4
	Negative	25	654

Any eating disorder		**MINI Interview**	
		Positive	Negative
Self-report	Positive	0	1
	Negative	8	674

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CHAPTER 4: Trauma and post-traumatic stress disorder in patients treated for opioid use disorder: findings from a 12-month cohort study

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ABSTRACT

Background: Exposure to traumatic events is both a risk factor for substance use and an adverse outcome of substance use disorders; therefore, identifying and managing post-traumatic stress disorder (PTSD) in patients with addiction requires attention.

Aims: To examine the lifetime prevalence of traumatic events and past-month prevalence of PSTD in a cohort of patients treated for opioid use disorder (OUD) and to explore the association between trauma, PTSD, and treatment outcomes.

Methods: Participants (n=674) receiving methadone treatment in 20 community clinics across Ontario, Canada were administered the Mini-International Neuropsychiatric Interview to identify self-reported traumatic events and PTSD. Participants were followed for 12 months with urine drug screens.

Results: Eleven percent of participants met past-month criteria for PTSD (*n*=72), while another 48% reported history of traumatic events with no current PTSD (*n*=323). Participants with PTSD were more likely female (OR 2.13, 95% CI 1.20, 3.76) and less likely to be employed (OR 0.31, 95% CI 0.16, 0.61) or married (OR 0.51, 95% CI 0.26, 0.90) than those with no trauma history. Antidepressants (39% vs. 24%) and benzodiazepines (36% vs. 18%) were differentially prescribed to patients with and without PTSD. Length of time in treatment and opioid use were not associated with trauma; however, suicidal ideation was more common in PTSD (OR 2.29, 95% CI 1.04, 5.01).

Conclusions: Trauma and PTSD are prevalent amongst patients with OUD; for most patients in treatment, consideration of trauma symptoms and associated characteristics is warranted. Patients with and without comorbid PTSD differ clinically and psychosocially, highlighting the relevance of integrating addictions and mental health services for this population.

BACKGROUND

Exposure to traumatic events such as threatened death or serious injury, and the experience of trauma (the emotional response to a traumatic event) have been associated with the development of substance use disorders (SUDs).[1] Furthermore, individuals with SUDs may be at greater risk of experiencing violence and traumatic events.[2] Not all individuals who experience trauma develop post-traumatic stress disorder (PTSD); however, studies estimate that 11-50% of patients with SUD meet criteria for comorbid PTSD.[3] Less information is available on the rates of PTSD in patients with opioid use disorder (OUD), however they have been reported to be amongst the highest (41% lifetime, 33% current).[4] Fluctuations in PTSD symptoms are risk factors for opioid use in patients receiving treatment,[5] and may be associated with more intense cravings[6,7] and increased psychological distress.[8] Comorbid PTSD and SUD is also associated with higher rates of other psychiatric and physical comorbidities,[9] fewer social supports and higher rates of unemployment.[7] Patients with comorbid SUD and PTSD may have worse treatment outcomes,[10] and are at higher risk for suicide attempts, relapses to substance use, and treatment drop out.[6, 10] Despite these findings, there exists limited formal protocol and guidance to address these co-occurring issues.[11] First-line treatments for PTSD include psychotherapies such as Trauma-focused Cognitive Behavioral Therapy, Cognitive Processing Therapy, Prolonged Exposure, and Eye Movement Desensitization and Reprocessing Therapy, while first-line medication treatments include antidepressant treatment with selective serotonin reuptake inhibitors or serotonin and norepinephrine reuptake inhibitors, and targeted symptom treatments such as the use of prazosin for nightmares have been recommended.[12,13] No specific guidelines for the treatment of PTSD in patients with OUD have been published and the availability of these first-line psychotherapies in addiction treatment settings is limited.[14,15] Acknowledging the high prevalence of PTSD in patients with SUDs and the associated negative impact on treatment, we sought to further examine traumatic events and PTSD in a cohort of patients receiving opioid agonist treatment for OUD. The objectives of this study were to:

1. Assess the prevalence of traumatic events, with and without current PTSD, in a cohort of patients receiving treatment for OUD;
2. Describe demographic and clinical characteristics of patients with history of traumatic events or PTSD;
3. Explore the association between traumatic events and PTSD and psychosocial and clinical outcomes during OUD treatment.

METHOD

We used prospective data from the GENetics of Opioid Addiction (GENOA) study conducted in Southern Ontario, Canada between June 2011 and April 2017. The GENOA study sought to explore biological, psychological, and social factors associated with treatment outcomes for patients with OUD. Data were collected from participants older than 18 years of age who were receiving methadone maintenance treatment (MMT) for a diagnosis of OUD (as per the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition text revision (DSM-IV-TR).[16] Methadone remains the most commonly prescribed pharmacological treatment for OUD in Canada and at the time that this study was conducted, buprenorphine-naloxone was not covered through the Ontario provincial drug plan. The diagnosis of OUD was established by treating physicians and is an eligibility criterion for clinical follow up at the clinics included in this study. Participants could be enrolled in MMT for any length of time prior to recruitment (median 3 years) and participants with polysubstance use or co-occurring SUDs (in addition to OUD) were included. No other inclusion or exclusion criteria were applied in order to increase the generalizability of the sample. Participants were recruited from 20 community-based outpatient clinics that are run centrally through a single management team and follow the same clinical protocols. Patients enrolled in participating clinics have access to a multidisciplinary team of health professionals including addiction physicians, nurses, pharmacists, and staff experienced in addiction treatment. They receive medical examination and laboratory tests as indicated as well as supervised urine testing. All patients included in the present study were receiving methadone treatment but could be prescribed any other medications by their clinic physician or other physicians involved in their care. Patients have access to harm reduction services including naloxone kits and needle exchange programs as well as supports to connect with community agencies to provide services including counselling, housing support, job banks and primary care. No formal psychotherapy treatments are offered in the clinics.

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All procedures involving human subjects/patients were approved by the Hamilton Integrated Research Ethics Board (project ID 11-056) and all study procedures were conducted in accordance with their ethical guidelines. Written and verbal informed consent was obtained from every participant. Our study methods and findings are reported in accordance with the *Strengthening the Reporting of Observational Studies in Epidemiology* (STROBE) guidelines.[17]

Participants completed face-to-face interviews at the time of study entry to obtain information on demographic characteristics, medical and psychiatric history, medications, methadone dose, and length of time in treatment. The first 680 participants consecutively recruited into the study competed the Mini-International Neuropsychiatric Interview (MINI) version 6.0,[18] administered by trained interviewers at the time of study entry. Use of the MINI was subsequently discontinued in the study due to time burden of administration. Therefore, inclusion in the present study's analyses was limited to those participants who were administered the MINI (Figure 1, study flow diagram). Included in the MINI diagnostic interview is a screen for lifetime history of traumatic events, elicited through the question: "*Have you ever experienced or witnessed or had to deal with an extremely traumatic event that included actual or threated death or serious injury to you or someone else? Examples of traumatic events include: serious accidents, sexual or physical assault, a terrorist attack, being held hostage, kidnapping, fire, discovering a body, war, or natural disaster, witnessing the violent or sudden death of someone close to you, or a life-threatening illness.*" This screening question is based on DSM criterion A for the diagnosis of PTSD.[16] Subsequently, participants were asked about symptoms of PTSD as per the DSM-IV-TR[16] in order to determine a past-month diagnosis of PTSD. For the purposes of this study, participants who screen positive for past-month PTSD are considered as having "current PTSD". Individuals who report experiencing a traumatic event but do not meet past-month criteria for PTSD are categorized as having a history of "traumatic events without current PTSD". Individuals who deny lifetime history of traumatic events are considered to have had "no trauma". These three groups are considered mutually exclusive. Finally, participants were also asked to report past-month suicidal ideation and past-month suicide attempts in the MINI assessment.[18]

Participants were followed in the study for 12 months. Opioid, cocaine, and benzodiazepine use was measured using urine drug screen tests, generally administered weekly following clinical protocol. Urine testing for amphetamines and cannabis was conducted inconsistently and, therefore, not included in the present analyses. Urine toxicology screening was conducted using the iMDx Prep™ assay.[19] The percentage of positive urine drug screens was calculated for each patient for each substance. Ongoing opioid use was defined as at least one opioid-positive urine drug screen during the study.

Statistical Analyses

Analyses were conducted using STATA Version 15.1 (StataCorp LP, College Station, TX, USA). Our first objective was to determine the prevalence of traumatic events and current PTSD in our study cohort and our second objective was to describe the demographic and clinical characteristics of these groups. We present descriptive statistics based on group status (i.e., history of traumatic event without current PTSD, current PTSD, no trauma). Continuous variables were summarized as means and standard deviations (SD) if normally distributed, and as medians with interquartile range (IQR) for skewed data. Categorical variables were summarized using frequencies and percentages. Our third objective was to explore the association between trauma history and demographic characteristics and treatment outcomes. We constructed a multinomial logistic regression model with group status (history of traumatic event without current PTSD, current PTSD, or no traumatic events or PTSD) as the dependent variable. Covariates included in the model were selected based on previous literature suggesting associations with trauma history or MAT outcome: sex[20], methadone dose[21], employment status[7], and marital status[7]. We also included age of onset of opioid use, length of time in treatment, ongoing opioid use, and suicidal ideation as covariates in the model to explore their association with group status. Results are represented as Odds Ratios (OR) with 95% confidence interval (CI).

RESULTS

Altogether, 1,360 unique participants were recruited into the study, and 674 participants who were administered the MINI were included in the present analyses (Figure 4). Forty-one percent of participants were identified to have no trauma history (n = 279), while 48% of participants reported a lifetime history of traumatic events, without meeting criteria for PTSD in the last month (n = 323). Eleven percent of participants met past-month MINI criteria for PTSD (n = 72).

Table 7 details participants' sociodemographic and clinical characteristics by group. Amongst participants with PTSD, 63% were female, compared to 44% in the other two groups. The mean age of participants in all three groups was approximately 39 years. Amongst participants with no history of trauma, 35% were married, compared to 28% of participants with history of traumatic events but no PTSD, and 21% of participants with PTSD. Unemployment rate was highest for participants with PTSD (83%) followed by participants with traumatic events without PTSD (71%) and neither (56%). Participants were enrolled in treatment for median 3 years (IQR = 5). Participants with PTSD had the highest median methadone dose, 84.5 mg/day (IQR = 52.5), compared to 70 mg/day in the other two groups.

Antidepressant medications were prescribed for 39% of participants with PTSD, 28% of participants with past traumatic events without current PTSD, and 24% of participants with no history of trauma (Table 7). Just one participant in the entire study sample was prescribed prazosin. The prevalence of benzodiazepine prescription was 36% in participants with PTSD, 26% in participants with traumatic events but no PTSD, and 18% in participants with no history of trauma. Past-month suicidal ideation was reported by nearly 20% of participants with current PTSD, higher than in the other two groups in which 7% and 10% of participants reported suicidal ideation, respectively. Reports of past-month suicide attempts were lower at 1.8% in participants with no trauma history, 2.6% in participants with traumatic events but no PTSD, and 2.8% in participants with current PTSD. Seventy percent of participants with no trauma history had ongoing opioid use as evidenced by at least one opioid-positive urine drug screen, compared to 80% of participants with traumatic events and no PTSD, and 79% of participants with PTSD. Non-prescribed benzodiazepine use was identified in about 24% of both participants with PTSD and those with no trauma history, and in about 27% of participants reporting traumatic events and no current PTSD. Cocaine use was identified in 33% of participants with PTSD, 39% of participants with traumatic events and no current PTSD, and 36% of participants with no trauma history.

We present the results of multinomial regression analysis in Table 8. Participants with PTSD were more likely to be female than those with no trauma history (OR = 2.13, 95% CI 1.20, 3.76, $p = 0.009$). Compared to participants with no history of trauma, both those with traumatic events without PTSD and those with PTSD were less likely to be employed (OR = 0.53, 95% CI 0.37, 0.75, $p < 0.001$ and OR = 0.31, 95% CI 0.16, 0.61, $p = 0.001$, respectively). Similarly, compared to participants with no history of trauma, having traumatic events without PTSD or with PTSD were both associated with younger age of onset of opioid use (OR = 0.97, 95% CI 0.95, 0.99, $p = 0.002$ and OR = 0.95, 95% CI 0.92, 0.98, $p = 0.004$, respectively). Participants with PTSD were also less likely to be married than participants with no trauma history (OR = 0.51, 95% CI 0.26, 0.99, $p = 0.046$. There were no significant associations between trauma history and duration in MMT ($p = 0.204$, and $p = 0.691$. No association between ongoing opioid use and trauma status was seen (Table 2); however, participants with PTSD were more likely to report past-month suicidal ideation (OR = 2.29, 95% CI 1.04, 5.01, $p = 0.039$).

DISCUSSION

In our cohort of patients receiving MMT for OUD, we identified an 11% past-month prevalence of PTSD. An additional 48% of participants reported a lifetime history of traumatic events without current PTSD. Therefore, for most patients treated for OUD, a consideration of the presence of trauma symptoms, their impact on substance use course, and need for treatment is warranted. Factors associated with PTSD included female sex, unemployment, single marital status, younger age of onset of opioid use, and suicidal ideation; meanwhile, factors associated with a history of trauma without current PTSD included unemployment and younger age of onset of opioid use.

We found important differences in sociodemographic characteristics amongst patients with and without trauma. Patients with past traumatic events, with or without current PTSD, had a younger age of onset of opioid use. Early identification and management of trauma and PTSD could potentially impact the development or progression of OUD. While outside of the scope of the present study, the possibility that the identification and management of PTSD may impact OUD outcomes is an area that requires further research. Patients with comorbid OUD and PTSD were also more likely to be unemployed and single when compared to patients with no trauma history. These individuals may require different psychosocial supports within their treatment programs.[22]

Psychiatric Medications

Our examination of the psychiatric medications prescribed for patients with comorbid PTSD revealed several areas of concern. Only 39% were receiving treatment with antidepressants, which are evidence-based treatments for PTSD.[12,13] A limitation of this study is the lack of information on concurrent psychotherapeutic treatments; however, no recommended psychological treatments for PTSD are available through the clinics included in this study. It is also important to consider that SSRIs can be used for the treatment of multiple psychiatric diagnoses and their prescription does not imply treatment for PTSD. Furthermore, only one participant was receiving prazosin, a medication indicated in PTSD for reducing the severity and frequency of nightmares.[12] Sleep disturbance was reported by 92% of participants with PTSD and re-experiencing symptoms (including dreams, intense recollections or flashbacks) were reported by 100%. Previous studies have reported the prevalence of nightmares in PTSD to be 50-70%, while the prevalence of sleep disturbance is reported in 40-50% of patients.[23] Addressing chronic nightmares is of utmost importance as they result in decreased psychological and physical health and may amplify other PTSD symptoms, including suicidal ideation.[24] Our findings suggest that more can be done to offer evidence-based treatments for PTSD in patients with this comorbidity.

Additionally, 36% of patients with comorbid PTSD were prescribed benzodiazepines, which are neither a recommended treatment for PTSD[12,13] nor recommended for use in patients receiving opioid agonist treatment due to risks of respiratory suppression.[11] It is possible that benzodiazepines are being prescribed to alleviate symptoms of PTSD including anxiety, insomnia, and irritability.[25] While studies estimate that benzodiazepines are prescribed to approximately 30-75% of patients with PTSD, a recent systematic review has concluded that benzodiazepines are ineffective for this purpose with risks outweighing benefits.[25] The concomitant use of benzodiazepines and opioids increases the risk of respiratory suppression and death and has not been shown to improve treatment retention.[11] Our findings may inspire reflection amongst clinicians treating this patient population, and prompt further research into the pharmacological treatment of patients with comorbid OUD and PTSD.

Treatment Outcomes

We did not identify significant differences in the length of time in treatment, or in ongoing opioid use based on trauma history. In fact, many participants, more than 70% of the total study sample, had ongoing opioid use (defined as at least one opioid-positive urine drug screen during the study), regardless of trauma history. Severity of opioid use, as measured by the percentage of opioid-positive urine drug screens also was not associated with trauma status (data not shown). Other substances examined, including cocaine and non-prescribed benzodiazepines, were also used at comparable rates between groups. Our study did not examine drop out from treatment as the median length of time in treatment was quite long, at 3 years (IQR = 5). A previous study of patients enrolled in an outpatient buprenorphine treatment program found that individuals with childhood trauma were more likely to drop out of treatment;[26] meanwhile, two studies of patients enrolled in methadone maintenance treatment found no significant association between the diagnosis of PTSD and 3-month[27] or one-year retention in treatment.[28] Future studies that further examine the impact of trauma and PTSD on retention in treatment in patients newly starting opioid agonist treatment may be helpful.

The psychological outcomes of patients with comorbid OUD and PTSD are also important to consider. A previous study including patients with comorbid SUDs and PTSD identified these patients as having greater difficulty with coping skills and adaptive cognitions, resulting in increased psychological distress.[8] In our study, nearly 20% of participants with PTSD reported suicidal ideation in the last month, while nearly 3% reported suicide attempts in the last month. Suicidal ideation and suicide attempts were reported at lower rates in the other groups, with the PTSD group more than twice as likely to report suicidal ideation, adjusting for other covariates. This finding highlights that PTSD is not a benign comorbidity in OUD. Patients with OUD and suicidal ideation are at risk for high-lethality overdoses.[29] Taken together, these findings suggest that some patients with trauma history or PTSD may have comparable substance use outcomes in treatment but have psychiatric and psychosocial differences that require attention. Our findings are consistent with two previous studies that have found good substance use outcomes in opioid agonist treatment, but poor or unchanged psychiatric outcomes for comorbid PTSD,[30,31] suggesting that additional services are required for these patients.

Implications

Improving treatment of PTSD in patients with SUD is critical; [30] studies have demonstrated that remitted PTSD is associated with decreased substance use,[32] while a lack of improvement in PTSD symptoms is associated with increased substance use.[33] Patients with SUD, regardless of comorbidity, are often solely treated for their substance use upon first clinical contact.[34] After achieving sobriety, these patients may then be referred for PTSD treatment.[34] However, this model of sequential treatment in which OUD is treated prior to the initiation of PTSD treatment may be ineffective and inconsistent with research, which supports an integrated approach.[10,34] A number of different treatment models have found success with integrated treatment programs.[10] The basis for these integrated programs is that improvement in PTSD symptoms is more likely to attenuate SUD symptoms, while the reverse does not result in the same effect.[10] Despite these findings, the uptake of such programs has been low, and more research is needed to identify potential barriers that prevent implementation of integrated treatment.[10]

Strengths and Limitations

Strengths of this study include its sample size and use of the validated MINI tool to identify trauma comorbidity. Healthy user and volunteer biases may limit the findings of this study such that patients with trauma comorbidity may have been less likely to participate, therefore we likely under-estimate the prevalence of traumatic events and PTSD.

Through the use of broad inclusion criteria and multi-site sampling we increase the generalizability of our findings. Participants included in this study were recruited from 20 different community-based outpatient addictions clinics in Southern Ontario. The Canadian Agency for Drugs and Technologies in Health (CADTH) published an environmental scan of programs for the treatment of opioid addiction in Canada in September 2019. Findings from this report suggest that most services accept patients who have a DSM diagnosed opioid use disorder with not many other restrictions.[35] This suggests that the inclusion criteria for our study are appropriate and reflective of individuals who would be eligible to enter treatment in the general population. Ontario Public Health data from 2017 indicate that the population of patients receiving opioid agonist therapy in Ontario is comparable in age and sex to the patients recruited in our study: 64% of patients treated in Ontario were 25-44 years of age and males accounted for 63% of patients treated.[36] As in all studies, there are possible limitations to generalizability that must be considered. For example, all patients in this study were receiving MMT, thus findings may not be applicable to individuals with OUD who are not enrolled in treatment. Further, all patients in this study were agreeable to be recruited and were able to complete the assessments, therefore there is a possibility of volunteer bias. Although we use UDS results to measure opioid use, we are unable to quantify the extent or severity of OUD based on the extent or amount of opioid used. Finally, in Ontario, and more generally in Canada, opioid agonist treatment takes on a harm reduction role, meaning that patients are not discharged from treatment due to relapse to opioid or other substance use. Our results may not be generalizable to settings in which ongoing treatment is contingent on abstinence from opioids or other substances.

As this is an observational study, we cannot make conclusions about causality and there is risk of unmeasured confounding in our analyses. Future studies that examine the longitudinal course of trauma and PTSD in this population will be beneficial as will studies that shed light on patient goals and treatment priorities in the context of trauma and substance use comorbidity.

In conclusion, patients with OUD and history of trauma or comorbid PTSD differ from patients without trauma comorbidity on a number of clinical and psychosocial factors. We found that patients with trauma history or PTSD may have comparable substance use outcomes in treatment of OUD but have psychiatric and psychosocial differences that require attention. We also identified that the psychopharmacological treatment of PTSD in patients receiving opioid agonist treatment is an area requiring attention. Our findings emphasize the relevance of better integrating addictions and mental health services for this population.

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Author Contribution:

TR, VYOA, AW, DCM, LT, and ZS are responsible for the study concept and design. TR and ZS developed the methods and data analysis. LT provided feedback on statistical analyses. TR and VYOA wrote the first draft of the manuscript, and AW, DCM, LT, and ZS contributed to writing and critically revising the final manuscript. All authors reviewed and approved the final manuscript.

FIGURES AND TABLES

Figure 4. Study flow diagram

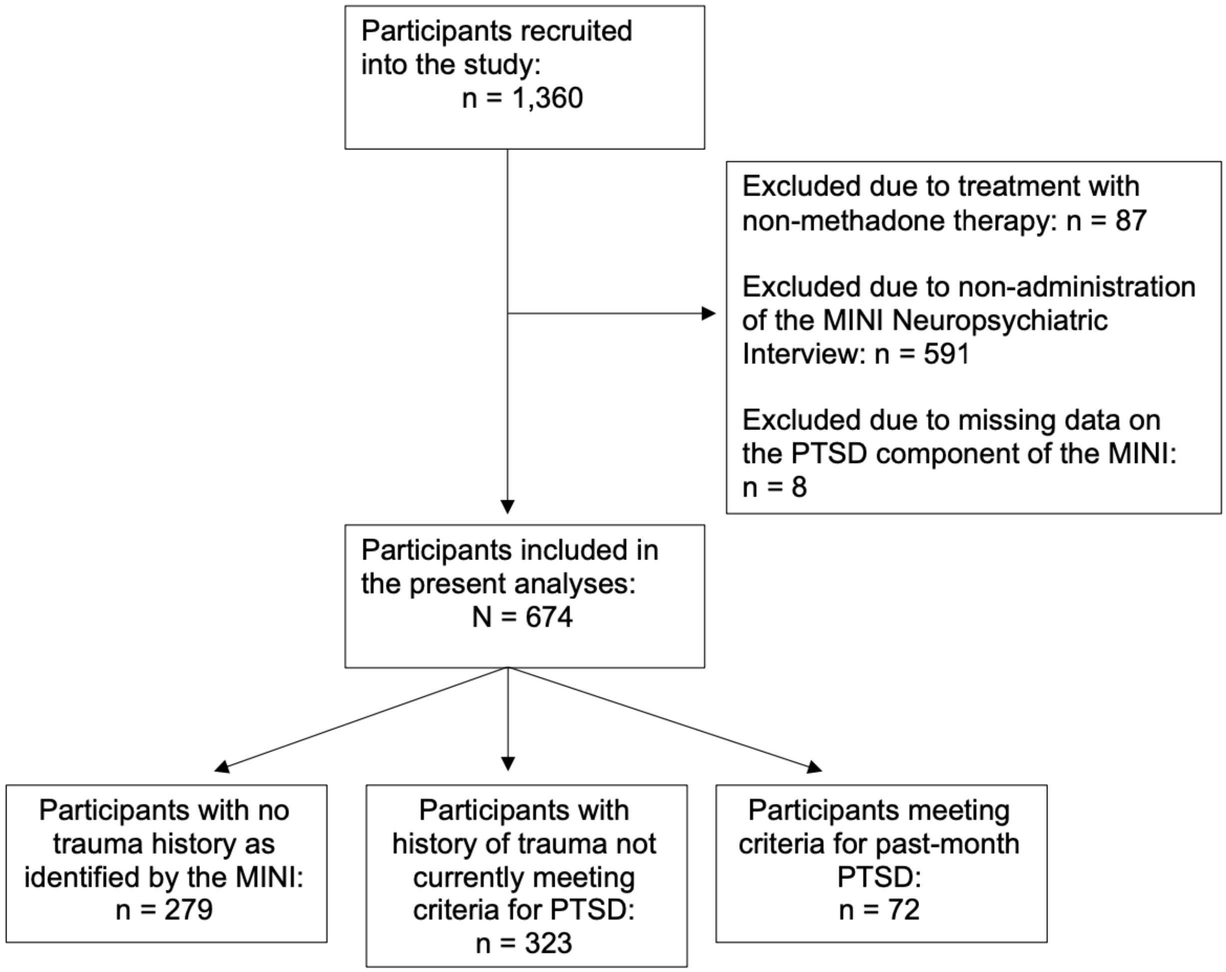

Table 7. Baseline demographics and clinical information (N = 674)

Characteristic	**Total sample N = 674**	**No trauma n = 279**	**Traumatic events without current PTSD n = 323**	**Current PTSD n = 72**
Sociodemographic				
Age (years); mean (SD)	38.8 (11.1)	38.7 (11.2)	38.9 (11.2)	38.7 (10.7)
Female sex; *n* (%)	310 (46%)	124 (44.4%)	141 (43.7%)	45 (62.5%)
Married or common law; *n* (%)	202 (30%)	97 (34.8%)	90 (27.9%)	15 (20.8%)
Unemployment; *n* (%)	444 (65.9%)	155 (55.6%)	229 (70.9%)	60 (83.3%)
Clinical				
Age of onset of opioid use (years)[a]; mean (SD)	25.5 (8.76)	26.9 (9.3)	24.6 (8.2)	23.3 (8.1)
Methadone Dose (mg / day); median (IQR)	70 (55)	70 (55)	70 (62)	84.5 (52.5)
Duration in treatment (years); median (IQR)	3 (5)	2.8 (4.3)	3 (6)	2.9 (6)
Psychiatric medication prescription; *n* (%) Antidepressant Prazosin Benzodiazepine	 187 (27.7%) 1 158 (23.4%)	 68 (24.4%) 0 49 (17.6%)	 91 (28.2%) 1 (0.31%) 83 (25.7%)	 28 (38.9%) 0 26 (36.1%)
Self-reported past-month suicidal ideation; *n* (%)	66/666 (9.9%)	20/276 (7.3%)	32/319 (10%)	14/71 (19.7%)
Self-reported past-month suicide attempt; *n* (%)	15/658 (2.3%)	5/275 (1.8%)	8/312 (2.6%)	2/71 (2.8%)
Ongoing use of opioids (non-abstinence); *n* (%)	515 (76.4%)	201 (72%)	257 (79.6%)	57 (79.2%)
Percentage of opioid-positive urine drug screens amongst non-abstainers; mean (SD)	23.2 (27.1)	23.8 (26.7)	24.3 (28.1)	16 (23)
Use of other substances; *n* (%) Non-prescribed benzodiazepines[b] Cocaine	 172 (25.5%) 250 (37.1%)	 68 (24.4%) 101 (36.2%)	 87 (26.9%) 125 (38.7%)	 17 (23.6%) 24 (33.3%)
Percentage of positive urine drug screens amongst users of other substances; median (IQR) Non-prescribed benzodiazepines[b] Cocaine	 27.9 (52.8) 26.7 (56.7)	 30 (53.2) 29.4 (71.4)	 26.8 (53.3) 24 (55.2)	 31.6 (54.7) 25.8 (56.3)
SD = Standard Deviation, IQR = Interquartile Range				

[a]Data available for 653 participants: 274 participants in no trauma group, 308 participants in the traumatic events without current PTSD group, and 71 participants in the PTSD group. [b]Non-prescribed benzodiazepine use was defined as benzodiazepines use detected on urine drug screening with no benzodiazepine prescription in the clinic medical chart.

Table 8. Multivariable model of demographic and clinical factors associated with trauma history.

Trauma history	**Covariate**	**OR**	**95% CI**	***p* value**
No trauma	(reference group)			
Traumatic event without current PTSD	Male sex Female sex	[reference] 0.91	 0.64, 1.28	 0.577
	Methadone dose	1.0	1.0, 1.0	0.872
	Years in MMT [a]	1.03	0.98, 1.07	0.204
	Employed	0.53	0.37, 0.75	< 0.001
	Married or common law	0.74	0.51, 1.06	0.098
	Age of onset of opioid use [b]	0.97	0.95, 0.99	0.002
	Opioid abstinence Opioid use	[reference] 1.41	 0.95, 2.10	 0.090
	Suicidal ideation	1.12	0.61, 2.06	0.710
Current PTSD	Male sex Female sex	[reference] 2.13	 1.20, 3.76	 0.009
	Methadone dose	1.0	1.0, 1.0	0.264
	Years in MMT [a]	1.01	0.95, 1.08	0.691
	Employed	0.31	0.16, 0.61	0.001
	Married or common law	0.51	0.26, 0.99	0.046
	Age of onset of opioid use [b]	0.95	0.92, 0.98	0.004
	Opioid abstinence Opioid use	[reference] 1.43	 0.73, 2.81	 0.294
	Suicidal ideation	2.29	1.04, 5.01	0.039

OR = Odds Ratio, CI = Confidence Interval, MMT = Methadone Maintenance Treatment
[a] Scaled for every one-year increase in length of time in MMT
[b] Scaled for every one-year increase in age at onset of opioid use

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CHAPTER 5: Cross-sectional exploration of differences between youth and adults receiving opioid agonist treatment for opioid use disorder

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ABSTRACT

Background: There is an underutilization of opioid agonist treatment (OAT) in youth with opioid use disorder, necessitating increased understanding of the unique characteristics of this population. We explored characteristics of youth (<25 years) compared to adults (≥25 years) enrolled in OAT.

Method: We recruited 261 youth and 3,184 adults receiving OAT at 36 outpatient clinics in Ontario, Canada. Cross-sectional data on sociodemographic, treatment, and substance use were obtained, and the Mini-International Neuropsychiatric Interview was administered to identify psychiatric comorbidity. We used logistic regression to explore characteristics associated with youth compared to adults in OAT.

Results: Compared to adults, youth had higher odds of being female (Odds Ratio[OR] 1.67, 95% Confidence Interval[CI] 1.25,2.23) and lower odds of finishing high school (OR 0.53, 95% CI 0.39,0.71). Youth had higher odds of intravenous drug (OR 1.47, 95% CI 1.08,2.01), and cannabis (OR 1.78, 95% CI 1.32,2.39) use; they had lower odds of starting opioid use following a physician prescription (OR 0.19, 95% CI 0.13,0.29). Youth were enrolled in treatment for less time than adults (OR 0.76, 95% CI 0.71,0.82) but had higher odds of abstinence from opioids (OR 1.65, 95% CI 1.22,2.22). Youth had higher odds of meeting criteria for bipolar (OR 2.41, 95% CI 1.20,4.83) and anxiety disorders (OR 1.85, 95% CI 1.08,3.17).

Conclusion: Youth in OAT differ from adults in their demographic characteristics, substance use, health risk behaviors, and psychiatric comorbidity. These findings suggest areas of attention

for clinical programs treating youth with OUD, including educational supports and management of co-occurring psychiatric disorders.

BACKGROUND

North America is experiencing an ongoing opioid crisis. In 2019, data from the United States indicate that opioids were involved in nearly 50,000 overdose deaths, accounting for more than 70% of all drug overdose-related deaths.[1] Meanwhile, in Canada, which has a population 10 times smaller than that of the United States, 6,214 deaths related to apparent opioid toxicity occurred in 2020.[2] Concerningly, the prevalence of opioid misuse in adolescents and young adults continues to rise.[3] In 2017, the Ontario Student Drug Use and Health Survey demonstrated that 10.6% of students in grades 7-12 had used non-prescription opioids within the previous 1 year,[4] although data on the prevalence of opioid use disorder (OUD) in North American youth are lacking.

OUD treatment for adolescents has traditionally been limited to psychosocial treatment interventions and short-term inpatient withdrawal management programs. Less than 25% of adolescents and young adults (ages 13-25) diagnosed with OUD are prescribed medications, and for those younger than 18, less than 2% receive opioid agonist treatment (OAT) with buprenorphine-naloxone or methadone;[5,6] meanwhile, OAT rates for adult populations are estimated to be 57%.[7] Even after a nonfatal opioid-related overdose, only 28% of young adults aged 18 to 21 receive OAT within 12 months, compared to 36% of adults aged 26 to 45.[8] Adolescents and young adults who receive timely access to OAT are more likely to be retained in treatment compared to the use of behavioural strategies only.[9] Youth with OUD have limited access to opioid agonist medications, and standard models of opioid agonist-based care for OUD youth are lacking.[9,10] This is despite both the American Academy of Pediatrics recommendation for the use of OAT for youth with OUD[11] and several randomized controlled trials demonstrating evidence that OAT safely reduces opioid use and improves treatment retention in adolescents and young adults.[12-14]

For youth who do receive access to OAT, there is evidence to suggest that they experience lower rates of treatment retention compared with adults (56% versus 78% at 3 months and 17% versus 45% at 12 months), as well as higher rates of relapse, testing positive for opioids, and dropping out of treatment.[14] Youth also experience unique risk factors as well as barriers to care, including the potential long lasting effects of substance use on the developing brain, stigma, lack of perceived need for treatment, and minimum age for treatment approval for opioid agonist therapy.[15] Given that there is an underutilization of OAT in youth with OUD, understanding unique characteristics of this population may inform improvements for treatment engagement and outcomes. In this study, we explored characteristics of youth younger than 25 years of age, compared to adults 25 years and older enrolled in OAT to explore similarities and differences in (1) sociodemographic characteristics, (2) substance use characteristics, and (3) psychiatric comorbidity in youth compared to adult patients.

METHOD

We use data collected in the Genetics of Opioid Addiction (GENOA)[17] and Pharmacogenetics of Opioid Substitution Treatment Response (POST)[18] research programs based in Ontario, Canada. The objective of these studies was to examine factors associated with treatment outcomes for patients receiving methadone or buprenorphine-naloxone for OUD using a naturalistic study design. GENOA study recruitment took place between 2013 and 2016, and the POST study was developed in 2018 as an extension of the former study. Study procedures were approved by, and followed in accordance with, the ethical standards of the Hamilton Integrated Research Ethics Board (project IDs 11-056 and 4556).

We recruited participants from 36 outpatient OAT clinics across Ontario, Canada that are part of a larger network of Canadian Addiction Treatment Centres (CATC) run centrally by one management team. Participants were consecutively approached for study recruitment upon attending regularly scheduled clinical appointments using a convenience sampling strategy with no stratification parameters; all participants provided verbal and written informed consent. Eligible participants were at least 16 years old and receiving methadone or buprenorphine-naloxone for OUD, as diagnosed by treating physicians using Diagnostic and Statistical Manual of Mental Disorders, 4th Edition TR criteria in the GENOA study[19] and 5th Edition criteria in the POST study.[20] Participants who were enrolled into both studies were identified by medical record number and only data from their initial recruitment were retained.

At study entry, we obtained cross-sectional data using a semi-structured interview with trained research staff to collect information on sociodemographic characteristics, treatment history, and self-reported past-month substance use using the Maudsley Addiction Profile questionnaire.[21] We administered the Mini-International Neuropsychiatric Interview[22] to all patients recruited from 2013-2016, including 66 youths and 617 adults, to identify psychiatric comorbidity including mood disorder (major depression or bipolar disorder), anxiety disorder (generalized anxiety disorder, social anxiety disorder, posttraumatic stress disorder, obsessive compulsive disorder, panic disorder and agoraphobia), psychotic disorder (schizophrenia, schizoaffective disorder, brief psychotic disorder, delusional disorder, substance-induced psychosis, and psychosis not otherwise specified), and eating disorder (anorexia nervosa and bulimia nervosa). Use of this tool was subsequently discontinued due to time burden of administration. Routine urine drug screens (UDSs), conducted as part of regular clinical management were reviewed at the time of study entry to identify opioid use including morphine, oxycodone, fentanyl, methadone metabolite, and buprenorphine using the IMDx Prep Assay in the GENOA Study (NOVX Systems, Richmond Hill, Ontario, Canada) and the FaStep Assay in the POST study (Trimedic Supply Network Ltd, Concord, Ontario, Canada).

We conducted all statistical analyses using Stata Version 15.1 (StataCorp LP, College Station, TX, USA). We used descriptive statistics and reported sociodemographic and clinical variables summarized as means with standard deviation (SD) for normally distributed variables, and medians with first and third quartiles for non-normally distributed data. We summarized categorical variables with frequencies and percentages. To achieve our objectives and compare characteristics of youth and adults enrolled in OAT, we used logistic regression analyses, which allowed us to adjust for potential confounding variables and obtain effect estimates. We ran both unadjusted logistic regressions examining the association between characteristics of interest and youth versus adult subgroups, as well as models adjusted for all covariates of interest. Our first logistic regression was constructed to include the binary dependent variable youth versus adult and our covariates of interest including sociodemographic characteristics (biological sex, married or common law status, high school completion, unemployment, and having children), clinical characteristics (methadone versus buprenorphine-naloxone treatment, years in treatment, starting opioid use by physician prescription versus not, having an emergency department (ED) visit for overdose in the last 12 months, and reporting suicidal ideation versus not), opioid abstinence as per urine drug screens at study entry, and past-month self-reported substance use (intravenous drug use, cannabis use, and alcohol use). We conducted a sensitivity analysis using multinomial logistic regression to assess whether trends in our findings held when examining youth aged 21 years and younger separately from older youth and adults. This model was constructed using the same covariates as the logistic regression analysis described above.

We constructed our second logistic regression to estimate the association between psychiatric comorbidity and youth versus adults and adjusted only for biological sex due to the smaller sample size of available data, using the rule of thumb of 10 events needed per covariate included in a logistic regression model.[23] We report results using odds ratios (OR) with 95% confidence intervals (CI) such that an OR greater than 1 indicates greater odds of association with youth and an OR less than 1 indicates lower odds of association with youth.

Missing data affected 1.1% of our study sample (n = 38). Given that only one youth patient had missing data on only a single covariate, and the overall proportion of missing data was small, we did not pursue multiple imputation methods for analysis. This paper is reported in keeping with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[24]

RESULTS

A total of 1,360 individuals were recruited into the GENOA study and another 2,359 were recruited in the POST study (Figure 5). Following exclusion of participants enrolled in duplicate (n = 274), our final study cohort consisted of 3,445 unique participants, of which 7.6% were youth (n = 261).

Participants' sociodemographic, clinical, mental health and substance use characteristics at the time of study enrolment are recorded in Table 9. The mean age of youth participants was 22.5 years (SD = 1.7) and for adults was 40 years (SD = 10.2). We present the age distribution of youth in Figure 2. Most youth (83%) and adults (87%) were treated with methadone, while a minority received buprenorphine-naloxone. The prevalence of comorbid psychiatric disorders, as identified using the MINI, is presented in Table 10.

Our first two objectives were to explore similarities and differences in the sociodemographic and substance use characteristics of youth receiving OAT compared to adults (Table 11). Youth and adults were equally likely to be prescribed methadone compared to buprenorphine-naloxone (OR 0.93, 95% CI 0.63, 1.36). There was also no significant difference in their odds of unemployment (OR 1.24, 95% CI 0.91, 1.68). Compared to adults, youth were more likely to be female (OR 1.67, 95% CI 1.25, 2.23) and less likely to have finished high school (OR 0.53, 95% CI 0.39, 0.71). Youth were also less likely to have children (OR 0.25, 95% CI 0.18, 0.34). Youth were less likely to have started opioid use following a physician prescription (OR 0.19, 95% CI 0.13, 0.29) and more likely to use drugs intravenously (OR 1.47, 95% CI 1.08, 2.01). They were more likely to self-report past-month cannabis use (OR 1.78, 95% CI 1.32, 2.39) and no significant difference was identified in the odds of reporting past-month alcohol use (OR 1.16, 95% CI 0.88, 1.54). Youth were enrolled in treatment for less time than adults (OR 0.76, 95% CI 0.71, 0.82) but were more likely to be abstinent from opioids as measured by urine drug screens before study entry (OR 1.65, 95% CI 1.22, 2.22).

The results of our sensitivity analysis separately examining youth aged 21 years and younger are outlined in Table 12 and revealed findings similar to those for all youth younger than 25 years. Youth aged 21 years and younger were more likely to be female, use intravenous drugs and use cannabis compared to adults. They were less likely to have finished high school, have children, and start opioid use following physician prescription. Youth aged 21 and younger were also more likely to be abstinent from opioids before study entry than adults.

Our final objective was to explore differences in psychiatric comorbidity in youth and adults in our study cohort (Table 13). Notably, youth had 2.4 times greater odds of meeting criteria for bipolar disorder (OR 2.41, 95% CI 1.20, 4.83) and 1.8 times greater odds of meeting criteria for anxiety disorders (OR 1.85, 95% CI 1.08, 3.17) than adults. Meanwhile, we did not identify any significant differences in the odds of meeting criteria for major depression (OR 1.15, 95% CI 0.62, 2.15), psychotic disorders (OR 0.31, 95% CI 0.04, 2.44), or eating disorders (OR 1.06, 95% CI 0.12, 9.46).

DISCUSSION

In this study we set out to identify similarities and differences in sociodemographic, substance use, and psychiatric characteristics between youth and adults receiving treatment for OUD. Consideration of these characteristics may inform an understanding of patient experiences as well as strategies to improve treatment and outcomes.

The biological sex distribution in both youth and adult patients was skewed towards a slightly higher percentage of males; however, youth were more likely to be female than their adult counterparts. Sex- and gender-related unmet healthcare needs[25] are a significant concern across the healthcare system, but particularly for patients with substance use disorders. Studying the sex and gender disparities in OUD highlights potential sources for intervention; females are much more likely to experience psychiatric comorbidity, chronic pain, and have higher rates of overdose under the age of 16.[26] Additionally, females with addiction are more likely to experience greater unpleasant withdrawal symptoms and greater levels of stress during attempts at abstinence.[27,28] They have also been shown to be more likely to relapse and do so more sporadically compared to their male counterparts.[28] Furthermore, females receiving OAT are less likely to be employed (OR 0.39, 95% CI 0.21 to 0.73), more likely to have childcare responsibilities (OR 2.88, 95% CI 1.90, 4.36), and more likely to have comorbid physical and psychological health problems.[29,30] There is evidence to suggest that female youths who have substance use disorders experience greater psychosocial adversity in childhood and family environment as well as more severe substance use and mental health symptoms.[31] Similarly, a US study of youth with nonfatal opioid overdoses found that females had a higher prevalence of mood or anxiety disorders (65.5% versus 51.9%), trauma-related disorders (16.4% versus 10.1%), and suicide attempt or self-harm (14.6% versus 9.9%) compared to male youths.[32]

Although we identified similar prevalence of unemployment affecting about two thirds of youth and adult patients, youth were 50% less likely to have finished high school. Drug use in adolescence confers a reduction in sustained academic engagement whereas treatment programs targeted at reducing substance use have conferred increased school attendance.[33] Opioid use affects intrinsic motivation, leads to an inability to focus on schoolwork, increases the likelihood of delaying or stopping education completely, and may lead to prioritization of drug seeking behavior over education.[34] This is a risk factor for income-related health inequalities[35] putting these youth further at risk compared to their adult counterparts. The lower educational attainment may be associated with higher rates of low financial compensation, poorer healthcare benefits, and jobs that are more likely to involve manual or physical labor which are associated with higher rates of OUD relapse.[34, 36,37] Youth may require additional educational supports either embedded in substance use treatment programs or provided in parallel or sequentially.[38]

Youth were also found to be enrolled in treatment for shorter durations than adults. Previous data have indicated that youth have lower rates of treatment retention,[14] however this is improved by timely access to OAT.[8] There are several possible reasons for the lower program retention rates of youth compared to adults. Although this was not investigated as a part of this study, these reasons may include highly variable patient-reported treatment goals,[14] shorter durations of treatment with buprenorphine,[39] lack of timely receipt of OAT,[8] as well as interpersonal factors such as family conflict[8]. Many of these factors are unique to the youth population and highlight the need for specialized youth-specific clinical programs. Encouragingly, the results of urine drug screens indicated that youth were more likely to be abstinent from opioids than adults before study entry. Whether this can be interpreted to suggest superior treatment outcome, or if this finding simply reflects a recruitment bias is not possible to disentangle.

Both youth and adults were more likely to be prescribed methadone compared to buprenorphine-naloxone, reflecting broader trends in OAT prescribing in Ontario related to prescription drug coverage and clinical practice guidelines. Only in 2016 was buprenorphine-naloxone added to the Ontario Drug Benefit Formulary without limitations, therefore providing coverage for individuals who did not have private insurance for prescription medications. More recently, in the 2018 CRISM National Guideline for the Clinical Management of Opioid Use Disorder was buprenorphine-naloxone recommended as a first-line treatment for OUD.[40]

Youth were less likely to have initiated opioid use following a physician prescription and instead described first obtaining opioids from friends, from home, or "on the street". This suggests that public health interventions around reducing physician prescribing of opioid medications are unlikely to have as great an impact on youth opioid use, except in so far as they reduce the availability of prescription opioids in the illicit market through diversion. We also found that youth were more likely to use drugs intravenously, which independently raises their risk of skin and deep tissue infections, hepatitis C, HIV, and fatal overdose.[41,42] Youth were also more likely to report cannabis use. Cannabis use, on a population level, has been monitored rather closely since the 2018 legalization of recreational cannabis in Canada. Data collected in 2019 suggested that 33.3% of youth 18-24 years of age reported using cannabis in the preceding three months, the highest rate of use among all age groups and unchanged from before cannabis legalization.[43]

Most alarming are the substantial differences detected in rates of psychiatric comorbidity. Youth enrolled in this study were more than twice as likely as adults to meet criteria for bipolar disorder, and nearly twice as likely to have an anxiety disorder. The prevalence of these disorders in both youth and adults was considerably higher than prevalence estimates within the general population, which suggest that about 25% of adolescents aged 13-18 have a 12-month prevalence of anxiety disorders and about 2% have a 12-month prevalence of bipolar disorder while 19.1% and 2.8% of adults older than 18 have a 12-month prevalence of anxiety disorders and bipolar disorder, respectively.[44] Studies have shown that earlier onset of opioid use has been related to higher rates of both physical and psychiatric comorbidity.[45] Concurrent mental illness has been linked to higher mortality and acute care use but not to a change in treatment retention.[46] There is little evidence available to study the cause-effect relationship of opioid use and psychiatric comorbidities in youth, however studies have shown the onset of psychiatric disorders is typically earlier than the onset of substance use disorders in youth.[47] Studies have also shown that psychiatric comorbidities are important risk factors in premature drug-related deaths[48] as well as suicide attempts.[49] Given our finding that youth are more likely to suffer from comorbid anxiety and bipolar disorder, concern should be raised about long-term treatment outcomes for youth compared to adults. Treatment outcomes are improved in adults when concurrent mental health and addiction treatment is offered within an integrated treatment program,[47, 50, 51, 52] however no data exist similarly for youth. This highlights several areas of further study as well as targets of intervention for care providers.

Our investigation of differences between youth and adults in OAT identified a number of important factors and raises the question as to whether youth should be treated in the same programs as adults. Youth are developmentally different from adults and have different social and psychological needs. It was recognized as early as the 1950's that adolescent drug use behaviors are not the same to those of adults and that youth may benefit from modified treatment approaches.[53] However, programs did not truly start to materialize until the 1980's and into the 1990's, focusing on some of the unique susceptibilities of youth; higher rates of binge use, psychiatric comorbidity, lower problem recognition, and susceptibility to peer influence.[53] Studies have identified several essential elements of effective treatment that are unique to the adolescent population, including family involvement and developmentally appropriate therapies.[54, 55] However, the paucity of currently available treatments offered for youth are a rate-limiting step. US studies suggest that fewer than half of the addiction treatment programs for youth offer medication treatments for OUD.[56]

This study carries several limitations that impact the interpretation of our results. First, this is not a population-level study and is therefore not representative of all youth or adults with OUD or receiving OAT. All included participants agreed to be recruited into the study, therefore carrying a risk of bias related to volunteer bias and healthy user bias. Second, the data collected are cross-sectional in nature and does not capture the effect of time on our characteristics of interest, such as employment or co-occurring drug use. Third, youth represent a small minority of participants recruited into our study; although this may reflect the age distribution of individuals in OAT, it is possible that youth may have had a different participation rate and the details of this are not available. Data from the Ontario Drug Policy Research Network Ontario Prescription Opioid Tool[57] suggest that the count of patients aged 15-24 prescribed opioid agonist therapy in Ontario in 2013 was 6,236, representing 13.6% of all patients prescribed opioid agonist therapy in Ontario. In 2019, this figure was 3,574, representing 5.4% of all patients prescribed opioid agonist therapy in the province. Although the total number of patients receiving OAT increased between 2013 and 2019 (45,781 to 65,817), the proportion of youths younger than 24 receiving prescriptions decreased. The reasons for this are unclear and warrant further study. Given these provincial counts, our recruitment of youth between 2013 and 2019 to represent 7.6% of our total study sample appears reasonable. Importantly, youth treated in these clinics may differ from youth with OUD receiving OAT in other settings such as residential treatment, family physicians' offices, or youth-specific treatment programs.

CONCLUSION

Youth enrolled in OAT differ from adults in important ways, as demonstrated by their sociodemographic characteristics, their substance use, and their psychiatric comorbidity. In this paper, we highlight some of these differences and identify possible areas of attention for clinical programs treating youth with OUD. This includes attention to the relevance of sex differences in treatment, the need for educational supports, and the importance of identifying and managing co-occurring psychiatric disorders.

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Authors' contributions: TR and ZS are responsible for the study concept and design. TR and ZS developed the methods and data analysis. TR conducted the statistical analyses. TR and JM wrote the first draft of the manuscript, and AW, DM, LT and ZS contributed to writing and critically revising the final manuscript. All authors reviewed and approved the final manuscript.

FIGURES AND TABLES

Figure 5. Study flow diagram

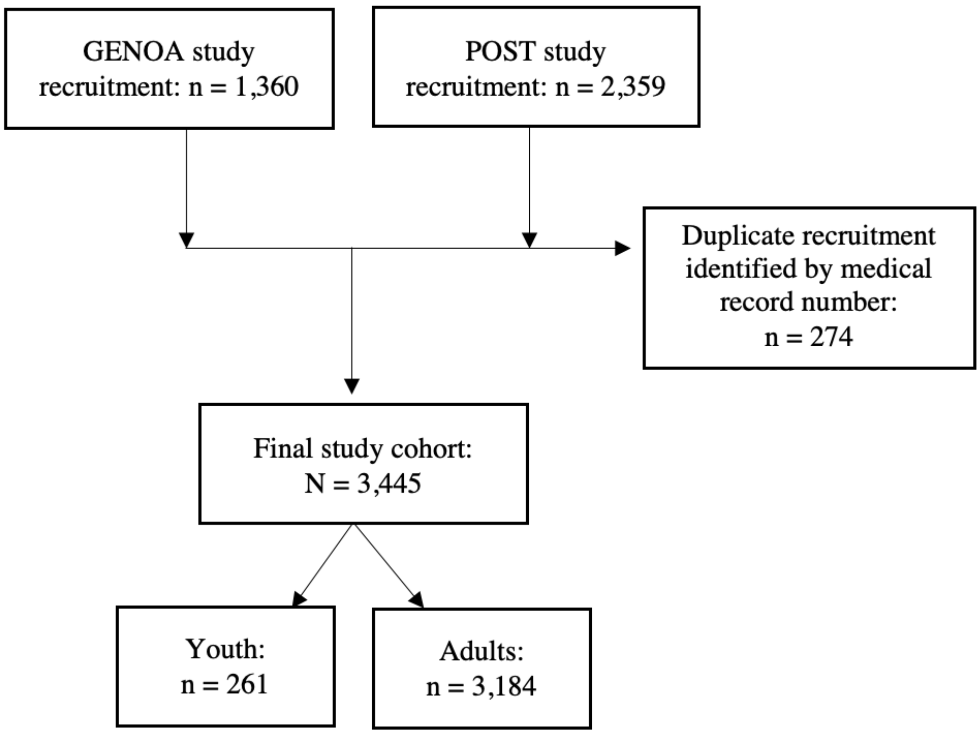

Figure 6. Age distribution of youth recruited into the study (n = 261).

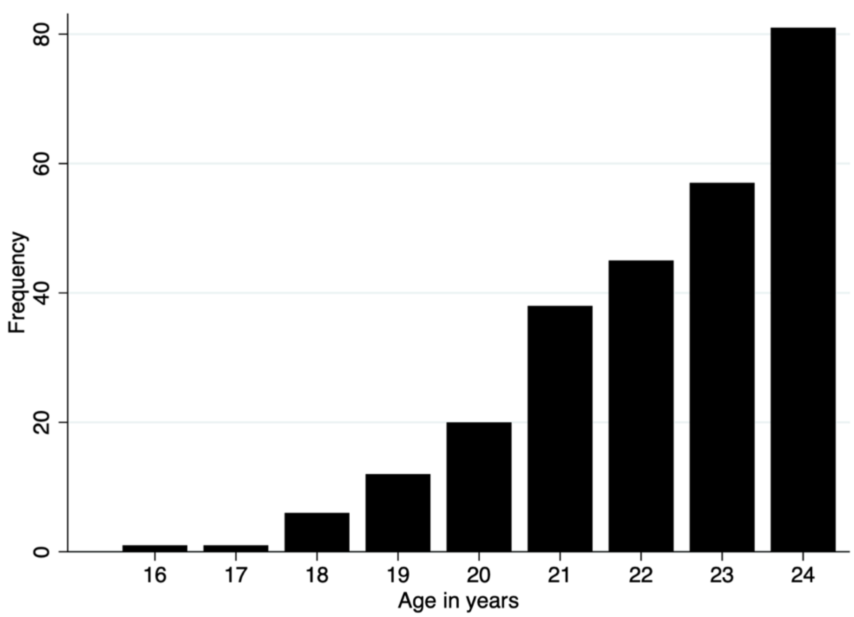

Table 9. Characteristics of youth and adults at study entry.

Characteristic	Total Sample (n = 3445)	Adults (n = 3184)	Youth (n = 261)
Sociodemographic			
Age (years); mean (SD)	38.7 (10.9)	40.0 (10.2)	22.5 (1.7)
Biological sex; *n* (%) Males Females	 1928 (56.0%) 1516 (44.0%)	 1787 (56.1) 1396 (43.9)	 141 (54.0%) 230 (46.0%)
Marital status; *n* (%) Married/common-law Single	 1038 (30.1%) 2407 (69.9%)	 981 (30.8%) 2203 (69.2%)	 57 (21.8%) 204 (78.2%)
Parenthood status[a]; *n* (%) Children No children	 2299 (66.8%) 1142 (33.2%)	 2212 (69.5%) 969 (30.5%)	 87 (33.5%) 173 (66.5%)
Education; *n* (%) Less than high school High school Post-secondary	 889 (25.8%) 1572 (45.6%) 984 (28.6%)	 793 (24.9%) 1429 (44.9%) 962 (30.2%)	 96 (36.8%) 143 (54.8%) 22 (8.4%)
Employment status[b]; *n* (%) Unemployed Employed	 2275 (66.1%) 1167 (33.9%)	 2096 (65.9%) 1085 (34.1%)	 179 (68.6%) 82 (31.4%)
Clinical			
Type of OAT; *n* (%) Methadone Buprenorphine-naloxone	 2983 (86.6%) 460 (13.4%)	 2766 (86.9%) 416 (13.1%)	 217 (83.1%) 44 (16.9%)
Dose (mg/day)[c]; mean (SD) Methadone Buprenorphine-naloxone	 69.3 (42.7) 12.1 (6.8)	 70.1 (43.2) 12.3 (6.8)	 58.4 (34.2) 10.6 (6.6)
Years in treatment[c]; median (Q1, Q3)	2 (0.7, 5.9)	2.3 (0.7, 6)	1 (0.25, 2)
Opioid use started following physician prescription[c]; *n* (%)	1551 (45.1%)	1523 (47.9%)	28 (10.7%)
Self-reported history of opioid overdose; *n* (%)	654 (31.4%)	585 (30.2%)	69 (47.6%)
Self-reported history of opioid overdose requiring ED visit in the last year; *n* (%)	230 (6.7%)	195 (6.1%)	35 (13.4%)
Self-reported past-month suicidal ideation; *n* (%)	744 (21.6%)	668 (21.0%)	76 (29.1%)
Substance use			
Opioid abstinence at study entry[d]; *n* (%)	1229 (35.8%)	1130 (35.6%)	99 (37.9%)
Self-reported past-month cannabis use[c]; *n* (%)	1757 (52.3%)	1578 (50.8%)	179 (69.7%)

Self-reported past-month alcohol use[e]; *n* (%)	1344 (39.2%)	1217 (38.4%)	127 (48.9%)
Self-reported intravenous drug use; *n* (%)	753 (21.9%)	666 (20.9%)	87 (33.3%)
SD = standard deviation, MAT = medication assisted treatment, Q1 = quartile 1, Q3 = quartile 3, ED = emergency department [a] Data missing for 4 participants. [b] Data missing for 3 participants. [c] Data missing for 7 participants. [d] Data missing for 12 participants. [e] Data missing for 18 participants.			

Table 10. Psychiatric disorders identified using the Mini-International Neuropsychiatric Interview in a subset of the study sample (n = 683).

MINI Diagnosis	**Total Sample** (n = 683)	**Adults** (n = 617)	**Youth** (n = 66)
Major Depression	190 (27.8%)	172 (27.9%)	18 (27.3%)
Bipolar Disorder	90 (13.2%)	74 (12.0%)	16 (24.2%)
Anxiety Disorder	262 (38.4%)	227 (36.8%)	35 (53.0%)
Psychotic Disorder	25 (3.7%)	24 (3.9%)	1 (1.5%)
Eating Disorder	8 (1.2%)	7 (1.1%)	1 (1.5%)

Table 11. Characteristics associated with youth compared to adults in treatment.

Unadjusted Analysis				**Adjusted Analysis** (n = 3407) [a]		
Covariate	**OR**	**95% CI**	***p***	**OR**	**95% CI**	***p***
Female sex	1.09	0.85, 1.40	0.507	1.67	1.25, 2.23	0.001
Married or common law	0.63	0.46, 0.85	0.003	0.93	0.67, 1.30	0.665
Completed high school	0.57	0.44, 0.74	< 0.001	0.53	0.39, 0.71	< 0.001
Unemployed	1.13	0.86, 1.48	0.378	1.24	0.91, 1.68	0.174
Have children	0.22	0.17, 0.29	< 0.001	0.25	0.18, 0.34	< 0.001
Type of Treatment Methadone Buprenorphine-naloxone	 [ref] 1.35	 - 0.96, 1.89	 - 0.085	 [ref] 0.93	 - 0.63, 1.36	 - 0.697
Years in treatment (for each one year longer in treatment)	0.75	0.70, 0.80	< 0.001	0.76	0.71, 0.82	< 0.001
Starting opioids by physician prescription	0.13	0.88, 0.19	< 0.001	0.19	0.13, 0.29	< 0.001
Intravenous drug use	1.89	1.44, 2.48	< 0.001	1.47	1.08, 2.01	< 0.001
Self-reported cannabis use	2.21	1.69, 2.90	< 0.001	1.78	1.32, 2.39	< 0.001
Self-reported alcohol use	1.53	1.19, 1.97	0.001	1.16	0.88, 1.54	0.298
Opioid abstinence at study entry	1.11	0.85, 1.43	0.448	1.65	1.22, 2.22	0.001
Self-reported suicidal ideation	1.55	1.17, 2.05	0.002	1.17	0.85, 1.61	0.328

OR = odds ratio, CI = confidence interval
[a] Sample size reflects missing data affecting 38 participants.

Table 12. Characteristics associated with youth younger than 21 years compared to youth aged 22 to 24 years and to adults older than 25.

	Adjusted Analysis (n = 3407) [a]			
	Covariate	**OR**	**95% CI**	***p***
Reference group: adults >25 years				
Youth ≤21years	Female sex	1.91	1.14, 3.19	0.014
	Married or common law	1.16	0.65, 2.10	0.612
	Completed high school	0.47	0.28, 0.78	0.004
	Unemployed	1.70	0.97, 2.97	0.064
	Have children	0.16	0.09, 0.28	<0.001
	Type of Treatment Methadone Buprenorphine-naloxone	 [ref] 1.19	 0.67, 2.17	 0.582
	Years in treatment (for each one year longer in treatment)	0.60	0.48, 0.72	<0.001
	Starting opioids by physician prescription	0.07	0.02, 0.24	<0.001
	Intravenous drug use	1.31	0.77, 2.24	0.321
	Self-reported cannabis use	2.48	1.40, 4.41	0.002
	Self-reported alcohol use	1.28	0.78, 2.09	0.332
	Opioid abstinence at study entry	1.87	1.11, 3.16	0.019
	Self-reported suicidal ideation	1.52	0.90, 2.56	0.115
Youth 22-24 years	Female sex	1.61	1.16, 2.23	0.004
	Married or common law	0.86	0.59, 1.26	0.452
	Completed high school	0.56	0.40, 0.79	0.001
	Unemployed	1.10	0.78, 1.56	0.582
	Have children	0.29	0.21, 0.41	<0.001
	Type of Treatment Methadone Buprenorphine-naloxone	 [ref] 0.81	 0.51, 1.28	 0.365
	Years in treatment (for each one year longer in treatment)	0.80	0.75, 0.86	<0.001
	Starting opioids by physician prescription	0.24	0.15, 0.37	<0.001
	Intravenous drug use	1.52	1.07, 1.52	0.019
	Self-reported cannabis use	1.59	1.14, 2.21	0.007

	Self-reported alcohol use	1.11	0.80, 1.53	0.530
	Opioid abstinence at study entry	1.58	1.13, 2.22	0.008
	Self-reported suicidal ideation	1.05	0.73, 1.52	0.783
OR = odds ratio, CI = confidence interval [a] Sample size reflects missing data affecting 38 participants.				

Table 13. Estimates of psychiatric disorders in youth compared to adults in treatment (n = 683).

Unadjusted				**Adjusted** [a]		
Covariate	**OR**	**95% CI**	***p***	**OR**	**95% CI**	***p***
Female sex	0.84	0.50, 1.41	0.510	0.66	0.38, 1.13	0.129
Major Depression	0.97	0.55, 1.71	0.917	1.15	0.62, 2.15	0.649
Bipolar Affective Disorder	2.35	1.27, 4.34	0.006	2.41	1.20, 4.83	0.013
Anxiety Disorder	1.94	1.16, 3.23	0.011	1.85	1.08, 3.17	0.025
Psychotic Disorder	0.38	0.05, 2.86	0.347	0.31	0.04, 2.44	0.268
Eating Disorder	1.34	0.16, 11.07	0.785	1.06	0.12, 9.46	0.958
OR = odds ratio, CI = confidence interval [a] Model adjusted for biological sex, major depression, bipolar affective disorder, anxiety disorder, psychotic disorder and eating disorder						

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CHAPTER 6: Hospital and physician-based mental health care during 12 months of opioid agonist treatment for opioid use disorder: exploring costs and factors associated with acute care

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ABSTRACT

Background: Individuals with opioid use disorder (OUD) have a high prevalence of co-occurring mental health disorders. While comorbidity has been associated with worse treatment outcomes, there is little information on mental health service use for this population.

Aims: We aimed to determine the prevalence of non-substance-related mental health emergency department (ED) visits, hospitalizations, and outpatient physician visits for individuals receiving treatment for OUD over one year. We also explored individual-level characteristics associated with acute mental health care service use and estimated the costs of this care.

Method: We linked observational cohort data collected from 3,430 individuals receiving treatment for OUD in Ontario with health administrative records available for all individuals enrolled in Ontario's public health insurance program. Starting on the day of cohort enrolment, we included health service data for up to 12 months. We identified ED visits and hospitalizations for non-substance use-related mental health disorders using ICD-10-CA diagnostic codes. Outpatient mental health visits to primary care providers and psychiatrists were ascertained by examining the diagnostic codes of physician billing claims. We used logistic regression to explore the association between demographic and clinical factors of interest and acute mental health-related care measured as ED visits or hospitalizations. Mean one-year mental healthcare costs, calculated in 2022 Canadian dollars, were estimated. We fit a two-part zero-inflated negative binomial model to explore the association between factors of interest and healthcare costs.

Results: Altogether, 14.9% of individuals had mental health-related acute care ED visits or hospitalizations and 37.3% had outpatient mental health visits during the follow up period. For participants with at least one visit, we determined the mean number of ED visits (1.93, standard deviation [SD] = 2.15), hospitalizations (1.46, SD = 1.05), primary care visits (3.51, SD = 4.31), and psychiatry visits (4.04, SD = 4.73). Lower odds of ED use and hospitalization was associated with older age (46+ compared to less than 25 years: odds ratio [OR] 0.43, 95% confidence interval [CI]: 0.29, 0.63) and being employed (OR 0.48, 95% CI 0.37, 0.61). Higher odds of ED use and hospitalization was associated with positive opioid urine drug screens (50% positive urine drug screens compared to 0%: OR 1.45, 95% CI 1.02, 2.01), having more comorbid conditions (7+ health conditions compared to 0-2 health conditions: OR 3.76, 95% CI 1.95, 2.92), and receipt of outpatient mental health care (OR 2.38, 95% CI 1.95, 2.92) were associated with higher odds of ED visits or hospitalizations. Mean one-year mental healthcare costs for individuals receiving ED visits or hospitalizations totaled $9,117.80 (95% CI 7,372.90, 10,862.70) per person. Mean one-year costs for individuals with outpatient mental healthcare alone totaled $382.30 (95% CI 343.20, 421.30) per person.

Conclusion: Individuals receiving treatment for OUD were seen in EDs, inpatient units, and outpatient clinics for mental health conditions other than substance use-related diagnoses. Healthcare costs were considerably higher for those receiving acute care treatment for mental health conditions. Studying integrated mental health and substance use disorder treatment in the outpatient setting should be a priority to bolster care for this population.

BACKGROUND

Opioid use disorder (OUD) remains an unrelenting public health problem, affecting the lives of millions and causing substantial morbidity and mortality across North America.[1,2] To plan services, allocate resources, and appreciate the public health burden of the opioid crisis, efforts have been made to measure health care utilization and costs for individuals with OUD, particularly in relation to opioid misuse, poisonings, and treatment.[3-5] Individuals with OUD also experience a disproportionate number of other comorbid medical problems related to or precipitated by their illness, including infectious diseases, liver disease, cardiac disease, and pain disorders, among others. These comorbidities, too, contribute to a high level of health care service utilization.[6-9] While some studies have explored patterns and predictors of health care service use related to medical comorbidities of OUD, there is a dearth of information on the mental health service use patterns of this population.

Many people with OUD experience other mental health disorders comorbidly. A systematic review and meta-analysis by Santo and colleagues found that among 104,135 individuals with OUD across 345 studies, the prevalence of depression was 36.1% (95% confidence interval [CI] 32.4, 39.7), and anxiety was 29.1% (95% CI 24.0, 33.3).[10] Across Canada, more than half of hospitalizations for OUD include a co-diagnosis of another mental disorder (56%) with sex differences observed in the prevalence and distribution of this comorbidity. Co-occurring substance use disorders are diagnosed more commonly diagnosed among males than females (32% versus 23%, respectively), while mood disorders (8% versus 17%), anxiety disorders (3% versus 8%) and personality disorders (2% versus 6%) are more commonly co-diagnosed in females.[11] Mental health comorbidity is associated with worse OUD treatment outcomes,[12] opioid overdoses,[13] and medical complications of substance use disorders.[14] Mental health comorbidity is also associated with increased all-cause mortality and higher rates of opioid-related ED visits and hospitalizations.[15]

Without robust knowledge of the mental health care needs of patients with OUD, it is difficult to advocate or plan for increased resources, access, and changes in health care delivery. Considering the prevalence and impact of comorbid mental health disorders in this population, further investigation into mental health-related health service utilization is needed. The objective of the present study was to determine mental health-related health care service utilization for individuals with OUD during one year of opioid agonist treatment (OAT). Specifically, we aimed to first describe the prevalence of acute, hospital-based, care (emergency department (ED) visits and hospitalizations), and outpatient physician visits for non-substance-related mental health problems. We then sought to explore individual-level factors associated with acute, hospital-based, care. Finally, we estimated costs of care and explored factors associated with healthcare costs for acute care.

METHOD

We used data from two prospective cohort studies, the GENetics of Opioid Addiction (GENOA) study and the Pharmacogenetics of Opioid Substitution Treatment Response (POST) study. Both studies recruited individuals receiving OAT for OUD at outpatient OAT clinics across Ontario, Canada. The OAT clinics participating in this study are part of a network of clinics run centrally through the Canadian Addiction Treatment Centres. Inclusion and exclusion criteria have been previously described.[16] In the GENOA study, participants were enrolled between 2011 and 2017;

in the POST study, participants were enrolled between May 2018 and April 2021. Both studies were designed to study patient outcomes in OAT over 1 year and to understand biological, psychological, and social risk factors and protective factors related to course in treatment. These studies were approved by the Hamilton Integrated Research Ethics Board (GENOA project ID 11-056; POST project ID 4556; ICES linkage project IDs 12602 and 12767-C). Data from the GENOA and POST cohort studies were merged, and duplicate enrolments excluded such that the most complete record was kept for each individual (n = 272 excluded; Figure 1).

Data were then linked with data holdings of routinely collected Ontario provincial administrative health data housed at ICES (formerly known as the Institute for Clinical Evaluative Sciences), an independent, non-profit research institute in Toronto, Ontario, Canada. ICES holds administrative health records for all individuals enrolled in Ontario's public health insurance program. Individual-level cohort data were linked to ICES data holdings using Ontario health card number and date of birth for deterministic linkage. Additional exclusions were made at the time of data linkage due to limitations in the linkage process: invalid linkage and lack of OHIP eligibility or living out of province (Figure 1). From the ICES holdings, we pulled health care service data for up to 12 months, starting on the day of cohort study enrolment. Follow-up was shorter than 12 months for individuals who were censored due to death (n = 39) or due to recruitment after April 1, 2021 (n = 1) as ICES data were only available up to March 31, 2022. All databases were linked using unique encoded identifiers and analysed at ICES, in compliance with Ontario privacy legislation. The use of these data was authorised under section 45 of Ontario's Personal Health Information Protection Act, which does not require review by a Research Ethics Board.

We follow reporting guidelines as described in Reporting of studies Conducted using Observational Routinely-collected Data (RECORD) and Strengthening the Reporting of Observational Studies in Epidemiology (STROBE).[17,18]

Mental health care service utilization

Data on ED visits and hospitalizations were obtained from the Canadian National Ambulatory Care Reporting System (NACRS), the Discharge Abstract Database (DAD), and the Ontario Mental Health Reporting System (OMRS), respectively. Data from the Ontario Health Insurance Program (OHIP) were used to identify outpatient physician visits. We identified non-substance-related mental health service utilization using International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Canada (ICD-10-CA) codes from the NACRS and DAD databases, and DSM-IV and DSM-5 codes from the OMHRS database as detailed in the ICES Mental Health and Addictions Program Framework.[19] This algorithm has been used in a number of previous ICES studies.[20,21] ED visits or hospitalizations with a main diagnosis of substance use-related problem (ICD codes F10-19) were excluded. Outpatient physician visits were identified as mental health-related if they were: a) any visit to a psychiatrist, or b) visit to a family physician or paediatrician with an OHIP non-substance use-related mental health diagnostic code. These OHIP diagnostic codes capture visits for anxiety, depressive disorders, adjustment reaction, personality disorders, schizophrenia, bipolar disorder, sexual deviations, psychosomatic disturbances, behavioural disorders of childhood, developmental delays, autism, and dementia. We excluded OHIP mental health diagnostic codes for alcoholism, drug dependence, and tobacco use if they were the only code billed for the visit.

Baseline characteristics

Age and sex were available from the Registered Persons Database housed at ICES. Other demographic and clinical characteristics were available from the GENOA and POST cohorts, including marital status, employment status, length of time in treatment, type of OAT (methadone or buprenorphine-naloxone), mean percentage of opioid-positive drug screens and total number of opioid screens taken prior to and during study enrolment.

Using ICES holdings (i.e., DAD, OHIP, and NACRS) on co-occurring health conditions, we were able to identify the number of health conditions experienced by each participant. The number of clinically unrelated health conditions was assessed by applying the Canadian Institute for Health Information POP grouper algorithm to these data holdings.[22] Mental health and substance use disorders were included in the count of co-occurring health conditions.

Mental healthcare cost estimation

We used a cost estimation macro, available from ICES and used in numerous previous studies to estimate mental healthcare costs related to acute care (i.e., ED visits, hospitalizations, and inpatient physician visits) and outpatient physician visits at the individual level.[23-27] Individual episodes of care are assigned a cost or amount paid. In Ontario's public healthcare system, the Ontario Ministry of Health determines the amount paid for episodes of care. For acute care costs, data were obtained from the NACRS, DAD, OMHRS, and OHIP billings where the location of service was inpatient or ED. For outpatient mental health care costs, data were obtained from the OHIP billings claims database where the location of service was outpatient. We estimated mean one-year healthcare costs for ED visits-only, hospitalizations-only, and total acute healthcare costs for those individuals with at least one ED visit or hospitalization for mental health. We estimated mean one-year outpatient healthcare costs for outpatient mental health visits with physicians (primary care or psychiatry) for individuals with at least one such visit. Finally, we estimated total mental healthcare costs (acute care and outpatient) for individuals receiving any acute mental healthcare, and total mental health care costs for individuals receiving only outpatient mental healthcare. All costs are calculated in 2022 Canadian dollars.

Statistical methods

We reported descriptive statistics to summarize demographic and clinical characteristics for participants with acute mental health-related care measured by ED visits and hospitalizations and those without. We reported counts of mental health service use and costs of services using means with standard deviation. We used logistic regression analysis to explore the association between demographic and clinical factors of interest and acute mental health-related care measured by ED and hospital healthcare service use, reporting adjusted odds ratios (ORs) with 95% CIs. To explore the association between factors of interest and acute care mental health-related healthcare costs, we fit a two-part zero-inflated negative binomial model. The first component of the model includes a logistic regression, which estimates the risk of incurring a zero cost. The second component of the model includes a negative binomial regression to estimate the amount of healthcare costs given the risk of having any cost. This model was chosen due to excess zeros within the healthcare service use data and is commonly applied in other studies examining healthcare utilisation.[28-30] The results of this analysis are reported using ORs with 95% CI, and Cost Rate Ratios (CRR) with 95% CI, respectively. We addressed model assumptions and goodness-of-fit by examining the residuals. As missing data affected just 0.6% of the total sample, multiple imputation methods were not used. All analyses were conducted using SAS Enterprise Guide 7.1 (SAS/STAT® Software Version XX, Cary, NC, USA).

RESULTS

The total sample size of the merged GENOA and POST cohorts was 3,486 participants. Linkage with ICES holdings could only be accomplished for 3,430 participants (98.4% of the cohort; Figure 7). Another 20 participants were excluded due to missing data, such that the final study sample included 3,410 participants.

Mental health-related health service utilization

Among this cohort of individuals receiving OAT for OUD, 14.9% (n = 509) experienced a mental health-related ED visit or hospitalization during the study period of up to 12 months of follow up (Table 14). In Table 14, we summarize demographic and clinical characteristics for those with and without mental health-related ED visits or hospitalizations. Females accounted for 48.1% of those who received mental health-related ED visits or hospitalizations and 43.4% of those who did not. Most participants in the study cohort were between 25 and 45 years of age. Among those with mental health-related ED visits or hospitalizations, youth younger than 25 comprised 11%. Meanwhile, youth made up just 6.5% of the cohort without such presentations. In contrast, adults aged 46 and older represented a greater proportion of those who did not have mental health-related ED visits or hospitalizations (27.5% versus 20.8% of those who did). Methadone was the most common type of OAT (83.8% of the total sample). Some participants were abstinent from opioid use as measured by urine drug screens (29.7% of those who had mental health-related ED visits or hospitalizations, as compared to 36.1% of those who did not), while others had urine drug screen evidence of ongoing opioid use.

Altogether, 37.3% of individuals received at least one outpatient mental health visit with a primary care physician or psychiatrist during 12 months of OAT (n = 1,273). Outpatient mental health care was received by 59.7% of individuals who experienced mental health-related ED visits or hospitalizations, meanwhile 33.4% of individuals without mental health-related ED visits or hospitalizations had any outpatient mental health care. Visits with primary care physicians were more common than visits with psychiatrists for both groups. Summary statistics capturing counts of mental health care visits are presented in Table 15. For participants who had at least one visit, the mean number of ED visits was 1.93 (SD = 2.15) and the mean number of hospitalizations was 1.46 (SD = 1.05). For participants who saw primary care physicians for mental health, the mean number of visits over 12 months was 3.51 (SD = 4.31). For those who saw psychiatrists, the mean number of visits was 4.04 (SD = 4.73).

Individual-level factors associated with mental health-related health service utilization

We identified individual-level characteristics associated with having mental health-related ED visits or hospitalizations (Table 16). Adults aged 25-45 and those older than 46 had significantly lower odds of experiencing mental health-related ED visits or hospitalizations than youth younger than 25 (OR 0.64, 95% CI 0.45, 0.89, and OR 0.43, 95% CI 0.29, 0.63, respectively). Individuals who were employed were similarly 50% less likely to have ED visits or hospitalizations (OR 0.48, 95% CI 0.37, 0.61). Higher levels of ongoing opioid use during treatment, as measured by more than 50% of urine drug screens positive for opioids was associated with 1.45 greater odds of mental health-related ED visits or hospitalizations (95% CI 1.05, 2.01) than abstinence from opioids. Having more health conditions was associated with increasing odds of mental health-related ED visits and hospitalizations (3-4 health conditions: OR 1.72, 95% CI 1.15, 2.56; 5-6 health conditions: OR 2.18, 95% CI 1.46, 3.24; 7+ health conditions: OR 3.76, 95% CI 2.60, 5.44). Finally, receipt of outpatient mental health care (primary care or psychiatry) for up to 12 months of follow up was associated with higher odds of mental health-related ED visits and hospitalizations (OR 2.38, 95% CI 1.95, 2.92).

Mental health-related healthcare costs

Costs estimated for mental health-related visits over 12 months are presented in Table 17. On average, mean ED visits cost $775.50 (95% CI 686.00, 865.10) for each individual with at least one mental health-related ED visit. The mean costs attributed to hospitalizations were $9,103.30 (95% CI 7,181.60, 11,025.00). When acute, hospital-based, mental healthcare was considered together (ED visits and hospitalizations), the total mean cost estimated per individual was $7,664.80 (95% CI 6,122.30, 9,207.20) over 12 months. Outpatient mental health-related visits to primary care providers or psychiatrists cost considerably less at $441.30 (95% CI 405.50, 477.10) over 12 months for those individuals who had outpatient mental health-related visits. The total estimated mean cost of mental healthcare for individuals with any acute care visit was $9,117.80 (95% CI 7,372.90, 10,862.70) over 12 months, while the cost for individuals without any acute mental healthcare was estimated at $382.30 (95% CI 343.20, 421.30).

Individual-level factors associated with acute care mental health-related costs

In the logistic regression component of the model, we found that age older than 25 was significantly associated with lower odds of having any mental health-related acute care costs (25-45: OR 0.64, 95% CI 0.46, 0.89; 46+: OR 0.40, 95% CI 0.27, 0.58; Table 18). Employment was associated with lower odds of having any mental health-related acute care costs compared to unemployment (OR 0.52, 95% CI 0.41, 0.65). Factors associated with higher odds of having any mental health-related acute care costs were having greater than 50% of urine drug screens positive for opioids (OR 1.40, 95% CI 1.02, 1.91), and having a greater number of health conditions (7+ health conditions: OR 3.66, 95% CI 2.61, 5.14).

In the negative binomial component of the model, accounting for risk of non-zero acute healthcare costs, we found that older age was associated with higher costs (CRR 2.01, 95% CI 1.19, 3.34; Table 18), as was having any outpatient mental health care (CRR 1.47, 95% CI 1.09, 1.97). Being married or common law status was protective for acute care costs, as compared to being single (CRR 0.62, 95% CI 0.45, 0.87) as was being employed (CRR 0.51, 95% CI 0.36, 0.72).

DISCUSSION

Using observational cohort data linked with health administrative records, we examined mental health-related health care service utilization for individuals with OUD during one year of treatment. Nearly 15% of individuals in the cohort had ED visits or hospitalizations for mental health-related diagnoses during 12 months of OAT. These visits were not attributable to primary substance use-related diagnoses but rather represented health care use for other mental health comorbidities. Factors associated with receipt of acute, hospital-based care, in the form of ED visits and hospitalizations included younger age (less than 25 years), being unemployed, ongoing opioid use during OAT, and poorer health status (as measured by number of health conditions). We also found that 37.3% of individuals saw a primary care provider or psychiatrist for outpatient mental health care during OAT. Receipt of outpatient mental health care was associated with higher odds of ED visits or hospitalizations for mental health.

These findings shed some light on the mental health needs of individuals receiving OAT, as measured by health service use. Few prior studies have examined health service use specifically for mental health-related problems in this population. A study by Vekaria et al. found that among patients with major depressive disorder (MDD), co-occurring OUD was associated with psychiatric hospitalization (44% versus 36% for those with MDD only). The same was true for the use of psychiatric ED services (13% of those with MDD only compared to 25% of those with comorbid OUD).[31] ICES data from Ontario has previously revealed that among nearly 56,000 individuals enrolled in OAT treatment, 87% had a diagnosis of at least one other non-substance-related mental health disorder, with anxiety disorders (60%) and mood disorders (20%) being the most common.[15] Having OUD and a comorbid mental health disorder was associated with increased odds of death and increased incidence of ED visits or hospitalization, although reason for ED visit or hospitalization (OUD-related, medical, or mental health-related) was not explored.[15]

Across Ontario, in the general population, there has been an increase in rates of visits to the ED and hospitalizations. Between 2006 and 2014, the percentage of individuals in the general population with ED visits or hospitalizations for mental health increased from 1.07% to 1.22%, with anxiety and mood disorders being the most common reasons for visit.[32] Our data demonstrate that among those with OUD, the proportion of individuals receiving mental health-related ED visits and hospitalizations (15%) is much higher than in the general population.

The implications of needing and receiving acute, hospital-based mental health care have long been considered. The ED is frequently a first point of contact for many individuals seeking mental health care (nearly half of individuals seen for incident psychiatric ED visits in Ontario).[33] This is particularly true for individuals with substance use disorders or those not connected with primary care.[33] Hospitalizations for mental health disorders are typically indicated when acute safety concerns arise or when symptom severity so high that diagnostic clarification or treatment on an outpatient basis is inadequate. These acute, hospital-based services may be unavoidable for high acuity presentations, however in an optimally functioning health care system with timely access to outpatient mental health supports, they would not be required for lower acuity presentations.

The healthcare costs of opioid-related harms, often measured by poisonings and overdoses, have previously been studied.[34-37] However, little is known about the costs of care related to co-occurring mental health disorders in OUD. We described the 12-month costs of mental healthcare for individuals in our study cohort who received acute, hospital-based care and those who did not. Total costs were nearly 24 times higher for those with mental health-related ED visits and hospitalizations compared to those who received outpatient mental healthcare alone. As expected, many of the demographic and clinical factors we found to be associated with receipt of acute care mental health-related services were similarly associated with increased risk of healthcare costs, as more service use results in higher costs.

As it currently stands, many individuals receiving treatment for OUD do not have access to other outpatient mental health treatment. Results from a national survey conducted in the United States indicate that those with OUD and comorbid mental health disorders do not receive any mental health treatment or counseling (47% of those with mild to moderate illness and 21% of those with serious illness).[38] For those who do receive treatment, pharmacological treatment is the most common treatment modality.[38] Another Ontario-based study revealed that for those with OUD and comorbid mental health disorders, 38% do not receive other mental health services from a primary care physician or psychiatrist in their first year of treatment.[39] Meanwhile, 39.8% have visits with a primary care physician for mental health and 12.1% have visits with both psychiatry and primary care.[39]

Patients with OUD receiving treatment for their substance use disorder represent a group of individuals who may benefit from targeted health system interventions. With a high prevalence of comorbidity and numerous barriers to connection with mental health services, there is a clear need for integrated mental health and addictions care in OUD. Across substance use disorders, evidence demonstrates superior outcomes for integrated treatment of substance use and mental health comorbidity, compared to siloed or sequential treatment.[40] Such compelling evidence supports the collective investment in a system of care which prioritizes integrating OUD and other mental health disorder treatment to improve access to care and outcomes.[41,42] Through a randomized controlled trial, on-site integrated addiction and psychiatric care has demonstrated greater initiation of psychiatric care, longer treatment duration, greater appointment adherence, and improvement in Global Severity Index scores than off site and non-integrated care.[43] Interventions such as contingency management improve the utilization of psychiatric services integrated with OAT programming.[44] A Canadian study by Morin and colleagues found that during the first year of OAT, concurrent psychiatric care was associated with a reduction in all-cause mortality (Risk Ratio [RR] 0.80, 95% CI 0.73, 0.87), all-cause ED visits (RR 0.87, 95% CI 0.86, 0.88), and all-cause hospitalizations (RR = 0.92, 95% CI 0.91, 0.93).[45] There is also emerging evidence to suggest that clinical recommendations around type of OAT perhaps should be informed based upon consideration of mental health comorbidities,[46] although more research is required. Hser and colleagues found that treatment with buprenorphine-naloxone led to improved opioid abstinence for those with comorbid mental health disorders, as compared to treatment with methadone (OR 0.37, 95% CI 0.21 0.66).[46] To date, the most studied psychosocial interventions in the context of OAT are contingency management and cognitive behavioural therapy.[47] Further investigation into mental health interventions for this population is warranted and both patients and clinicians may be able to help identify interventions of interest for further study.

It is necessary to reconcile our finding that individuals who had primary care or psychiatry visits for mental health during OAT were also more likely to have ED visits and hospitalizations for mental health. Morin and colleagues somewhat similarly found that patients who received psychiatry or primary care mental health services while enrolled in OAT had higher odds of all-cause ED visits (OR 1.3, 95% CI 1.2, 1.4) but lower odds of all-cause hospitalizations (OR 0.5, 95% CI 0.4, 0.6).[39] Whether this association reflects the higher service needs of those who do become connected with other mental health care while receiving OAT cannot be elucidated from the present data. At the same time, although patients frequently access OAT services (often on a weekly basis), when mental health services are not integrated with addictions services, the ED may be the most direct and available route to receive care.

Finally, we found that much of the mental health care for individuals with OUD is conducted by primary care physicians (as compared to psychiatrists). This speaks to the need for increased resources and training for concurrent disorders treatment in the primary care setting. Current Canadian guidelines for OUD treatment do not provide guidance on management of co-occurring mental health conditions.[48] Increased research and knowledge mobilization in this area is necessary.

Strengths and Limitations

A primary strength of this study was the ability to link observational cohort data, rich with detail about participant characteristics, to health administrative data holdings to explore service use patterns. Information on employment, marital status, and outcomes in treatment such as urine drug screen results are not available in population-level health administrative data holdings at ICES. However, this cohort of individuals receiving OAT for OUD may not be representative of the general population of individuals with OUD given their lengthy time enrolled in OAT, on average greater than 6 years. The prevalence and distribution of mental health-related health service use may be different for those with new diagnoses of OUD or those who have not been successfully connected with OUD treatment. More research is needed to understand mental health-related health service utilization across the general population of individuals experiencing OUD. In the present study, the temporal relationship between acute, hospital-based visits and outpatient mental health visits could not be elucidated. As with all administrative health records data, this studied relied on diagnostic codes, which may be affected by errors in coding or misclassification and have not been validated. Additionally, we are only able to capture those cases of completed health care visits, and we are unable to determine how many individuals were referred to outpatient mental health care or whether they sought this care. Within the Canadian Addiction Treatment Centres network of OAT clinics included in this study, treatment is addiction focused and ancillary support services such as counseling services, care referrals, and community partnerships vary by location. ICES only include data on care provided by physicians, not other health care professionals such as psychologists, social workers, and nurses, who are often involved in providing mental healthcare to patients with OUD; if participants received non-physician-based mental healthcare, this would not be observed in the present data. Similarly, the costs of such non-physician-based outpatient care are not captured.

CONCLUSION

Individuals with OUD have health service use including ED visits, hospitalizations, and outpatient visits for mental health conditions other than substance use-related diagnoses. Acute mental health care in EDs and inpatient units is higher within our cohort of patients with OUD than in the general population. Furthermore, the costs of mental health-related acute care are far higher than those for outpatient mental health care. This study represents a starting point for understanding mental health service use patterns for individuals with OUD and associated individual-level factors and healthcare costs. Further understanding of mental health-related health service use for individuals with new diagnoses of OUD or those who are not enrolled in treatment is needed. Likewise, research into integrating mental health and substance use disorder treatment and increasing resources within primary care where a substantial proportion of patients with concurrent disorders are seen is necessary.

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ICES reviewed the plan for creating the data set and analyzing the data. Other than authors Glenda Babe and Richard Perez, ICES employees, ICES played no role in the management, analysis, and interpretation of the data; or the preparation or review of the manuscript. Author

Claire de Oliveira was the ICES responsible Scientist on this project and reviewed the manuscript to ensure that it complied with ICES and provincial data privacy laws and regulations.

Authors' Contributions: TR and ZS are responsible for the study concept and design. TR, GB, MR, RP, CdO and ZS developed the methods and statistical analysis plan. GB conducted data linkage and statistical analyses. TR wrote the first draft of the manuscript and TR, GB, MR, BBD, RP, CdO, AW, LT, and ZS contributed to writing and critically revising the final manuscript. All authors reviewed and approved the final manuscript.

FIGURES AND TABLES

Figure 7. Study Flow Diagram

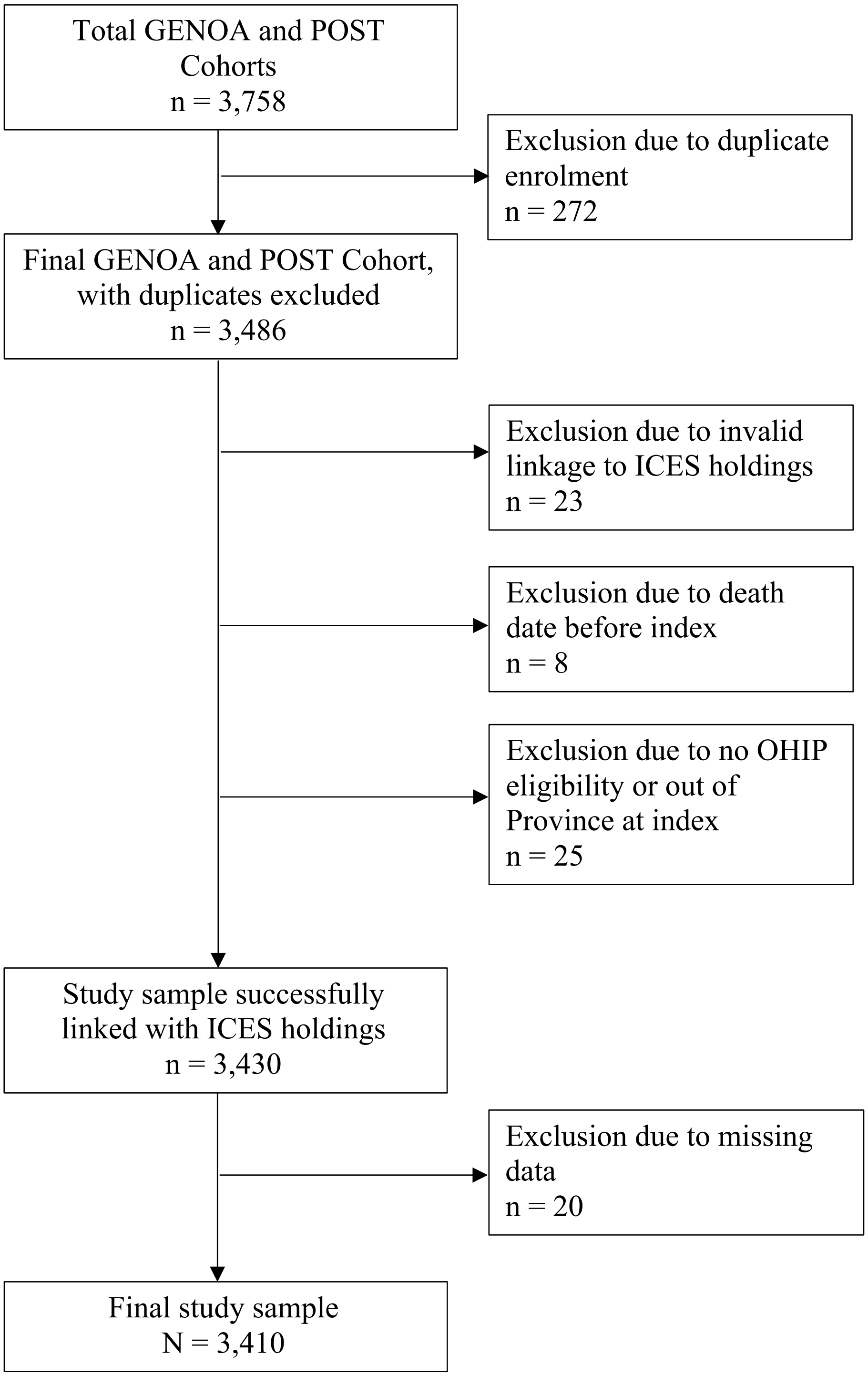

Table 19. Demographic and clinical characteristics (N = 3,410)

Characteristic	Acute Care (ED visit/Hospitalization) n = 509	No Acute Care (ED visit/Hospitalization) n = 2,901
Sex		
Female	245 (48.1%)	1258 (43.4%)
Male	264 (51.9%)	1643 (56.6%)
Age (years)		
<25	56 (11.0%)	189 (6.5%)
25-45	347 (68.2%)	1913 (65.9%)
46+	106 (20.8%)	799 (27.5%)
Marital status		
Single	367 (72.1%)	2017 (69.5%)
Married or common-law	142 (27.9%)	884 (30.5%)
Employment status		
Unemployed	411 (80.7%)	1843 (63.5%)
Employed	98 (19.3%)	1058 (36.5%)
Type of OAT		
Methadone	422 (82.9%)	2436 (84.0%)
Buprenorphine-naloxone	87 (17.1%)	465 (16.0%)
Length of time in OAT (years)		
<2	64 (12.6%)	243 (8.4%)
2-5	66 (13.0%)	276 (9.5%)
6+	379 (74.4%)	2382 (82.1%)
Percentage of Opioid-positive Urine Drug Screens at study enrolment (%)		
0	151 (29.7%)	1047 (36.1%)
1-49	275 (54.0%)	1501 (51.7%)
50+	83 (16.3%)	353 (12.2%)
Mean number of urine drug screens taken	33.54 (SD = 25.45)	36.41 (SD = 24.97)
Number of Health Conditions		
0-2	38 (7.5%)	646 (22.3%)
3-4	92 (18.1%)	774 (26.7%)
5-6	103 (20.2%)	609 (21.0%)
7+	276 (54.2%)	872 (30.0%)
Any Outpatient Mental Health Care		
Yes	304 (59.7%)	969 (33.4%)
No	205 (40.3%)	1932 (66.6%)
Outpatient Primary Care Visit for Mental Health		

Yes No	248 (48.7%) 261 (52.5%)	803 (27.7%) 2099 (72.3%)
Outpatient Psychiatry Visit for Mental Health Yes No	 165 (32.4%) 344 (67.6%)	 331 (11.4%) 2570 (88.6%)
ED = emergency department, OAT = opioid agonist treatment		

Table 20. Mental health service use over 12 months for individuals with at least one visit (n = 1,478)

Visit Type	**Statistic**
ED visit for mental health, mean (SD)	1.93 (2.15)
Hospitalization for mental health, mean (SD)	1.46 (1.05)
Outpatient primary care visit for mental health, mean (SD)	3.51 (4.31)
Outpatient psychiatry visit for mental health, mean (SD)	4.04 (4.73)
SD = standard deviation	

Table 21. Factors associated with acute care use (N = 3,410).

Covariate	OR	95% CI	*p* value
Sex			
Female	[ref]		
Male	1.08	0.88, 1.32	0.482
Age			
<25	[ref]		
25-45	0.64	0.45, 0.89	0.009
46+	0.43	0.29, 0.63	<0.001
Marital status			
Single	[ref]		
Married or common law	1.07	0.86, 1.34	0.530
Employment status			
Unemployed	[ref]		
Employed	0.48	0.37, 0.61	<0.001
Type of OAT			
Methadone (reference)	[ref]		
Buprenorphine-naloxone	1.04	0.80, 1.36	0.765
Length of time in OAT			
<2 years	[ref]		
2-5 years	1.0	0.66, 1.51	0.989
6+ years	0.80	0.58, 1.11	0.179
Percentage of opioid-positive urine drug screens			
0% (reference)	[ref]		
1-49%	1.13	0.90, 1.42	0.296
50%+	1.45	1.05, 2.01	0.023
Number of health conditions			
0-2 (reference)	[ref]		
3-4	1.72	1.15, 2.56	0.008
5-6	2.18	1.46, 3.24	<0.001
7+	3.76	2.60, 5.44	<0.001
Outpatient Mental Health Care (Primary care or Psychiatry)	2.38	1.95, 2.92	<0.001
ref = reference level, OR = odds ratio, CI = confidence interval			

Table 22. Costs in Canadian dollars of mental healthcare for those with at least one visit (n = 1,478).

Cost Type[a]	Mean (95% CI)
Acute care	
ED visits-only	$775.50 (686.00, 865.10)
Hospitalizations-only	$9,103.30 (7,181.60, 11,025.00)
Total acute care	$7,664.80 (6,122.30, 9,207.20)
Outpatient care	
Outpatient physician visits	$441.30 (405.50, 477.10)
Total Costs	
Total Mental Health Cost for individuals with acute care	$9,117.80 (7,372.90, 10,862.70)
Total Mental Health Cost for individuals with no acute care	$382.30 (343.20, 421.30)

[a] For individuals with more than one visit, the cost for each visits was summed to get a total cost
SD = standard deviation

Table 23. Two-part zero-negative binomial regression analysis to explore factors associated with total acute care mental health-related healthcare costs.

	Logistic regression component of the model[a]			Negative binomial regression component of the model[b]		
Covariate	**OR**	**95% CI**	***p* value**	**CRR**	**95% CI**	***p* value**
Sex						
Female	[ref]			[ref]		
Male	1.13	0.93, 1.37	0.235	0.83	0.62, 1.13	0.239
Age						
<25	[ref]			[ref]		
25-45	0.64	0.46, 0.89	0.008	1.45	0.93, 2.26	0.097
46+	0.40	0.27, 0.58	<0.001	2.01	1.19, 3.34	0.009
Marital status						
Single	[ref]			[ref]		
Married or common law	0.98	0.79, 1.22	0.855	0.62	0.45, 0.87	0.005
Employment status						
Unemployed	[ref]			[ref]		
Employed	0.52	0.41, 0.65	<0.001	0.51	0.36, 0.72	<0.001
Type of OAT						
Methadone (reference)	[ref]			[ref]		
Buprenorphine-naloxone	1.01	0.78, 1.31	0.940	1.28	0.86, 1.91	0.226
Length of time in OAT						
<2 years	[ref]			[ref]		
2-5 years	0.98	0.66, 1.46	0.925	1.01	0.59, 1.74	0.959
6+ years	0.77	0.57, 1.06	0.112	1.10	0.71, 1.70	0.675
Percentage of opioid-positive urine drug screens						
0% (reference)	[ref]			[ref]		
1-49%	1.16	0.93, 1.44	0.178	1.08	0.78, 1.50	0.632
50%+	1.40	1.02, 1.91	0.037	1.09	0.70, 1.71	0.705
Number of health conditions						
0-2 (reference)	[ref]			[ref]		
3-4	1.60	1.11, 2.32	0.012	1.0	0.55, 1.81	0.988
5-6	2.00	1.38, 2.90	<0.001	0.97	0.54, 1.72	0.905
7+	3.66	2.61, 5.14	<0.001	0.93	0.56, 1.57	0.796
Outpatient Mental Health Care (Primary care or Psychiatry)	2.38	1.96, 2.88	<0.001	1.47	1.09, 1.97	0.011

[a] Probability of non-zero cost.
[b] Expected change in cost for each unit increase in the corresponding covariate.
OR = odds ratio, RR = cost rate ratio, CI = confidence interval, ref = reference, OAT = opioid agonist treatment

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CHAPTER 7: Thesis Conclusion

OVERVIEW

Within this thesis, we examined different aspects of psychiatric comorbidity using data from a naturalistic observational cohort of individuals enrolled in OAT for OUD in Ontario, Canada. The inspiration for this work came from a clinical appreciation of unmet mental healthcare needs for individuals with substance use disorders. Psychiatric comorbidity is common among individuals with OUD and co-occurring mental health problems can be barriers to health and recovery from opioid use. We conducted five studies focused on understanding individual-level factors associated with mental health symptoms and psychiatric comorbidity, diagnosis of psychiatric disorders, and high-level exploration of treatment and use of mental healthcare services in this population. Our findings contribute to a growing literature that aims to help clinicians, substance use disorder treatment programs, and policy makers better understand which patients would benefit from additional mental health supports and consider how to improve services for concurrent disorders. This section summarizes the main findings and conclusions of each study included in the thesis. We discuss strengths and limitations of the work presented, challenges faced within this broader research area, and directions for further study of psychiatric comorbidity in individuals with OUD.

PSYCHIATRIC COMORBIDITY IN OPIOID USE DISORDER

In our first study (Chapter 2), we examined self-reported psychological symptoms, measured using the validated MAP tool, to understand the prevalence and impact of mental health symptoms in patients with OUD, without requiring individuals to meet full diagnostic criteria for psychiatric disorders. These symptoms included some typically attributed to anxiety (e.g., tension, fear, panic), and some typically attributed to depression (e.g., hopelessness, loneliness, anhedonia), as well as suicidal ideation. The vast majority of participants endorsed experiencing at least one psychological symptom in the past 30 days, and we identified that one out of five of individuals in our cohort experienced past-month suicidal ideation. Suicidal ideation is a particular concern in patients with OUD due to high rates of overdose and mortality, and the high-lethality nature of opioids in intentional or unintentional overdose ingestions. Not unexpectedly, individuals who met diagnostic criteria for psychiatric disorders also self-reported greater psychological symptoms. Higher symptom scores were associated with more opioid-positive and other drug-positive urine drug screens. Findings from this study highlight a clinical relevance for assessing psychological symptoms, including suicidal ideation, within this population. Extrapolated from principles of general mental healthcare, basic and routine monitoring of psychological symptoms could be integrated into general care for OUD. Future research will be required to evaluate possible clinical interventions for individuals reporting psychological symptoms.

We then went on in Chapter 3 to examine the utility of self-reported psychiatric diagnoses within this population, compared against the validated MINI diagnostic interview. We found that the sensitivity for any self-reported psychiatric diagnosis was quite low, raising questions about the use of self-reported diagnoses for clinical care or research. There were many new diagnoses identified using the MINI. Although enlightening and informative for clinical practice, we were unable to test potential explanations for our findings, such as the possibility that relapsing-remitting symptoms may have influenced participants' recall of diagnoses, or the impact of health literacy or stigma around mental health conditions in this population.

In the third study (Chapter 4), we focused in on trauma and PTSD to understand in more detail the prevalence of traumatic events and their relationship with OUD treatment outcomes. Traumatic life experiences and PTSD are well-described risk factors for substance use in general. More than half of all participants in our studies had lifetime experiences of trauma, and 11% met criteria for a current diagnosis of PTSD. Differences existed between those with and without trauma and PTSD in their treatment with psychotropic medications including antidepressants and benzodiazepines, which were more common in the former group. We did not find a relationship between trauma or PTSD and substance use outcomes; however, we did find that those with PTSD more commonly reported suicidal ideation. These findings suggest that mental health outcomes of patients with comorbid OUD and PTSD are important to consider and may not be captured by solely measuring substance-related outcomes in treatment.

Building upon our understanding of several aspects of psychiatric comorbidity, in the fourth study (Chapter 5), we aimed to understand whether there were differences between youth and adults enrolled in OAT, including their psychiatric comorbidities. We identified a number of areas in which youth younger than 25 differed from adults, from substance use and health risk behaviours (e.g., risk of intravenous drug use), to presence of comorbid psychiatric disorders and sociodemographic differences. These findings provide support for the impetus to develop distinct concurrent disorders treatment programs for transition aged youth who have different needs than adults and may benefit from specialized supports (e.g., educational supports) that may not be required for adult patients.

We completed our exploration of psychiatric comorbidity in OUD with a final study looking at healthcare service utilization patterns and costs of care for non-substance-related mental health disorders (Chapter 6). We leveraged linkage with Provincial health administrative data holdings at ICES to supplement our observational cohort data. This allowed us to collect additional information on hospital-based care and outpatient physician visits that was not otherwise captured in our observational study. We found that approximately one in seven individuals in our cohort had ED visits or hospitalizations for mental health, unrelated to a primary substance use diagnosis during one year of follow up and that more than one in three had outpatient primary care or psychiatry visits for the same. Much of the outpatient mental healthcare was conducted by primary care physicians, therefore supporting a need for increased resources and training for concurrent disorders care specifically in this setting. Those who experienced visits to acute care services (EDs and inpatient hospitalizations) had substantially higher healthcare costs associated with their mental healthcare overall.

STRENGTHS AND LIMITATIONS

Our use of a sizeable prospective observational cohort recruited across multiple sites in Ontario, Canada had many benefits for the generalizability of our findings. Broad inclusion criteria were applied to reflect a real-world sample of individuals treated for OUD. Individuals were not excluded on the basis of mental health or physical health comorbidities as is often the case in experimental studies within this population. Longitudinal follow up for up to 12 months with routine urine drug screens and the ability to link data to health administrative data holdings to examine health service use were additional strengths. Using multiple approaches of design and methods, accessing data from different sources, and exploring self-report and objective measures add further to the strength of this work. At the same time, biases including healthy user and volunteer biases may influence results and represented limitations. More information is needed on patients newly starting in OAT or those who are not enrolled in treatment as these individuals were not well-represented within our cohort. As with all observational studies, we are not able to establish causation and are limited to understanding associations between factors of interest and outcomes. Our use of administrative health data to identify health service use also carried limitations related to possible diagnostic coding errors or misclassification and we were limited to quantifying solely physician-based healthcare services and could not capture care provided by other multidisciplinary clinicians.

Broader challenges remain in studying psychiatric comorbidity in individuals with OUD. As described, experimental studies evaluating the efficacy and effectiveness of OAT have largely excluded patients with psychiatric comorbidities. As observational studies represent the primary method by which psychiatric comorbidity can be studied in this population, their limitations are important to consider. There are challenges in assessing and identifying psychiatric comorbidities in this population. There are also challenges related to studying those who do not seek care. Use of administrative health records from sources such as EDs may help to identify some of these individuals, however pervasive stigma and negative healthcare interactions experienced by this population mean that many individuals may be missed even this way. Furthermore, the ability of administrative health records to capture in detail the mental health of individual patients or a population is limited. There is currently little research describing patient-important outcomes within OUD (although this field is growing) and even less information on patient-important outcomes related to mental health and OUD. Within this thesis, we were unable to examine any mental health-related outcomes beyond self-reported symptoms and healthcare service utilization. It will be critically important to know what patients themselves identify as important mental health-related treatment goals, and to begin to ascertain measurable outcomes such that meaningful data may be collected.

FUTURE DIRECTIONS

There is a need for further research on psychiatric comorbidity among patients with OUD and other concurrent disorders in general. The studies included herein provide a foundation for future work to expand our knowledge. We need more information on the longitudinal course of psychiatric comorbidity in OUD, knowing that symptoms of these disorders remit and recur over time, pose barriers for treatment, and are associated with outcomes related to substance use. Moreover, future research should aim to bridge the gap between observation and intervention. Clinicians and treatment programs require evidence-informed guidelines on the management of concurrent OUD and other mental health disorders. Investment is required to study specific interventions (biological, psychological, and social) for treatment of psychiatric comorbidities that occur alongside OUD. Individuals with psychiatric comorbidity should not be excluded from trials given the high prevalence of comorbidity in this population. It will be particularly important to determine patient-important mental health-related outcomes for this field.

CONCLUDING REMARKS

Psychiatric comorbidity is common among patients with OUD and concurrent disorders require greater clinical and research attention. In this thesis work, we have established that: 1) psychological symptoms are common in people with OUD and are associated with substance use, 2) the sensitivity of self-reported psychiatric diagnoses is low and we need other tools to identify psychiatric comorbidity in this population, 3) trauma and PTSD are prevalent in patients with OUD and may require focused intervention, particularly given the risks of associated suicidal ideation, 4) youth differ from adults in their psychiatric comorbidity and in other sociodemographic and substance use characteristics, suggesting a need for specialized youth-targeted services, and 5) individuals receiving treatment for OUD also present to healthcare services for other mental health disorders, both in acute care settings (which are associated with greater healthcare costs) and in outpatient settings. Studying specific interventions or treatments for psychiatric comorbidity in OUD was outside the scope of this work. Future studies are needed to provide valuable insights into effective interventions for this population and grow an evidence base that will be later used to develop clinical management guidelines.

Appendix i. Published copy of study 1

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Exploring psychological symptoms and associated factors in patients receiving medication-assisted treatment for opioid-use disorder

Tea Rosic, Andrew Worster, Lehana Thabane, David C. Marsh and Zainab Samaan

Background

Patients receiving treatment for opioid-use disorder (OUD) may experience psychological symptoms without meeting full criteria for psychiatric disorders. The impact of these symptoms on treatment outcomes is unclear.

Aims

To determine the prevalence of psychological symptoms in a cohort of individuals receiving medication-assisted treatment for OUD and explore their association with patient characteristics and outcomes in treatment.

Method

Data were collected from 2788 participants receiving ongoing treatment for OUD recruited in two Canadian prospective cohort studies. The Maudsley Addiction Profile psychological symptoms subscale was administered to all participants via face-to-face interviews. A subset of participants ($n = 666$) also received assessment for psychiatric disorders with the Mini International Neuropsychiatric Interview. We used linear regression analysis to explore factors associated with psychological symptom score.

Results

The mean psychological symptom score was 12.6/40 (s.d. = 9.2). Participants with psychiatric comorbidity had higher scores than those without (mean 16.8 *v*. 8.6, $P<0.001$) and 31% of those with psychiatric comorbidity reported suicidal ideation. Higher psychological symptom score was associated with female gender ($B = 1.59$, 95% CI 0.92–2.25, $P<0.001$), antidepressant prescription ($B = 4.35$, 95% CI 3.61–5.09, $P<0.001$), percentage of opioid-positive urine screens ($B = 0.02$, 95% CI 0.01–0.03, $P<0.001$), and use of non-opioid substances ($B = 1.92$, 95% CI 0.89–2.95, $P<0.001$). Marriage and employment were associated with lower psychological symptoms.

Conclusions

Psychological symptoms are associated with treatment outcomes in this population and the prevalence of suicidal ideation is an area of concern. Our findings highlight the ongoing need to optimise integrated mental health and addictions services for patients with OUD.

Declaration of interest

None.

Keywords

Comorbidity; methadone; buprenorphine; addiction; psychiatric symptoms.

Background

In recent years, public and scientific attention surrounding addictions has been dominated by the 'opioid epidemic', which remains an ongoing public health crisis across North America and increasingly in Europe.[1] High rates of opioid use, opioid-use disorder (OUD) and opioid-related deaths persist despite efforts to reduce prescribing of opioid medications and increase available treatments and harm-reduction strategies. The rise in opioid-related deaths, increasing by more than 20% on average between 2011 and 2016, has been most pronounced in the USA, Canada, Sweden, Norway, Ireland, and England and Wales.[1] Medication-assisted treatment (MAT) for OUD, including methadone, a full opioid agonist and buprenorphine, a partial opioid agonist, have demonstrated benefits in the reduction of prescription and non-prescription opioid use;[2,3] however, not all patients have favourable outcomes in treatment.[4] Individuals with OUD have a high prevalence of comorbid psychiatric disorders including depression and anxiety.[5,6] These comorbidities have been associated with worse retention in treatment,[7] opioid use[5,6] and mortality.[8] Many patients may also experience psychological symptoms that do not meet full diagnostic criteria for psychiatric disorders but may compromise well-being or impair function nonetheless.[7]

The problem of psychological symptoms in patients receiving treatment for substance use disorders is one of significant complexity. It has long been acknowledged that individuals with substance use disorders have a high prevalence of other comorbid psychiatric disorders.[9,10] Psychological symptoms may also be 'substance-induced' and occur secondary to a primary substance use disorder, or in the context of intoxication or withdrawal.[11,12] Numerous theories exist to explain the high rate of comorbidity including common underlying genetic predisposition, common neurobiological pathways and diagnostic confounding.[12,13] The natural history of psychological symptoms during MAT, and the implications for treatment outcomes, are not definitively understood. Unfortunately, patients with psychiatric comorbidity are often excluded from experimental studies of MAT for OUD on the basis of their comorbidity.[14] Therefore, observational studies must be relied upon to obtain information on these patients and their course in treatment. There is an enduring need to optimise the integration of mental health and addictions services; parallel, rather than integrated, treatment continues to be the dominant conceptual framework and therefore the dominant approach to care.[15] Resources available in addictions treatment to address psychological or psychiatric comorbidity are often limited.[15] A better understanding of the psychological symptoms experienced by patients with OUD has the potential to inform clinical assessments, management of underlying comorbidity, treatment decision-making and resource allocation.

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Objectives

The objectives of this study are as follows: (a) to determine the prevalence of psychological symptoms in a cohort of patients receiving MAT for OUD; (b) to determine the prevalence of psychological symptoms among patients in this cohort with known comorbid psychiatric disorders versus those without psychiatric comorbidity; and (c) to explore the association between psychological symptoms and demographic and clinical characteristics, including treatment outcomes such as ongoing opioid and non-opioid substance use.

Method

Data

We used data from two large, prospective, cohort studies: the GENetics of Opioid Addiction (GENOA) study and the Pharmacogenetics of Opioid Substitution Treatment Response (POST) study. Study methods for the GENOA project have been previously described.[5,16] Briefly, data collection for the GENOA cohort occurred between 2011 and 2017, and information is available on 1390 individuals receiving treatment for OUD across 20 out-patient MAT clinics within Ontario, Canada. Participants were eligible for study inclusion if they were at least 18 years old, diagnosed with OUD as per the DSM-IV criteria,[17] and enrolled in MAT for their OUD. At study entry, participants provided information on demographic characteristics, medical history, medications and clinical information on their MAT medication, dose and duration in treatment. The POST study began recruitment in May 2018 from out-patient MAT clinics within Ontario, Canada and 1769 participants were recruited as of June 2019. Inclusion criteria for this study were similar to that of the GENOA study: individuals diagnosed with OUD as per the DSM-5 criteria[18] and receiving MAT. Participants completed a similar baseline assessment including demographic and clinical information. Participants recruited to both studies were enrolled in ongoing MAT, for varying lengths of time, at the time of study recruitment. In both studies, participants were followed for 12 months and urine drug screens to assess for ongoing opioid or other substance use were conducted as per clinical protocol. All clinical sites included in the studies are run centrally by the same management teams through the Canadian Addiction Treatment Centres and all follow the same treatment protocols. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. Ethics approval was obtained from the Hamilton Integrated Research Ethics Board (GENOA project ID 11-056; POST project ID 4556), and all participants provided verbal and written informed consent.

Records from these two cohort studies were merged and duplicate enrolment was identified using patient name and birth date. In the event of duplicate enrolment, data collected in the GENOA study were retained and the duplicate from the POST study was removed. Duplicate enrolment in both studies affected 339 participants (Fig. 1, study flow diagram). Participants were excluded from this study's main analyses if they were missing baseline data on psychological symptoms (Fig. 1). This study is reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[19]

Study instruments and measures

The primary objective of this study was to determine the prevalence of psychological symptoms in patients receiving MAT for OUD. At study entry all participants were administered the Maudsley

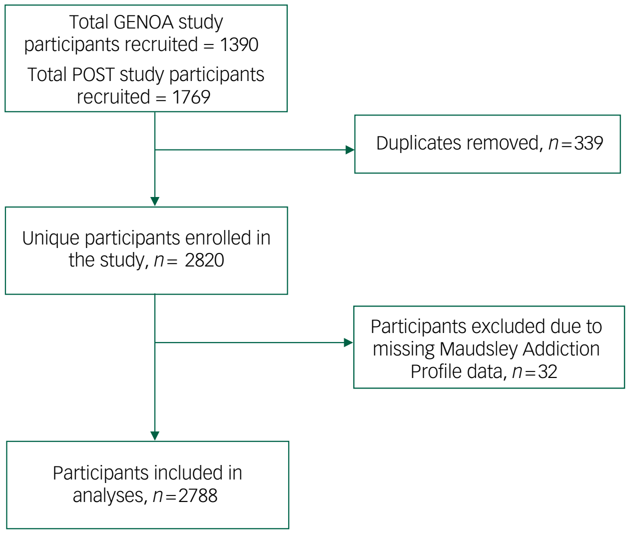

Fig. 1 Study flow diagram.

GENOA, GENetics of Opioid Addiction; POST, the Pharmacogenetics of Opioid Substitution Treatment Response study.

Addiction Profile (MAP),[20] a validated questionnaire examining individuals' self-reported substance use, physical and psychological symptoms and social functioning in the past 30 days. Psychological symptoms of depression and anxiety are measured by ten items rated on five-point Likert scales and participants are asked to report the frequency of symptoms including tension, fear, nervousness, panic, hopelessness, worthlessness, anhedonia, loneliness and suicidal ideation they have experienced in the past month.[20] Each item is rated as occurring 'never', 'rarely', 'sometimes', 'often', or 'always'.[20] A total score for psychological symptoms is calculated by adding the item scores for a total symptom score that can range from 0 to 40.[20] The psychological symptoms subscale is derived from the Brief Symptom Inventory,[21] which is derived from the Symptom Check List 90.[22] All participants received face-to-face interviews with a research assistant and the data were entered into the Research Electronic Data Capture tool.[23,24] The first 666 participants consecutively recruited into the GENOA study received extensive assessment of psychiatric comorbidity using the MINI International Neuropsychiatric Interview version 6.0.[25] This allowed for identification of comorbid psychiatric disorders including mood disorders, anxiety disorders, psychotic disorders, substance use disorders and eating disorders. The MINI was not administered to subsequently recruited participants because of the time burden of administration.

Assessment of treatment outcome was conducted using urine drug screen results to identify continued opioid use. An opioid-positive urine screen was defined as a non-methadone- or buprenorphine-positive opioid screen. We were therefore able to calculate the percentage of opioid-positive urine screens for each participant. As participants report on psychological symptoms in the past 30 days at time of study entry, we elected to examine urine drug screens also in the period prior to study entry. By doing so, the results of both psychological symptom assessment and urine drug screens were as close in time as possible. In the GENOA study, the results of urine drug screens were available for the 3-month interval prior to study entry and the mean number of urine drug screens was 16. In the POST study, the results of urine drug screens were available for up to 12 months prior to study entry and the mean number of urine drug screens was 45. To further assess treatment outcome, we also examined the percentage of

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non-opioid-positive urine drug screens collected during the same period prior to study entry. This includes urine screens positive for amphetamines, benzodiazepines and cocaine. Amphetamine- or benzodiazepine-positive urines were not counted for patients with confirmed amphetamine or benzodiazepine prescriptions in their medical chart. Urine drug screens were conducted as per routine clinical care at the Canadian Addiction Treatment Centre sites, at a weekly or fortnightly frequency, using the IMDx™ Prep assay[26] for morphine, oxycodone, fentanyl, cocaine, amphetamine, methamphetamine, diazepam, methadone metabolite and buprenorphine.

Analysis

Our first objective was to determine the prevalence of psychological symptoms in this study cohort. We used Stata version 15.1[27] to conduct all statistical analyses. We present data on demographic characteristics and psychological symptoms using descriptive statistics with continuous variables summarised as means and s.d. for normally distributed variables, and medians with interquartile range (IQR) for skewed data. Categorical variables were summarised as percentages. Our second objective was to assess the prevalence of psychological symptoms among patients with known comorbid psychiatric disorders identified using the MINI, who we compared with those patients with no psychiatric comorbidity identified. Group differences were assessed using independent samples *t*-tests for continuous variables and chi-square tests for dichotomous variables. Our third and final objective was to explore the association between participant characteristics and psychological symptoms.

We constructed a linear regression model with total psychological symptom score (ranging from 0 to 40) as the dependent variable. Sociodemographic characteristics included as covariates in the regression analysis were selected based on previous research suggesting potential influence on psychological symptoms. These included: (a) age, as older age has been associated with underreporting of psychological symptoms;[28] (b) gender, because of known gender differences in mental health disorders and psychological patterns such as internalising and externalising;[29] (c) marital status, which has been demonstrated to confer mental health benefits for both men and women;[30] and (d) employment status, as unemployment has been established in numerous studies to impair mental health.[31]

The clinical characteristics included as covariates in the regression model included: (a) type of MAT (i.e. methadone or buprenorphine), (b) duration in treatment, and (c) prescription of an antidepressant medication. Finally, we included the percentage of opioid-positive urine drug screens (continuous), and the presence of non-opioid substance use (dichotomous) as covariates in the model in order to assess the association between psychological symptoms and substance use during treatment, adjusting for the other aforementioned factors.

The linear regression model was constructed as described above. Model diagnostics were assessed to ensure that the assumptions for linear regression analysis were adequately met. This included testing for multicollinearity with variance inflation factor, testing for homoscedasticity by plotting residuals against fitted values, graphing residuals against a normal curve and assessing P-P and Q-Q plots for assessment of the normality of residuals. The level of significance for hypothesis testing was set at $\alpha = 0.05$ for all analyses. Our sample size of 2788 participants was sufficiently powered to conduct the analyses described above, such that there were at least ten participants per covariate included in the model.[32] Finally, we conducted subgroup analysis by gender in light of increasing awareness that gender is associated with biological and social differences that contribute to differential health outcomes, which warrant understanding.

Results

Demographic and clinical characteristics

Altogether, 2788 participants met study inclusion criteria and were included in the analyses (Fig. 1). Information on participant demographic and clinical characteristics is detailed in Table 1: men accounted for 57% of the cohort ($n = 1575$), and participants' mean age was 38.5 years (s.d. = 11). The majority of participants held at least a high school diploma ($n = 2098$; 75.3%) but were unemployed ($n = 1819$; 65.2%). Methadone was the most commonly prescribed MAT (85%) and the median methadone dose was 65 mg per day (IQR = 60), and the median dose of buprenorphine was 12 mg per day (IQR = 8). In addition to their MAT medication, 26.4% of participants were prescribed an antidepressant medication ($n = 737$). The median duration in treatment was 2 years (IQR = 4.42). In total, 37% of participants were abstinent from any ongoing opioid use, as measured by urine drug screens, for the 3 months prior to study entry. Individuals with ongoing opioid use had on average 30% of urine screens positive for opioids (s.d. = 29.3). Only 11% of participants were entirely abstinent from non-opioid substances (i.e., amphetamines, benzodiazepines and cocaine).

Psychological symptoms

In the entire study sample of 2788 participants, the mean total psychological symptoms score was 12.6 out of 40 (s.d. = 9.2; Table 2). Altogether, 92% of participants endorsed at least one psychological symptom present in the past 30 days (data not shown). The most

Table 1 Participant demographic and clinical characteristics ($N = 2788$).

Characteristic	Value
Sociodemographic	
Age, years: mean (s.d.)	38.5 (11)
Male gender, *n* (%)	1575 (56.5)
White ethnicity, *n* (%)	2207 (79.2)
Married or common law, *n* (%)	840 (30.1)
Education, *n* (%)	
Less than high school	690 (24.8)
High school	1295 (46.5)
Post-secondary	803 (28.8)
Unemployment, *n* (%)	1819 (65.2)
Clinical	
Type of medication-assisted treatment, *n* (%)	
Methadone	2369 (85.0)
Buprenorphine	419 (15.0)
Dose, mg/day: median (IQR)	
Methadone	65 (60)
Buprenorphine	12 (8)
Duration in treatment, years: median (IQR)	2 (4.42)
Number of opioid urine drug screens, mean (s.d.)	31.3 (24.2)
Opioid abstinence, *n* (%)	1031 (37.0)
Percentage of opioid-positive urine drug screens among non-abstainers; mean (s.d.)	30.1 (29.3)
Abstinence from other substances, *n* (%)	317 (11.4)
Percentage of positive urine drug screens among non-abstainers of other substances, mean (s.d.)	
Amphetamines ($n = 229$)	57.2 (35.4)
Benzodiazepines ($n = 559$)	32.1 (29.6)
Cocaine ($n = 935$)	49.2 (34.7)
Antidepressant medication prescription, *n* (%)	737 (26.4)

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Table 2 Psychological symptoms ($N = 2788$)

Psychological symptoms[a]	Total sample ($N = 2788$)	Participants assessed for comorbid psychiatric disorders[b] ($n = 666$): Psychiatric comorbidity[c] ($n = 400$)	No psychiatric comorbidity[d] ($n = 266$)	χ^2	*t*-test	*P*
Total score; mean (s.d.)	12.6 (9.2)	16.8 (8.9)	8.6 (6.9)	–	−12.79	<0.001
Feeling tense, *n* (%)	2230 (80.0)	372 (93.0)	206 (77.4)	85.8	–	<0.001
Suddenly scared for no reason, *n* (%)	1187 (42.6)	230 (57.5)	85 (32.0)	62.9	–	<0.001
Feeling fearful, *n* (%)	1304 (46.8)	252 (63.0)	98 (36.8)	72.7	–	<0.001
Nervousness or shakiness inside, *n* (%)	1741 (62.4)	320 (80.0)	139 (52.3)	92.5	–	<0.001
Spells of terror or panic, *n* (%)	1224 (43.9)	251 (62.8)	78 (29.3)	84.9	–	<0.001
Feeling hopeless about the future, *n* (%)	1795 (64.4)	328 (82.0)	148 (55.6)	85.4	–	<0.001
Feelings of worthlessness; *n* (%)	1580 (56.7)	292 (73.0)	115 (43.2)	83	–	<0.001
Feeling no interest in things, *n* (%)	1942 (69.7)	332 (83.0)	158 (59.4)	60.6	–	<0.001
Feeling lonely, *n* (%)	1825 (65.5)	323 (80.8)	144 (54.0)	77.2	–	<0.001
Thoughts of ending your life, *n* (%)	594 (21.3)	123 (31.0)	30 (11.3)	35.4	–	<0.001

a. Each item in the Maudsley Addiction Profile psychological symptoms subscale is assessed on a five-point Likert scale ranging from 'never' (score of 0) to 'always' (score of 4) experiencing the symptom. In this table we present the frequency of scores of >1 for each symptom, indicating the presence of the symptom but not the intensity.
b. A subset of participants received the Mini International Neuropsychiatric Interview (MINI) diagnostic interview to identify comorbid psychiatric disorders ($n = 666$).
c. Participants identified as meeting criteria for a comorbid mood, anxiety, psychotic or eating disorders using the MINI.
d. Participants identified as not meeting criteria for a comorbid mood, anxiety, psychotic or eating disorders using the MINI.

commonly endorsed symptoms were feeling tense (80%), feeling no interest in things (70%), feeling lonely (66%) and feeling hopeless about the future (64%; Table 2). The mean total psychological symptoms score was lower in men compared with females (11.4 (s.d. = 8.7) *v.* 14.1 (s.d. = 9.5); $t = -7.5$, $P<0.001$; data not shown).

Among the subset of 666 participants who received comprehensive assessment of psychiatric comorbidity using the MINI, 400 individuals (60%) were identified to have a comorbid mood, anxiety, psychotic or eating disorders. We compared the prevalence of psychological symptoms in these participants, with the prevalence of psychological symptoms in participants identified not to have a psychiatric comorbidity (Table 2). The prevalence of every symptom was higher among those patients with psychiatric comorbidity (Table 2). The total psychological symptoms score was also significantly higher in patients with psychiatric comorbidity than those without (16.8 *v.* 8.6, $P<0.001$; Cohen's $d = -1.01$, 95% CI −1.18 to −0.85). Notably, 31% of participants with psychiatric comorbidity endorsed thoughts of ending their life in the past 30 days, whereas this figure was 11% in participants who were not identified to have psychiatric comorbidity ($P<0.001$). Overall, the prevalence of suicidal ideation was similar in men and women (22% *v.* 20%, $\chi^2 = 1.68$, $P = 0.195$; data not shown)

Factors associated with psychological symptom score

Higher psychological symptom score was associated with female gender, antidepressant prescription, ongoing opioid use and use of non-opioid substances (Table 3). Female gender was associated with two points higher on the psychological symptom score, on average, adjusting for the other covariates ($B = 1.59$, 95% CI 0.92–2.25, $P<0.001$). For each percentage point more of opioid-positive urine drug screens, psychological symptom score was associated with a 0.02 increase ($B = 0.02$, 95% CI 0.01–0.03, $P<0.001$). Any use of non-opioid substances detected by urine drug screens was associated with about two points higher psychological symptom score, on average ($B = 1.92$, 95% CI 0.89–2.95, $P<0.001$). Lower psychological symptom score was associated with younger age, ($B = -0.08$, 95% CI −0.11 to −0.05, $P<0.001$), being married or in a common-law relationship ($B = -1.72$, 95% CI −2.43 to −1.02, $P<0.001$), being employed ($B = -2.75$, 95% CI −3.45 to −2.05, $P<0.001$) and treatment with buprenorphine ($B = -1.13$, 95% CI −2.06 to −0.02, $P = 0.017$; Table 3).

Subgroup analysis by gender resulted in similar findings to those of the primary analysis described above (Table 3). For both men and women, psychological symptom score was associated with age, marital status, employment, antidepressant prescription and use of non-opioid substances (Table 3). The association between higher psychological symptom score and more ongoing opioid use appears to be present in women ($B = 0.04$, 95% CI 0.02 to 0.06, $P<0.001$) but not in men ($B = 0.01$ 95% CI −0.003 to 0.03, $P = 0.134$; Table 3). Treatment with buprenorphine as compared with methadone was not associated with psychological symptom score in men ($B = -0.89$, 95% CI −2.08 to 0.30, $P = 0.141$), but showed a trend towards statistical significance in women ($B = -1.45$, 95% CI −2.93 to 0.03, $P = 0.054$; Table 3).

Table 3 Multivariable model of demographic and clinical factors associated with psychological symptom score ($N = 2778$)

	Primary analysis			Subgroup analysis					
	Total sample			Women			Men		
Covariate	B^a	95% CI	*P*	B^a	95% CI	*P*	B^a	95% CI	*P*
Age, years	−0.08	−0.11 to −0.05	<0.001	−0.08	−0.14 to −0.03	0.002	−0.07	−0.11 to −0.03	<0.001
Female gender	1.59	0.92 to 2.25	<0.001	–	–	–	–	–	–
Married	−1.72	−2.43 to −1.02	<0.001	−2.84	−4.03 to −1.65	<0.001	−1.25	−2.17 to −0.34	<0.001
Employed	−2.75	−3.45 to −2.05	<0.001	−2.24	−3.36 to −1.13	<0.001	−2.72	−3.58 to −1.86	<0.001
Buprenorphine	−1.13	−2.06 to −0.02	0.017	−1.45	−2.93 to 0.03	0.054	−0.89	−2.08 to 0.30	0.141
Duration in treatment, years	0.06	−0.02 to 0.13	0.149	0.11	−0.01 to 0.23	0.072	0.003	−0.10 to 0.11	0.953
Antidepressant Prescription	4.35	3.61 to 5.09	<0.001	4.08	2.98 to 5.18	<0.001	4.61	3.60 to 5.62	<0.001
Percentage of opioid-positive urine screens	0.02	0.01 to 0.03	<0.001	0.04	0.02 to 0.06	<0.001	0.01	−0.003 to 0.03	0.134
Use of non-opioid substances	1.92	0.89 to 2.95	<0.001	1.84	0.19 to 3.49	0.029	1.98	0.67 to 3.29	0.003

a. Estimated beta coefficient.

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Discussion

Main findings

In this large study involving two cohorts of patients receiving outpatient MAT for OUD, we found that the majority of participants reported psychological symptoms during treatment. Higher psychological symptoms were associated with worse treatment outcomes including more opioid use in women and use of non-opioid substances in both men and women. Our results highlight psychological symptoms as an area of need for patients enrolled in this treatment. These data contribute to a growing body of literature on the mental health of patients with OUD.

Comparison with findings from other studies

A challenge for situating our findings in the pre-existing literature is the considerable variation between studies in the measures used for the assessment of psychological symptoms. A systematic review by Fingleton *et al* in 2015 examined changes in mental health during MAT and identified 19 different instruments used to measure psychological symptoms in the included studies.[33] This review concluded that mental health significantly improved in 14 out of 22 included studies though improvements were not always sustained.[31]

There are a handful of previous studies that examined psychological symptoms using the MAP with which our results can be compared.[34–37] In a small observational study of 15 patients beginning MAT for OUD, psychological symptoms were measured at baseline and following 8 weeks of treatment.[37] The authors found that the mean psychological symptoms score at baseline was 20.1, and at 8-week follow-up this decreased to 13.[34] These findings are consistent with ours, seeing as patients in our study were enrolled in treatment for significantly longer than 8 weeks on average (and had a mean psychological symptom score of 12.6 out of 40). The most commonly reported symptoms were ‘feeling tense’ and ‘feeling no interest in things’;[34] the same was the case in our study. We caution careful interpretation of specific items being more commonly reported as there is a possibility that the individual items reported more frequently reflect a property of the questionnaire itself, rather than symptoms experienced by patients, if these items are worded in a way that makes them more likely to be endorsed. Another observational study including 404 participants found a slightly lower prevalence of symptoms of anxiety and depression than those identified in our cohort.[35] For example, for the two most commonly reported symptoms, ‘feeling tense’ and ‘feeling no interest in things’, rates in the study were 62–66% and 50–60% at study intake, respectively.

Finally, two randomised controlled trials also used the MAP to assess change in psychological symptoms during treatment.[36,37] The first study included 235 participants and found the mean psychological symptoms score at baseline to be 29.7 (s.d. = 7.7) with a reduction to 24 after 36 months of treatment.[37] The second randomised controlled trial also identified ‘feeling tense’ and ‘feeling no interest in things’ as the most commonly reported psychological symptoms at baseline in a cohort of 45 patients receiving methadone treatment in a community setting.[36] This study also identified a slightly lower prevalence of these symptoms than that in our study: 58 and 56%, respectively, with decreases in prevalence to 53 and 54%, respectively, after 1 year of treatment.[36]

Interpretation of our findings

What level of psychological symptoms, as measured using the MAP, is clinically significant in terms of having an impact on functioning and requiring intervention is unknown. There are no defined standards for interpretation of the MAP or validation against clinical diagnosis of anxiety or depressive disorders. Our finding that individuals with confirmed psychiatric diagnoses had significantly higher psychological symptom scores than individuals without psychiatric comorbidity supports the suggestion that higher symptoms may have a clinical relevance. This finding suggests that intervention, whether psychological or pharmacological, may be warranted and raises questions about the services provided for managing psychological or psychiatric symptoms in MAT clinics. We also found an association between antidepressant prescription and increased psychological symptoms, suggesting that antidepressant treatment alone is insufficient to eliminate psychological symptoms, although it is certainly possible that without antidepressant treatment these individuals would have even higher psychological symptoms.

Suicidal ideation

A troubling finding of this study was that 21% of participants reported suicidal thinking in the past 30 days. This rate was higher among participants with identified psychiatric comorbidity at 31%. Our findings are consistent with previous studies in patients with OUD that have documented suicidal ideation in about 20–25% of patients.[35,36] In comparison, a study of patients using substances in primary care (most with non-opioid substance use) found a 12.1% prevalence of past month suicidal ideation.[38] Suicidal ideation is a significant concern in patients with OUD, a population in which rates of overdose and mortality are alarmingly high and increasing.[1] Recent US estimates indicate that more than 40% of suicide and overdose deaths in 2017 involved opioids[39] and rates of suicide by opioid overdose are likely underestimated as it is difficult to assess intent in overdose deaths.[40] Opioids have high lethality in overdose, whether unintentional or intentional and there is strong evidence that access to lethal means increases risk for suicide.[41] This points to a pressing need to identify and manage suicidal ideation in this high-risk population.

Buprenorphine versus methadone

We found that treatment with buprenorphine was associated with lower psychological symptoms, as compared with treatment with methadone, although this finding did not hold in subgroup analysis by gender. There is no readily discernible biological explanation for this finding and its significance is unclear. Notably, Fingleton *et al* identified tentative evidence to suggest methadone was less effective at improving mental health than other types of MAT.[33] It is possible that there are systematic differences between patients who end up on treatment with buprenorphine as compared with methadone that could explain the finding that they have fewer psychological symptoms. We examined differences in demographic characteristics in our participants with methadone compared with buprenorphine treatment and found no significant differences between the groups in age (mean age 38.6 *v.* 37.7, $P = 0.133$), gender (57% *v.* 56%, $P = 0.876$), high school education (47% *v.* 44%, $P = 0.259$) or marital status (30% *v.* 32%, $P = 0.312$). In contrast, there was a significant difference between the two treatment groups in mean duration in treatment (methadone 4.2 years *v.* buprenorphine 1.8 years, $P<0.001$) and ongoing opioid use (mean percentage of opioid-positive urine screens: methadone 20.1, buprenorphine 12.5, $P<0.001$). Finally, the finding that employment and marital status was associated with a positive impact on psychological symptoms (i.e. lower symptoms) highlights the importance of supporting patients to achieve improvements in social functioning during treatment.

Strengths and limitations

This study is strengthened by its large sample size and multisite design, which lends increased confidence in the results. The use of the MAP, a validated tool for assessment of symptoms in patients

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with substance use disorders, is an added strength. This study, like others, was susceptible to healthy user and volunteer biases, such that individuals with fewer psychological symptoms may have been more likely to participate. We have no way to explore this issue empirically. As is the case in all observational studies, we are unable to establish a causal relationship; whether a greater burden of psychological symptoms leads to increased substance use, or increased substance use causes a greater burden of psychological symptoms is unknown. The measurement of psychological symptoms in this study using the MAP[20] (derived from the Brief Symptom Inventory,[21] itself derived from the Symptom Check List 90[22]) does not capture the complete psychological profile of respondents, but rather focuses on anxiety and depression symptoms – a limitation of this study. However, the ability of the psychological symptoms subscale to discriminate between patients with psychiatric comorbidity as diagnosed by the MINI (higher psychological symptom scores) and those without psychiatric comorbidity (lower psychological symptom scores) as evidenced by a large effect size (Cohen's $d = -1.01$, 95% CI $-1.18, -0.85$) suggests that despite limitations, the measure discriminates between these groups of patients well.

This study is also limited by the assessment of psychological symptoms cross-sectionally. We note that the median duration in treatment was 2 years; whether these results generalise to patients newly starting MAT is unknown. We would hypothesise that patients newly starting MAT may be at greater risk of experiencing psychological symptoms in the context of possible opioid withdrawal, relapses to substance use or undertreatment of comorbid psychiatric disorders in the initial stages of MAT. In contrast to this hypothesis, we found that longer time in treatment was associated with slightly higher report of psychological symptoms.

How well these results would generalise to settings outside of Ontario, Canada, to other settings in North America or to other areas of the world is unclear. In Canada, MAT primarily takes on a harm-reduction role, such that retention in treatment is not contingent on abstinence from opioid or other substance use. In this setting, concerns around patient factors that may be associated with ongoing opioid or polysubstance use is inherently heightened, particularly because of risks of opioid overdose and mortality.

This study focused solely on one dimension of treatment outcome, namely substance use, as measured by urine drug screens. There are many other potentially important treatment outcomes that should be considered but fell outside of the scope of this study, including treatment retention, suicide-related behaviours, opioid overdose or death and the use of psychiatric or emergency department services.

Directions for future study

Considering the notable prevalence and risks associated with suicidal ideation in this population, future research should explore the association between suicidal ideation and overdose, death and contact with psychiatric services. Whether different forms of MAT produce different outcomes with respect to psychological symptoms should also be investigated. Finally, future studies may wish to examine psychological symptoms over time and identify factors that influence their trajectory.

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Data availability

The authors have ongoing access to all study data.

Author contributions

T.R., A.W., L.T., D.C.M. and Z.S. are responsible for the study concept and design. T.R. and Z.S. developed the methods and data analysis. T.R. wrote the first draft of the manuscript, and T.R., A.W., L.T., D.C.M. and Z.S. contributed to writing and critically revising the final manuscript. All authors reviewed and approved the final manuscript.

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Appendix ii. Published copy of study 2

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RESEARCH Open Access

Sensitivity and specificity of self-reported psychiatric diagnoses amongst patients treated for opioid use disorder

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Abstract

Background: Patients with opioid use disorder (OUD) frequently present with comorbid psychiatric illnesses which have significant implications for their treatment outcomes. Notably, these are often identified by self-report. Our study examined the sensitivity and specificity of self-reported psychiatric diagnoses against a structured diagnostic interview in a cohort of patients receiving outpatient pharmacological treatment for OUD.

Methods: Using cross-sectional data from adults receiving outpatient opioid agonist treatment for OUD in clinics across Ontario, Canada, we compared participants' self-reported psychiatric diagnoses with those identified by the Mini Neuropsychiatric Interview (MINI) Version 6.0 administered at the time of study entry. Sensitivity and specificity were calculated for self-report of psychiatric diagnoses.

Results: Amongst a sample of 683 participants, 24% ($n = 162$) reported having a comorbid psychiatric disorder. Only 104 of these 162 individuals (64%) reporting a comorbidity met criteria for a psychiatric disorder as per the MINI; meanwhile, 304 (75%) participants who self-reported no psychiatric comorbidity were in fact identified to meet MINI criteria for a psychiatric disorder. The sensitivity and specificity for any self-reported psychiatric diagnoses were 25.5% (95% CI 21.3, 30.0) and 78.9% (95% CI 73.6, 83.6), respectively.

Conclusions: Our findings raise questions about the utility of self-reported psychiatric comorbidity in patients with OUD, particularly in the context of low sensitivity of self-reported diagnoses. Several factors may contribute to this including remittance and relapse of some psychiatric illnesses, underdiagnosis, and the challenge of differentiating psychiatric and substance-induced disorders. These findings highlight that other methods should be considered in order to identify comorbid psychiatric disorders in patients with OUD.

Keywords: Opioid use disorder, Psychiatric diagnoses, Self-reported diagnoses

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Background

The opioid crisis continues to be a major public health problem worldwide [1–4]. In 2017, it was estimated that 40.5 million people globally were dependent on opioids, although trends varied between countries [1]. The burden of opioid use and dependence is significantly more prevalent in North America compared to other parts of the world [1]. In Canada, overdose deaths and hospitalizations related to opioid use disorder (OUD) have remained high despite increasing awareness and intervention [5, 6]. In the United States, opioids are involved in the majority of deaths related to drug overdose, which rose to an all-time high in 2019 with 49,860 overdose deaths involving opioids [7–9]. The impacts of the COVID-19 pandemic have additionally exacerbated preexisting issues relating to access to appropriate treatment and interventions, ensuring that the opioid crisis will remain an ongoing concern for patients and families, healthcare workers, and policymakers alike [9].

Patients with substance use disorders (SUD) experience comorbid psychiatric disorders, such as depression and anxiety, at rates higher than the general population [10]. Canadian data suggest that the 12-month prevalence of psychiatric comorbidity is 5 to 6 times higher among individuals with substance dependence compared to the general population (OR 5.29, 95% CI 3.90, 7.17) [10]. Additionally, patients with psychiatric disorders report higher rates of substance use problems and are approximately twice as likely to have SUDs [10, 11]. This comorbidity is exacerbated in patients with OUD who appear to have even higher lifetime prevalence of psychiatric disorders compared to those with other SUDs and the general population; lifetime rates are generally greater than 40%, although there is considerable variability in reported rates across studies [12]. We have previously found that among patients receiving methadone maintenance treatment for OUD, approximately 80% of participants had a comorbid psychiatric disorder, with 43% having an anxiety disorder, and 41% having a mood disorder [11]. Psychiatric disorders are similarly associated with an increased risk of developing OUD in individuals who are prescribed opioids for pain (OR 1.46, 95% CI 1.12, 1.91) [13].

The importance of understanding a patient's psychiatric comorbidities in the context of their OUD should not be understated. When assessing patients, it may be challenging to determine whether their symptoms are due to a psychiatric comorbidity, or secondary to substance use [14]. These comorbidities also must be considered in the context of treatment. For patients with OUD, psychiatric comorbidities have been associated with worse clinical outcomes. A study examining retention in buprenorphine treatment found the presence of any comorbid mental illness to have a hazard ratio of 1.05 (95% CI 1.01, 1.10) for treatment discontinuation at three years [15] while inpatient mental health treatment was associated with a hazard ratio of 1.2 (95% CI 1.19, 1.30) for treatment discontinuation [16]. Similarly, psychiatric comorbidity conferred higher hazard for attrition from methadone treatment (hazard ratio 1.20, 95% CI 1.06, 1.35) [15]. In studying the impact of psychological symptoms in OUD treatment outcomes, we have previously found that psychological symptoms were associated with higher percentages of opioid-positive drug screens ($B = 0.02$, 95% CI 0.01–0.02 = 3) and non-opioid-positive drug screens ($B = 1.92$, 95% CI 0.89, 2.95) [14]. The prevalence of depression and anxiety disorders in opioid-related overdoses reaches rates greater than 30% [17], and severe depression (OR 2.46, 95% CI 1.24, 4.89), post-traumatic stress disorder (PTSD) (OR 2.77, 95% CI 1.37, 5.60), and psychosis (OR 2.39, 95% CI 1.10, 5.15) are significantly associated with opioid overdoses [18]. In a study looking at factors associated with mortality among heroin users, a history of psychiatric treatment was associated with a hazard ratio of 6.21 (95% CI 2.52, 15.33) for all-cause mortality [19].

Psychiatric comorbidity is also associated with lower reported quality of life for patients with OUD [20]. Epidemiological data on patient outcomes, in addition to other clinical and systems-level research, have reinforced the need for concurrent disorders treatment that integrates treatment for psychiatric disorders and addictions [10, 21].

Most commonly in substance use treatment programs, the record of historical mental health diagnoses is based on patient self-report [22]. The utility of self-reported psychiatric diagnoses within patients with SUDs was examined by Neumann and colleagues [22] who found self-reported diagnoses of bipolar disorder and depression were often not confirmed by current clinical measures, and many participants had undiagnosed psychiatric disorders. In light of these findings and a clinical reliance on patient self-report, the objective of this study was to examine the sensitivity and specificity of patient-reported psychiatric diagnoses in a cohort of patients receiving outpatient pharmacological treatment for OUD.

Methods

Data were collected in the GENetics of Opioid Addiction (GENOA) prospective cohort study conducted in Ontario, Canada. The objective of the GENOA study was to examine biological and social factors affecting treatment outcome and course for patients with OUD [23]. Participants were recruited from 20 outpatient opioid agonist treatment clinics between 2011 and 2017. All clinics were run by the same management teams and followed the same treatment protocols. Inclusion criteria required participants to be a minimum of 18 years of age, to meet diagnostic criteria for OUD as per DSM-IV criteria, [24] and to be enrolled in opioid agonist therapy (primarily methadone). At the time that this study was conducted, buprenorphine-naloxone was not covered through the Ontario provincial drug plan, thus greatly limiting its access, and making methadone the primary opioid substitution treatment available. No restrictions were placed on participants' duration in treatment; therefore, individuals were enrolled in treatment for different lengths of time at the time of study entry. This study was conducted in accordance with the Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects. Ethics approval was obtained from the Hamilton Integrated Research Ethics Board (project ID 11–056) and all participants provided informed consent. We report the present study following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [25].

At study intake, all participants completed extensive baseline assessments performed by trained interviewers, including assessment of sociodemographic and clinical information (including opioid agonist treatment history). All participants were asked to self-report their medical history, with the open-ended question: "Do you have any medical conditions or health problems?" Responses to this question were recorded in an open-ended text field and later summarized into diagnostic categories by two study authors (KL and EX) in duplicate for consistency and accuracy.

Self-reported psychiatric diagnoses were compared against a diagnostic interview using the Mini Neuropsychiatric Interview (MINI) version 6.0 [26] a standardized and structured tool widely used in research and clinical settings [24]. The MINI has been validated against the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders (SCID) and the Composite International Diagnostic Interview (CIDI) [26]. In comparison to the SCID, the sensitivity of the MINI was 70% or greater for 19 out of 22 diagnoses evaluated by the SCID while the specificity was 85% or higher for all diagnoses. When compared to the CIDI, the MINI had a sensitivity of 70% or greater for 7 out of 11 diagnoses captured by the CIDI and had a specificity of 70% or greater for all diagnoses. The MINI had excellent interrater reliability with 70% of interrater kappa values 0.90 or above. The retest reliability of the MINI was good with 61% of the retest kappa values being above 0.75. Additionally, the agreement between diagnoses made by general practitioners using the MINI and diagnoses from psychiatrists was 85% [26]..

The first 690 participants consecutively recruited into the study were administered the MINI version 6.0 [26]. Use of the MINI was subsequently discontinued due to time burden of administration. The MINI interview encompasses assessments of mood disorders (major depression and bipolar disorder), anxiety disorders (panic disorder, agoraphobia, social anxiety disorder, generalized anxiety disorder), obsessive-compulsive disorder (OCD), PTSD, psychotic disorders (schizophrenia, schizoaffective disorder, schizophreniform disorder, brief psychotic disorder, substance induced psychotic disorder, and psychotic disorder not otherwise specified), and eating disorders (anorexia nervosa and bulimia nervosa). In order to reasonably compare self-reported psychiatric diagnoses with diagnoses identified by structured diagnostic interview, we only considered relevant the diagnoses assessed for in the MINI (for example, attention deficit hyperactivity disorder is not included in the MINI and was therefore excluded from self-report). Antisocial personality disorder is examined in the MINI, however this diagnosis was not self-reported by any of the study participants and was therefore excluded from the present analyses. No other personality disorders are identified using the MINI.

We used descriptive statistics to summarize participant demographic and clinical characteristics, using mean values with standard deviation (SD) or median values with interquartile range (IQR) for continuous variables, and frequencies for categorical variables. Sensitivity and specificity values were calculated for each of the following disorders: any psychiatric disorder, depression, bipolar disorder, anxiety disorder, OCD, PTSD, psychotic disorder, and eating disorder. All analyses were conducted using Stata version 15.1.

Results

Altogether, 1390 participants were recruited into the GENOA study, and upon exclusion of participants recruited in duplicate ($n = 30$) and participants who did not receive the MINI diagnostic interview ($n = 677$), our final study sample consisted of 683 participants (Fig. 1. Study flow diagram). We summarize participant characteristics in Table 1: the mean age was 39.1 years (SD = 11.4) and males composed 58% of the cohort ($n = 395$).

The unemployment rate was 66% ($n = 450$). The reported mean age at first opioid use was 25.5 years (SD = 8.8) and the median years spent in treatment was 3 (Q1, Q3 = 1, 6). The mean methadone dose for the participants was 77 mg/day (SD = 46.5). Three participants in this study sample were prescribed buprenorphine-naloxone (0.4%) at the time of recruitment. At study entry, the percentage of participants that reported being abstinent from opioids was 49% ($n = 335$). The median percentage of opioid-positive drug screens in participants who reported being non-abstinent at the beginning of the study was 25% (Q1, Q3 = 10, 58.2).

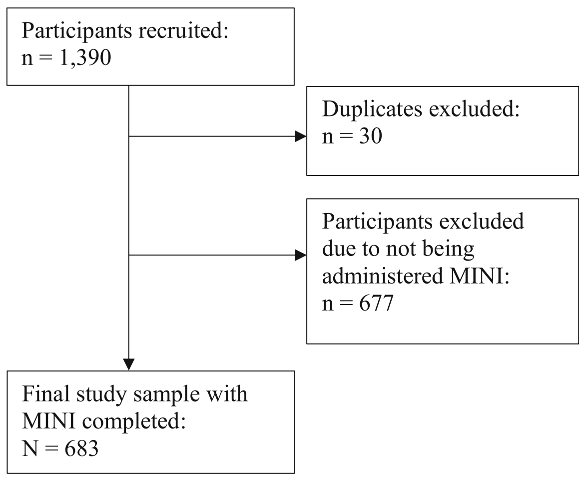

Fig. 1 Study Flow Diagram

Amongst all study participants, 104 (15.2%) reported a diagnosis of depression, 15 (2.2%) reported a diagnosis of bipolar disorder, 102 (14.9%) reported a diagnosis of an anxiety disorder, and 27 (4.0%) reported a diagnosis of PTSD. Less frequently reported diagnoses were OCD, psychotic disorders, and eating disorders. In total, 162 (23.7%) participants self-reported a history of psychiatric comorbidity (Table 2).

The sensitivity and specificity of self-reported psychiatric diagnoses are reported in Table 3.

Of the 162 participants who self-reported any psychiatric comorbidity, 104 met criteria for a comorbidity as per the MINI and 58 did not. Furthermore, 304 participants who reported no psychiatric comorbidity were identified to meet MINI criteria for a psychiatric disorder. The sensitivity and specificity for any self-reported psychiatric diagnoses was 25.5% (95% CI 21.3, 30.0) and 78.9% (95% CI 73.6, 83.6), respectively.

The sensitivity and specificity for self-reported depression was 17.9% (95% CI 12.7, 24.1) and 85.8% (95% CI 82.4, 88.8), respectively; meanwhile the sensitivity and specificity for self-reported anxiety disorders was 14.8% (95% CI 10.5, 20.1) and 85% (95% CI 81.4, 88.2), respectively; and the sensitivity and specificity for self-reported PTSD was 4.2% (95% CI 0.8, 11.7) and 96.1% (95% CI 94.2, 97.5), respectively. The sensitivity for each of self-reported bipolar disorder, OCD, psychotic disorder, and eating disorders was 0% (95% CI for bipolar disorder 0, 4.0; 95% CI for OCD 0, 4.7; 95% CI for psychotic disorder 0, 13.7; 95% CI for eating disorder 0, 36.9). The specificity was 97.5% for self-reported bipolar disorder (95% CI 95.9, 98.6), 99.3% for OCD (95% CI 98.3, 99.8), 99.4% for psychotic disorder (95% CI 98.5, 99.8), and 99.9% for eating disorders (95% CI 99.2, 99.996). There were many new diagnoses identified using the MINI including 156 diagnoses of depression, 195 diagnoses of anxiety, 69 diagnoses of PTSD, 90 diagnoses of bipolar disorder, 76 diagnoses of OCD, 25 diagnoses of psychotic disorders, and 8 diagnoses of eating disorders.

Discussion

Overall, we found that the sensitivity of self-reported psychiatric comorbidity was low, when compared to the MINI, particularly for self-reported depression, anxiety disorder, PTSD, and overall psychiatric diagnoses. In addition, none of the patients with a self-reported history of bipolar disorder, OCD, psychotic disorder, or eating disorder met the criteria for a current diagnosis of each disorder. Many new diagnoses were made in participants who did not report a history of these disorders - including but not limited to depression, anxiety, PTSD, and bipolar disorder. Although the specificity of self-report was higher for certain diagnoses (including anxiety disorder and PTSD), the overall low sensitivity

Table 1 Participant characteristics at study entry (*N* = 683)

Characteristic	Total sample *N* = 683	Self-reported psychiatric comorbidity *n* = 162 (23.7%)	No self-reported psychiatric comorbidity *n* = 521 (76.3%)
Age (years); mean (SD)	39.1 (11.4)	37.8 (11.6)	39.4 (11.3)
Sex; n (%)			
Males	395 (57.8%)	94 (58.0%)	301 (57.8%)
Females	288 (42.2%)	68 (42.0%)	220 (42.2%)
Unemployment; *n* (%)	450 (65.9%)	108 (66.7%)	342 (65.5%)
Age at first opioid use (years); mean (SD)	25.5 (8.8)	25.2 (8.7)	25.6 (8.8)
Years in treatment; median (Q1, Q3)	3 (1, 6)	2 (1, 5)	3 (1, 7)
Methadone dose (mg/d); mean (SD)	77.0 (46.5)	71.8 (39.8)	78.7 (48.3)
Opioid abstinence at study entry; *n* (%)	335 (49.1)	71 (43.8)	264 (50.7)
Percentage (%) of opioid-positive drug screens at study entry if non-abstinent; median (Q1, Q3)	25 (10, 58.2)	29.6 (12, 64.3)	23.5 (9.1, 55.6)

SD Standard Deviation, *Q1* Quartile 1, *Q3* Quartile 3

Table 2 Psychiatric comorbidity identified within the study sample ($N = 683$)

Psychiatric comorbidity	Self-reported	MINI-Diagnosed
Any psychiatric disorder; *n* (%)	162 (23.7%)	408 (59.7%)
Depression; *n* (%)	104 (15.2%)	190 (27.8%)
Bipolar disorder; *n* (%)	15 (2.2%)	90 (13.2%)
Anxiety disorder; *n* (%)	102 (14.9%)	229 (33.5%)
PTSD; *n* (%)	27 (4.0%)	72 (10.5%)
OCD; *n* (%)	4 (0.6%)	76 (11.1%)
Psychotic disorder; *n* (%)	4 (0.6%)	25 (3.7%)
Eating disorder; *n* (%)	1 (0.2%)	8 (1.2%)

MINI Mini-International Neuropsychiatric Interview, *PTSD* Post-traumatic Stress Disorder, *OCD* Obsessive Compulsive Disorder

illustrates that self-report did not accurately capture the patients' present clinical picture. Thus, the utility of self-reported psychiatric comorbidity is in question.

There are several potential explanations for the low sensitivity of self-reported psychiatric disorders. Psychiatric disorders can be episodic in nature, with recurrent symptoms that cycle through relapsing-remitting courses. Participants who reported a historical diagnosis may no longer be experiencing symptoms and no longer meet the criteria for that disorder at the time of assessment. Similarly, participants for whom new psychiatric diagnoses were made may not have previously met criteria for the respective diagnoses. In addition, psychiatric disorders are likely under-diagnosed in the OUD population as evidenced by the under-diagnosis of concurrent disorders as a whole [27]. There may be poor health literacy within the OUD population which can negatively impact an individual's ability to recognize symptoms of a mental disorder and then communicate these issues to a healthcare provider, contributing to underdiagnosis [28]. Furthermore, treatment for mental health and substance abuse disorders continues to be offered separately, despite the evidence supporting concurrent treatment, and between navigating both systems diagnoses may be missed.

Table 3 Sensitivity and specificity of self-reported psychiatric disorders ($N = 683$)

	Sensitivity (95% CI)	Specificity (95% CI)
Any psychiatric disorder	25.5% (21.3, 30.0)	78.9% (73.6, 83.6)
Any depressive disorder	17.9% (12.7, 24.1)	85.8% (82.4, 88.8)
Bipolar disorder	0% (0, 4.0)	97.5% (95.9, 98.6)
Any anxiety disorder	14.8% (10.5, 20.1)	85% (81,4, 88.2)
PTSD	4.2% (0.8, 11.7)	96.1% (94.2, 97.5)
OCD	0% (0, 4.7)	99.3% (98.3, 99.8)
Psychotic disorder	0% (0, 13.7)	99.4% (98.5, 99.8)
Any eating disorder	0% (0, 36.9)	99.9% (99.2, 99.996)

CI Confidence Interval, *PTSD* Post-traumatic Stress Disorder, *OCD* Obsessive Compulsive Disorder

Most studies examining the sensitivity and specificity of self-reported psychiatric diagnoses do not include participants with SUDs. For instance, studies have found moderate to high agreement between self-reported and clinically-diagnosed depression in groups of university graduates and adults being followed for osteoporosis [29, 30]. Conversely, a self-report tool used to screen members of the United States Armed Forces for deployment was found to have low validity in identifying individuals with diagnosed mental health disorders [31]. Much of the related literature in the patients with SUDs examines self-reported substance use, rather than psychiatric comorbidity [32]. Neumann et al. compared self-reported historical psychiatric diagnoses with current clinical diagnoses assessed using the MINI screen, MINI Plus 500 structured interview, and Personality Diagnostics Questionnaire-4th edition. They found that self-reported diagnoses such as bipolar disorder and depression were often not verified by current clinical measures [22]. In addition, many patients had undiagnosed personality disorders, depression, and anxiety disorders [22]. To our knowledge, no other studies have examined the sensitivity and specificity of self-reported psychiatric diagnoses in SUD or OUD populations.

As discussed, individuals with OUD have higher rates of co-occurring psychiatric comorbidities compared to the general population, with rates reaching greater than 40% across their lifetime, [12] and these comorbidities are associated with increased psychiatric distress, rates of SUD, and poorer response to substance use treatment [10, 11, 33]. Despite this, the evidence surrounding the efficacy of psychiatric treatment in these individuals remains equivocal. Literature on pharmacotherapy (mostly consisting of placebo-controlled medication trials) has shown mixed results, with many studies showing no difference from placebo in reducing psychiatric symptoms or substance use [33]. With respect to psychosocial interventions, a Cochrane review found that patients receiving psychosocial interventions in addition to OAT did not show improved outcomes compared to individuals receiving OAT alone; whereas another systematic review did support their efficacy to improve clinical outcomes [34]. There is emerging evidence that some of these inconsistent findings may be indicative of other variables impacting patient responses to psychiatric treatment, including ongoing substance use and complex psychosocial such as housing and employment [9, 33, 35].

The varied, interlinked, and complex needs of individuals with OUD (and other SUDs) have led to a movement towards concurrent treatment [10, 21]. While the evidence for how psychiatric treatment impacts outcomes for patients with SUDs is conflicting, there have been encouraging results from literature evaluating integrated care for both psychiatric and SUDs. In patients receiving both OAT and psychiatric care, those who received on-site and integrated care of both had improved psychiatric outcomes compared to those who received their psychiatric care off-site and non-integrated with their substance use treatment; however no difference was found in outcomes related to substance use [36]. This remains an area requiring further research to elucidate how to best support these clinically complex patients and improve their outcomes.

For patients experiencing SUDs, clinicians also face challenges differentiating between psychiatric disorders and substance-induced disorders as both intoxication and withdrawal from opioids can mimic the symptomatology seen in mood, anxiety, and psychotic disorders [12, 37, 38]. The difficulty in delineating between psychological symptoms as a result of a primary psychiatric disorder versus secondary to SUD (including OUD) makes diagnosing mental illness in this population a complex challenge [12, 37]. In fact, due to the overlap in symptoms between symptom intoxication/withdrawal and affective disorders, Quello et al. advise that definitive assessments of psychiatric diagnoses should be postponed until individuals have achieved a reasonable period of abstinence, although the length of this period varies [39]. Instead they suggest using screening methods to identify possible mood disorders, with associated follow-up after abstinence for definitive diagnosis [39]. Furthermore, individuals may not recall, choose not to disclose, or disagree with a previous psychiatric diagnosis; in addition to self-diagnosing themselves incorrectly. This could occur for various reasons relating to the social stigma of substance use, the impacts of chronic substance use or untreated psychiatric disorders on memory, lack of access to healthcare for appropriate psychiatric assessment, among others.

Our results highlight the need for improved methods to ascertain comorbid psychiatric disorders in the OUD population during treatment. While the specificities of many psychiatric disorders were high, the sensitivities remained poor. That several patients in this study received new diagnoses additionally highlights the issue of under-diagnosis of psychiatric comorbidities in this population, and the need for better ways to identify them [27]. Potential alternatives to patient self-report of psychiatric diagnoses may include structured interviews or questionnaires. In the setting of an addiction treatment clinic, time and resource limitations, and clinical expertise influence the ability to conduct diagnostic interviews and comprehensively assess psychiatric symptomatology. The GENOA study, from which our data were obtained, initially used the MINI structured diagnostic interview, which takes approximately 20 min to administer and use of this tool was later discontinued due to the time burden of administration on participants who did not like the additional 20 min it took to complete the interview. However, the MINI is one of the quickest diagnostic tools used to assess for psychiatric disorder, and other standardized assessments such as the CIDI [40] or the SCID [41] require more time to administer compared to the MINI [42].

Since diagnostic tools require significant time resources, an alternative option would be to administer screening tools that take less time to complete in order to identify the patients who may benefit from a more detailed diagnostic interview. This would be particularly pertinent in relation to the low sensitivities of our results as a way to provide diagnostic clarification when patients self-report psychiatric concerns. Examples of screening tools which require less than 10 min to complete include the Brief Symptom Inventory, [43] Modified MINI screen, [44] and the General Health Questionnaire [45]. The Dual Diagnosis Screening Instrument [46] and Mental Health Screening Form-III [47] are both screening tools that have been developed specifically for the detection of psychiatric comorbidity in patients with SUDs. Another potential solution would be to have a psychiatrist on-site who would be able to administer assessments for psychiatric disorders, which has also been shown to increase patient engagement with psychiatric services [48].

A limitation of this study was the way self-reported psychiatric disorders were elicited, with an open-ended question inquiring about any medical or health problems. This question may have been understood as asking for solely non-psychiatric medical problems or only for current issues that the patient is experiencing, not past diagnoses that are now in remittance. A question that explicitly asks around a history of mental health disorders both past and present would be less susceptible to misinterpretation. Additionally, the MINI does not assess for personality disorders, which are heavily implicated in SUD, [49] or attention deficit hyperactivity disorder. Thus, analysis regarding the sensitivity and specificity of self-report for these disorders is unavailable. Importantly, there is an under-reporting and under-recognition of psychiatric comorbidities in the context of OUD despite the demonstrated impact of such comorbidity on treatment outcomes. Health care providers need to be aware of the prevalence of such disorders in this population and policies regarding systematic screening of patients attending treatment for SUDs for comorbid psychiatric conditions are needed. The choice of a screening tool or clinical assessment that is feasible to use must balance accuracy, effort, and scalability. It is also possible that for some patients, poor mental health literacy in the SUD population likely further exacerbates the issue of self-recognition of psychiatric symptoms and subsequently seeking help with diagnosis.

Conclusion

The sensitivity and specificity of self-reported psychiatric comorbidity in patients with OUD was found to be low when compared to standardized, structured, diagnostic interviews. The remitting-relapsing nature of psychiatric disorders, under-diagnosis, the difficulty in differentiating independent psychiatric disorders from substance-induced disorders, and patient factors likely contributed to these findings. These findings highlight that other methods should implemented in order to identify co-morbid psychiatric disorders in patients with OUD.

Abbreviations

OUD: Opioid use disorder; MINI: Mini International Neuropsychiatric Interview; SUD: Substance use disorder; GENOA: GENetics of Opioid Addiction; SCID: Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders; CIDI: Composite International Diagnostic Interview; OCD: Obsessive compulsive disorder; PTSD: Post-traumatic stress disorder

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12888-021-03489-4.

Additional file 1: Appendix A. Paired contingency tables comparing results of self-reported diagnosis to MINI diagnosis.

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Authors' contributions

TR, and ZS are responsible for the study concept and design. KL and EX cleaned and prepared the data for analysis and TR conducted statistical analyses. KL and EX wrote the first draft of the manuscript, and TR, AW, LT, and ZS contributed to writing and critically revising the final manuscript. All authors reviewed and approved the final manuscript.

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Availability of data and materials

The data that support the findings of this study are available from the corresponding author, ZS, upon reasonable request.

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects. Ethics approval was obtained from the Hamilton Integrated Research Ethics Board (project ID 11–056). All participants were provided informed consent.

Consent for publication

Not applicable.

Competing interests

The authors report no conflict of interest.

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Appendix ii. Published copy of study 3

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Trauma and post-traumatic stress disorder in patients treated for opioid use disorder: findings from a 12-month cohort study

Tea Rosic, Vivian Y. O. Au, Andrew Worster, David C. Marsh, Lehana Thabane and Zainab Samaan

Background

Exposure to traumatic events is both a risk factor for substance use and an adverse outcome of substance use disorders. Identifying and managing post-traumatic stress disorder (PTSD) in patients with addiction requires attention.

Aims

To examine the lifetime prevalence of traumatic events and past-month prevalence of PSTD in patients treated for opioid use disorder, and explore the association between trauma, PTSD and treatment outcomes.

Method

Participants (*n* = 674) receiving methadone treatment in 20 community clinics across Ontario, Canada, were administered the Mini-International Neuropsychiatric Interview to identify self-reported traumatic events and PTSD. Drug use was measured for 12 months by urine drug screens.

Results

Eleven per cent of participants met past-month criteria for PTSD (*n* = 72), and 48% reported history of traumatic events with no current PTSD (*n* = 323). Participants with PTSD were more likely to be female (odds ratio 2.13, 95% CI 1.20–3.76) and less likely to be employed (odds ratio 0.31, 95% CI 0.16–0.61) or married (odds ratio 0.51, 95% CI 0.26–0.90) than those with no trauma history. Antidepressants (39 *v*. 24%) and benzodiazepines (36 *v*. 18%) were differentially prescribed to patients with and without PTSD. Length of time in treatment and opioid use were not associated with trauma; however, suicidal ideation was more common in PTSD (odds ratio 2.29, 95% CI 1.04–5.01).

Conclusions

Trauma and PTSD are prevalent among patients with opioid use disorder, and consideration of trauma symptoms and associated characteristics is warranted. Patients with and without comorbid PTSD differ clinically and psychosocially, highlighting the relevance of integrating addiction and mental health services for this population.

Keywords

Addiction; opioid use disorder; post-traumatic stress disorder; comorbidity; opioid agonist therapy.

Exposure to traumatic events such as threatened death or serious injury, and the experience of trauma (the emotional response to a traumatic event), have been associated with the development of substance use disorders (SUDs).[1] Furthermore, individuals with SUDs may be at greater risk of experiencing violence and traumatic events.[2] Not all individuals who experience trauma develop post-traumatic stress disorder (PTSD); however, studies estimate that 11–50% of patients with SUD meet the criteria for comorbid PTSD.[3] Less information is available on the rates of PTSD in patients with opioid use disorder (OUD); however, they have been reported to be among the highest (41% lifetime, 33% current).[4] Fluctuations in PTSD symptoms are risk factors for opioid use in patients receiving treatment,[5] and may be associated with more intense cravings[6,7] and increased psychological distress.[8] Comorbid PTSD and SUD is also associated with higher rates of other psychiatric and physical comorbidities,[9] fewer social supports and higher rates of unemployment.[7] Patients with comorbid SUD and PTSD may have worse treatment outcomes,[10] and are at higher risk for suicide attempts, relapses to substance use and treatment drop-out.[6,10] Despite these findings, there exists limited formal protocol and guidance to address these co-occurring issues.[11] First-line treatments for PTSD include psychotherapies such as trauma-focused cognitive–behavioural therapy, cognitive processing therapy, prolonged exposure, and eye movement desensitisation and reprocessing therapy; first-line medication treatments include antidepressant treatment with selective serotonin reuptake inhibitors or serotonin–norepinephrine reuptake inhibitors, and targeted symptom treatments have been recommended such as the use of prazosin for nightmares.[12,13] No specific guidelines for the treatment of PTSD in patients with OUD have been published, and the availability of these first-line psychotherapies in addiction treatment settings is limited.[14,15] Acknowledging the high prevalence of PTSD in patients with SUDs and the associated negative impact on treatment, we sought to further examine traumatic events and PTSD in a cohort of patients receiving opioid agonist treatment for OUD. The objectives of this study were to (a) assess the prevalence of traumatic events, with and without current PTSD, in a cohort of patients receiving treatment for OUD; (b) describe demographic and clinical characteristics of patients with history of traumatic events or PTSD and (c) explore the association between traumatic events and PTSD and psychosocial and clinical outcomes during OUD treatment.

Method

We used prospective data from the Genetics of Opioid Addiction (GENOA) study conducted in Southern Ontario, Canada, between June 2011 and April 2017. The GENOA study sought to explore biological, psychological and social factors associated with treatment outcomes for patients with OUD. Data were collected from participants older than 18 years of age, who were receiving methadone maintenance treatment (MMT) for a diagnosis of OUD (as per the DSM-IV-TR).[16] Methadone remains the most commonly prescribed pharmacological treatment for OUD in Canada, and at the time that this study was conducted,

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buprenorphine/naloxone was not covered through the Ontario provincial drug plan. The diagnosis of OUD was established by treating physicians and is an eligibility criterion for clinical follow-up at the clinics included in this study. Participants could be enrolled in MMT for any length of time before recruitment (median 3 years) and participants with polysubstance use or co-occurring SUDs (in addition to OUD) were included. No other inclusion or exclusion criteria were applied, to increase the generalisability of the sample. Participants were recruited from 20 community-based out-patient clinics that are run centrally through a single management team and follow the same clinical protocols. Patients enrolled in participating clinics have access to a multidisciplinary team of health professionals, including addiction physicians, nurses, pharmacists and staff experienced in addiction treatment. They receive medical examination and laboratory tests as indicated, as well as supervised urine testing. All patients included in the present study were receiving methadone treatment but could be prescribed any other medications by their clinic physician or other physicians involved in their care. Patients have access to harm reduction services, including naloxone kits and needle exchange programmes, as well as supports to connect with community agencies to provide services including counselling, housing support, job banks and primary care. No formal psychotherapy treatments are offered in the clinics.

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All procedures involving human patients were approved by the Hamilton Integrated Research Ethics Board (project identifier 11-056), and all study procedures were conducted in accordance with their ethical guidelines. Written and verbal informed consent was obtained from every participant. Our study methods and findings are reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[17]

Participants completed face-to-face interviews at the time of study entry, to obtain information on demographic characteristics, medical and psychiatric history, medications, methadone dose and length of time in treatment. The first 680 participants consecutively recruited into the study competed the Mini-International Neuropsychiatric Interview (MINI) version 6.0,[18] administered by trained interviewers at the time of study entry. Use of the MINI was subsequently discontinued in the study because of the time burden of administration. Therefore, inclusion in the present study's analyses was limited to those participants who were administered the MINI (Fig. 1, study flow diagram). Included in the MINI diagnostic interview is a screen for lifetime history of traumatic events, elicited through the following question: 'Have you ever experienced or witnessed or had to deal with an extremely traumatic event that included actual or threated death or serious injury to you or someone else? Examples of traumatic events include: serious accidents, sexual or physical assault, a terrorist attack, being held hostage, kidnapping, fire, discovering a body, war, or natural disaster, witnessing the violent or sudden death of someone close to you, or a life-threatening illness'. This screening question is based on DSM-IV-TR criterion A for the diagnosis of PTSD.[16] Subsequently, participants were asked about symptoms of PTSD as per the DSM-IV-TR,[16] to determine a past-month diagnosis of PTSD. For the purposes of this study, participants who screen positive for past-month PTSD are considered as having 'current PTSD'. Individuals who report experiencing a traumatic event but do not meet past-month criteria for PTSD are categorised as having a history of 'traumatic events without current PTSD'. Individuals who deny lifetime history of traumatic events are considered to have had 'no trauma'. These three groups are considered mutually exclusive. Finally, participants were also asked to report past-month suicidal ideation and past-month suicide attempts in the MINI assessment.[18]

Participants were followed in the study for 12 months. Use of opioids, cocaine and benzodiazepines were measured with urine drug screen tests, generally administered weekly, following clinical protocol. Urine testing for amphetamines and cannabis was conducted inconsistently, and is therefore not included in the present analyses. Urine toxicology screening was conducted with the iMDx Prep assay.[19] The percentage of positive urine drug screens was calculated for each patient, for each substance. Ongoing opioid use was defined as at least one opioid-positive urine drug screen during the study.

Statistical analyses

Analyses were conducted with Stata version 15.1 for Mac (StataCorp, USA). Our first objective was to determine the prevalence of traumatic events and current PTSD in our study cohort, and our second objective was to describe the demographic and clinical characteristics of these groups. We present descriptive statistics based on group status (i.e. history of traumatic event without current PTSD, current PTSD, no trauma). Continuous variables were summarised as means and s.d. if normally distributed, and as medians with interquartile range (IQR) for skewed data. IQR represents the difference between Q3 and Q1 and is defined as $IQR = Q3 - Q1$. Categorical variables were summarised with frequencies and percentages. Our third objective was to explore the association between trauma history and demographic characteristics and treatment outcomes. We constructed a multinomial logistic regression model with group status (history of traumatic event without current PTSD, current PTSD or no traumatic events or PTSD) as the dependent variable. Covariates included in the model were selected based on previous literature suggesting associations with trauma history or medication-assisted treatment outcome: gender,[20] methadone dose,[21] employment status[7] and marital status.[7] We also included age at onset of opioid use, length of time in treatment, ongoing opioid use and suicidal ideation as covariates in the model, to explore their association with group status. Results are represented as odds ratios with 95% confidence intervals.

Results

Altogether, 1360 unique participants were recruited into the study and 674 participants who were administered the MINI were included in the present analyses (Fig. 1). Forty-one per cent of participants were identified to have no trauma history ($n = 279$), and 48% of participants reported a lifetime history of traumatic events, without meeting criteria for PTSD in the past month ($n = 323$). Eleven per cent of participants met past-month MINI criteria for PTSD ($n = 72$).

Table 1 details sociodemographic and clinical characteristics of participants, by group. Among participants with PTSD, 63% were female, compared with 44% in the other two groups. The mean age of participants in all three groups was approximately 39 years. Among participants with no history of trauma, 35% were married, compared with 28% of participants with history of traumatic events but no PTSD and 21% of participants with PTSD. Unemployment rate was highest for participants with PTSD (83%), followed by participants with traumatic events without PTSD (71%) and participants with neither (56%). Participants were enrolled in treatment for a median of 3 years (IQR = 5). Participants with PTSD had the highest median methadone dose at 84.5 mg/day (IQR = 52.5), compared with 70 mg/day in the other two groups.

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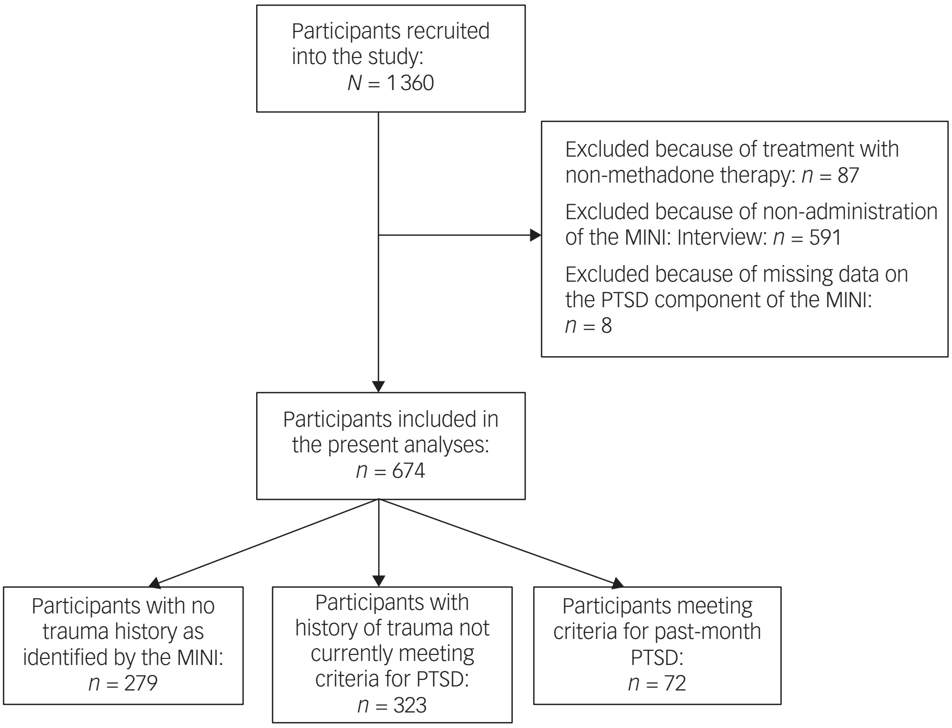

Fig. 1 Study flow diagram. MINI, Mini-International Neuropsychiatric Interview; PTSD, post-traumatic stress disorder.

Antidepressant medications were prescribed for 39% of participants with PTSD, 28% of participants with past traumatic events without current PTSD and 24% of participants with no history of trauma (Table 1). Just one participant in the entire study sample was prescribed prazosin. The prevalence of benzodiazepine prescription was 36% in participants with PTSD, 26% in participants with traumatic events but no PTSD and 18% in participants with no history of trauma. Past-month suicidal ideation was reported by nearly 20% of participants with current PTSD; higher than in the other two groups, in which 7% and 10% of participants reported suicidal ideation, respectively. Reports of past-month suicide attempts were lower at 1.8% in participants with no trauma history, 2.6% in participants with traumatic events but no PTSD and 2.8% in participants with current PTSD. Seventy per cent of participants with no trauma history had ongoing opioid use as evidenced by at least one opioid-positive urine drug screen, compared

Table 1 Baseline demographics and clinical information (*N* = 674)

Characteristic	Total sample (*N* = 674)	No trauma (*n* = 279)	Traumatic events without current PTSD (*n* = 323)	Current PTSD (*n* = 72)
Sociodemographic				
Age, years, mean (s.d.)	38.8 (11.1)	38.7 (11.2)	38.9 (11.2)	38.7 (10.7)
Female gender, *n* (%)	310 (46%)	124 (44.4%)	141 (43.7%)	45 (62.5%)
Married or common law, *n* (%)	202 (30%)	97 (34.8%)	90 (27.9%)	15 (20.8%)
Unemployment, *n* (%)	444 (65.9%)	155 (55.6%)	229 (70.9%)	60 (83.3%)
Clinical				
Age at onset of opioid use (years),[a] mean (s.d.)	25.5 (8.76)	26.9 (9.3)	24.6 (8.2)	23.3 (8.1)
Methadone dose, mg/day, median (IQR)	70 (55)	70 (55)	70 (62)	84.5 (52.5)
Duration in treatment, years, median (IQR)	3 (5)	2.8 (4.3)	3 (6)	2.9 (6)
Antidepressant prescription, *n* (%)	187 (27.7%)	68 (24.4%)	91 (28.2%)	28 (38.9%)
Prazosin prescription, *n* (%)	1	0	1 (0.31%)	0
Benzodiazepine prescription, *n* (%)	158 (23.4%)	49 (17.6%)	83 (25.7%)	26 (36.1%)
Self-reported past-month suicidal ideation, *n* (%)	66/666 (9.9%)	20/276 (7.3%)	32/319 (10%)	14/71 (19.7%)
Self-reported past-month suicide attempt, *n* (%)	15/658 (2.3%)	5/275 (1.8%)	8/312 (2.6%)	2/71 (2.8%)
Ongoing use of opioids (non-abstinence), *n* (%)	515 (76.4%)	201 (72%)	257 (79.6%)	57 (79.2%)
Percentage of opioid-positive urine drug screens among non-abstainers, mean (s.d.)	23.2 (27.1)	23.8 (26.7)	24.3 (28.1)	16 (23)
Use of other substances, *n* (%)				
Non-prescribed benzodiazepines[b]	172 (25.5%)	68 (24.4%)	87 (26.9%)	17 (23.6%)
Cocaine	250 (37.1%)	101 (36.2%)	125 (38.7%)	24 (33.3%)
Percentage of positive urine drug screens among those who use other substances, median (IQR)				
Non-prescribed benzodiazepines[b]	27.9 (52.8)	30 (53.2)	26.8 (53.3)	31.6 (54.7)
Cocaine	26.7 (56.7)	29.4 (71.4)	24 (55.2)	25.8 (56.3)

PTSD, post-traumatic stress disorder; IQR, interquartile range.
a. Data available for 653 participants: 274 participants in no trauma group, 308 participants in the traumatic events without current PTSD group and 71 participants in the PTSD group.
b. Non-prescribed benzodiazepine use was defined as benzodiazepines use detected on urine drug screening with no benzodiazepine prescription in the clinic medical chart.

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Table 2 Multivariable model of demographic and clinical factors associated with trauma history

Trauma history	Covariate	Odds ratio	95% CI	*P*-value
No trauma	(reference group)			
Traumatic event without current PTSD	Male gender	[Reference]		
	Female gender	0.91	0.64–1.28	0.577
	Methadone dose	1.0	1.0–1.0	0.872
	Years in MMT[a]	1.03	0.98–1.07	0.204
	Employed	0.53	0.37–0.75	<0.001
	Married or common law	0.74	0.51–1.06	0.098
	Age at onset of opioid use[b]	0.97	0.95–0.99	0.002
	Opioid abstinence	[Reference]		
	Opioid use	1.41	0.95–2.10	0.090
	Suicidal ideation	1.12	0.61–2.06	0.710
Current PTSD	Male gender	[Reference]		
	Female gender	2.13	1.20–3.76	0.009
	Methadone dose	1.0	1.0–1.0	0.264
	Years in MMT[a]	1.01	0.95–1.08	0.691
	Employed	0.31	0.16–0.61	0.001
	Married or common law	0.51	0.26–0.99	0.046
	Age at onset of opioid use[b]	0.95	0.92–0.98	0.004
	Opioid abstinence	[Reference]		
	Opioid use	1.43	0.73–2.81	0.294
	Suicidal ideation	2.29	1.04–5.01	0.039

PTSD, post-traumatic stress disorder; MMT, methadone maintenance treatment.
a. Scaled for every 1-year increase in length of time in MMT.
b. Scaled for every 1-year increase in age at onset of opioid use.

with 80% of participants with traumatic events and no PTSD and 79% of participants with PTSD. Non-prescribed benzodiazepine use was identified in about 24% of both participants with PTSD and those with no trauma history, and in about 27% of participants reporting traumatic events and no current PTSD. Cocaine use was identified in 33% of participants with PTSD, 39% of participants with traumatic events and no current PTSD and 36% of participants with no trauma history.

We present the results of multinomial regression analysis in Table 2. Participants with PTSD were more likely to be female than those with no trauma history (odds ratio 2.13, 95% CI 1.20–3.76, $P = 0.009$). Compared with participants with no history of trauma, both those with traumatic events without PTSD and those with PTSD were less likely to be employed (odds ratio 0.53, 95% CI 0.37–0.75, $P < 0.001$; and odds ratio 0.31, 95% CI 0.16–0.61, $P = 0.001$, respectively). Similarly, compared with participants with no history of trauma, having traumatic events without PTSD or with PTSD were both associated with younger age at onset of opioid use (odds ratio 0.97, 95% CI 0.95–0.99, $P = 0.002$; and odds ratio 0.95, 95% CI 0.92–0.98, $P = 0.004$, respectively). Participants with PTSD were also less likely to be married than participants with no trauma history (odds ratio 0.51, 95% CI 0.26–0.99, $P = 0.046$). There were no significant associations between trauma history and duration in MMT ($P = 0.204$ for patients with trauma without current PTSD and $P = 0.691$ for patients with PTSD). No association between ongoing opioid use and trauma status was seen (Table 2); however, participants with PTSD were more likely to report past-month suicidal ideation (odds ratio 2.29, 95% CI 1.04–5.01, $P = 0.039$).

Discussion

In our cohort of patients receiving MMT for OUD, we identified an 11% past-month prevalence of PTSD. An additional 48% of participants reported a lifetime history of traumatic events without current PTSD. Therefore, for most patients treated for OUD, a consideration of the presence of trauma symptoms, their impact on substance use course and need for treatment is warranted. Factors associated with PTSD included female gender, unemployment, single marital status, younger age at onset of opioid use, and suicidal ideation; factors associated with a history of trauma without current PTSD included unemployment and younger age at onset of opioid use.

We found important differences in sociodemographic characteristics among patients with and without trauma. Patients with past traumatic events, with or without current PTSD, had a younger age at onset of opioid use. Early identification and management of trauma and PTSD could potentially affect the development or progression of OUD. Although outside of the scope of the present study, the possibility that the identification and management of PTSD may affect OUD outcomes is an area that requires further research. Patients with comorbid OUD and PTSD were also more likely to be unemployed and single when compared with patients with no trauma history. These individuals may require different psychosocial supports within their treatment programmes.[22]

Psychiatric medications

Our examination of the psychiatric medications prescribed for patients with comorbid PTSD revealed several areas of concern. Only 39% were receiving treatment with antidepressants, which are evidence-based treatments for PTSD.[12,13] A limitation of this study is the lack of information on concurrent psychotherapeutic treatments; however, no recommended psychological treatments for PTSD are available through the clinics included in this study. It is also important to consider that selective serotonin reuptake inhibitors can be used for the treatment of multiple psychiatric diagnoses and their prescription does not imply treatment for PTSD. Furthermore, only one participant was receiving prazosin, a medication indicated in PTSD for reducing the severity and frequency of nightmares.[12] Sleep disturbance was reported by 92% of participants with PTSD and re-experiencing symptoms (including dreams, intense recollections or flashbacks) was reported by 100%. Previous studies have reported the prevalence of nightmares in PTSD to be 50–70%, whereas the prevalence of sleep disturbance is reported in 40–50% of patients.[23] Addressing chronic nightmares is of utmost importance as they result in decreased psychological and physical health and may amplify other PTSD symptoms, including suicidal ideation.[24] Our findings suggest that more can be done to offer evidence-based treatments for PTSD in patients with this comorbidity.

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Additionally, 36% of patients with comorbid PTSD were prescribed benzodiazepines, which are neither a recommended treatment for PTSD[12,13] nor recommended for use in patients receiving opioid agonist treatment, because of the risks of respiratory suppression.[11] It is possible that benzodiazepines are being prescribed to alleviate symptoms of PTSD, including anxiety, insomnia and irritability.[25] Although studies estimate that benzodiazepines are prescribed to approximately 30–75% of patients with PTSD, a recent systematic review has concluded that benzodiazepines are ineffective for this purpose, with the risks outweighing the benefits.[25] The concomitant use of benzodiazepines and opioids increases the risk of respiratory suppression and death, and has not been shown to improve treatment retention.[11] Our findings may inspire reflection among clinicians treating this patient population, and prompt further research into the pharmacological treatment of patients with comorbid OUD and PTSD.

Treatment outcomes

We did not identify significant differences in the length of time in treatment, or in ongoing opioid use based on trauma history. In fact, many participants (>70% of the total study sample) had ongoing opioid use (defined as at least one opioid-positive urine drug screen during the study), regardless of trauma history. Severity of opioid use, as measured by the percentage of opioid-positive urine drug screens, also was not associated with trauma status (data not shown). Other substances examined, including cocaine and non-prescribed benzodiazepines, were also used at comparable rates between groups. Our study did not examine drop-out from treatment because the median length of time in treatment was quite long, at 3 years (IQR = 5). A previous study of patients enrolled in an out-patient buprenorphine treatment programme found that individuals with childhood trauma were more likely to drop out of treatment;[26] however, two studies of patients enrolled in MMT found no significant association between the diagnosis of PTSD and 3-month[27] or 1-year retention in treatment.[28] Future studies that further examine the impact of trauma and PTSD on retention in treatment in patients newly starting opioid agonist treatment may be helpful.

The psychological outcomes of patients with comorbid OUD and PTSD are also important to consider. A previous study including patients with comorbid SUDs and PTSD identified these patients as having greater difficulty with coping skills and adaptive cognitions, resulting in increased psychological distress.[8] In our study, nearly 20% of participants with PTSD reported suicidal ideation in the past month, and nearly 3% reported suicide attempts in the past month. Suicidal ideation and suicide attempts were reported at lower rates in the other groups, with the PTSD group more than twice as likely to report suicidal ideation, adjusting for other covariates. This finding highlights that PTSD is not a benign comorbidity in OUD. Patients with OUD and suicidal ideation are at risk for high-lethality overdoses.[29] Taken together, these findings suggest that some patients with trauma history or PTSD may have comparable substance use outcomes in treatment, but have psychiatric and psychosocial differences that require attention. Our findings are consistent with two previous studies that have found good substance use outcomes in opioid agonist treatment, but poor or unchanged psychiatric outcomes for comorbid PTSD,[30,31] suggesting that additional services are required for these patients.

Implications

Improving treatment of PTSD in patients with SUD is critical;[30] studies have demonstrated that remitted PTSD is associated with decreased substance use,[32] whereas a lack of improvement in PTSD symptoms is associated with increased substance use.[33] Patients with SUD, regardless of comorbidity, are often solely treated for their substance use upon first clinical contact.[34] After achieving sobriety, these patients may then be referred for PTSD treatment.[34] However, this model of sequential treatment in which OUD is treated before the initiation of PTSD treatment may be ineffective and inconsistent with research, which supports an integrated approach.[10,34] A number of different treatment models have found success with integrated treatment programmes.[10] The basis for these integrated programmes is that improvement in PTSD symptoms is more likely to attenuate SUD symptoms, but the reverse does not result in the same effect.[10] Despite these findings, the uptake of such programmes has been low, and more research is needed to identify potential barriers that prevent implementation of integrated treatment.[10]

Strengths and limitations

Strengths of this study include its sample size and use of the validated MINI tool to identify trauma comorbidity. Healthy patient and volunteer biases may limit the findings of this study such that patients with trauma comorbidity may have been less likely to participate; therefore, we likely underestimate the prevalence of traumatic events and PTSD.

Through the use of broad inclusion criteria and multi-site sampling, we increase the generalisability of our findings. Participants included in this study were recruited from 20 different community-based out-patient addictions clinics in southern Ontario. The Canadian Agency for Drugs and Technologies in Health published an environmental scan of programmes for the treatment of opioid addiction in Canada in September 2019. Findings from this report suggest that most services accept patients who have a DSM-diagnosed OUD with not many other restrictions.[35] This suggests that the inclusion criteria for our study are appropriate and reflective of individuals who would be eligible to enter treatment in the general population. Public Health Ontario data from 2017 indicate that the population of patients receiving opioid agonist therapy in Ontario is comparable, in terms of age and gender, with the patients recruited in our study: 64% of patients treated in Ontario were 25–44 years of age, and 63% of patients treated were male.[36] As in all studies, there are possible limitations to generalisability that must be considered. For example, all patients in this study were receiving MMT, thus findings may not be applicable to individuals with OUD who are not enrolled in treatment. Further, all patients in this study were agreeable to being recruited and were able to complete the assessments, therefore there is a possibility of volunteer bias. Although we use urine drug screen results to measure opioid use, we are unable to quantify the extent or severity of OUD based on the extent or amount of opioid used. Finally, in Ontario, and more generally in Canada, opioid agonist treatment takes on a harm reduction role, meaning that patients are not discharged from treatment as a result of relapse to opioid or other substance use. Our results may not be generalisable to settings in which ongoing treatment is contingent on abstinence from opioids or other substances.

As this is an observational study, we cannot make conclusions about causality, and there is risk of unmeasured confounding in our analyses. Future studies that examine the longitudinal course of trauma and PTSD in this population will be beneficial, as will studies that shed light on patient goals and treatment priorities in the context of trauma and substance use comorbidity.

In conclusion, patients with OUD and history of trauma or comorbid PTSD differ from patients without trauma comorbidity on a number of clinical and psychosocial factors. We found that patients with trauma history or PTSD may have comparable substance use outcomes in treatment of OUD, but have psychiatric and psychosocial differences that require attention. We also identified that the psychopharmacological treatment of PTSD in patients receiving opioid agonist treatment is an area requiring attention. Our findings emphasise the relevance of better integrating addictions and mental health services for this population.

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Data availability

The data that support the findings of this study are available from the corresponding author, Z. S., upon reasonable request.

Supplementary material

Supplementary material is available online at https://doi.org/10.1192/bjo.2021.971

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Author contributions

T.R., V.Y.O.A., A.W., D.C.M., L.T. and Z.S. are responsible for the study concept and design. T.R. and Z.S. developed the methods and data analysis. L.T. provided feedback on statistical analyses. T.R. and V.Y.O.A. wrote the first draft of the manuscript, and A.W., D.C.M., L.T. and Z.S. contributed to writing and critically revising the final manuscript. All authors reviewed and approved the final manuscript.

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Declaration of interest

D.C.M. declares salary income as Chief Medical Director, Canadian Addiction Treatment Centres, and as Associate Dean of Research, Innovation and International Relations, Northern Ontario School of Medicine. The authors report no other conflict of interest. The authors alone are responsible for the content and writing of this paper.

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