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Psychosis and Comorbid Opioid Use Disorder: Characteristics and Outcomes in Opioid Substitution Therapy

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Background and Objectives: **Substance use disorders are highly prevalent among individuals with psychotic disorders and are associated with negative outcomes. This study aims to explore differences in characteristics and treatment outcomes for individuals with psychotic disorders when compared with individuals with other nonpsychotic psychiatric disorders enrolled in treatment for opioid use disorder (OUD).*Methods:* Data were collected from a prospective cohort study of 415 individuals enrolled in outpatient methadone maintenance treatment (MMT). Psychiatric comorbidity was assessed using the Mini-International Neuropsychiatric Interview. Participants were followed for 12 months. Participant characteristics associated with having a psychotic disorder versus another nonpsychotic psychiatric disorder were explored by logistic regression analysis.*Results:* Altogether, 37 individuals (9%) with a psychotic disorder were identified. Having a psychotic disorder was associated with less opioid-positive urine drug screens (odds ratio [OR] = 0.97, 95% confidence interval [CI] = 0.95, 0.99, *P* = .046). Twelve-month retention in treatment was not associated with psychotic disorder group status (OR = 0.73, 95% CI = 0.3, 1.77, *P* = .485). Participants with psychotic disorders were more likely to be prescribed antidepressants (OR = 2.12, 95% CI = 1.06, 4.22, *P* = .033), antipsychotics (OR = 3.57, 95% CI = 1.74, 7.32, *P* = .001), mood stabilizers (OR = 6.61, 95% CI = 1.51, 28.97, *P* = .012), and benzodiazepines (OR = 2.22, 95% CI = 1.11, 4.43, *P* = .024).*Discussion and Conclusions:* This study contributes to the sparse literature on outcomes of individuals with psychotic disorders and OUD-receiving MMT. Rates of retention in treatment and opioid use are encouraging and contrast to the widely held belief that these individuals do more poorly in treatment. Higher rates of coprescription of sedating and QTc-prolonging medications in this group may pose unique safety concerns.**

Key words: psychotic disorder/schizophrenia/opioid addiction/methadone/medication-assisted treatment/psychiatric comorbidity

Introduction

Opioid use disorder (OUD) has emerged as a major public health crisis and has drawn widespread public attention.[1] Among substance use disorders, OUD is the largest contributor to disability-adjusted life years worldwide, and prevalence of this disorder is increasing.[2,3] Substance use is also commonly associated with comorbidities including psychiatric disorders.[4]

Schizophrenia spectrum and other psychotic disorders (hereafter termed "psychotic disorders") are among the most disabling psychiatric conditions. Despite being a low prevalence disorder, schizophrenia ranked the 12th most disabling medical and psychiatric disorder globally in 2016 and the burden of this disease is increasing.[5,6] Individuals diagnosed with schizophrenia spectrum and other psychotic disorders have significantly elevated rates of substance use disorders when compared with the general population and to people with most other psychiatric disorders. These elevated rates are well-established for nicotine, alcohol, cannabis, cocaine, and methamphetamine use.[7–9] Much of the available epidemiological data in this area predates the current opioid epidemic. It is much less clear whether individuals with psychotic disorders may also have elevated rates of OUD and existing data yield conflicting results.[7,9–11] Individuals with schizophrenia and comorbid substance

use disorders have poorer outcomes including more severe psychiatric symptoms, higher rates of hospitalization and incarceration, and early mortality when compared with individuals with schizophrenia alone.[12,13]

In addition to the paucity of data regarding the epidemiology of OUD in persons with psychotic disorders, there is a significant lack of controlled studies looking at the efficacy of opioid substitution therapy in this population.[14] In fact, individuals with psychosis are often excluded from controlled trials of opioid substitution therapy.[15,16] The existing literature on outcomes in opioid substitution therapy in individuals with comorbid psychotic disorders includes a limited number of small observational studies,[16,17] one that identified a markedly lower rate of retention in treatment for individuals with schizophrenia[16] and the other that found no significant difference in treatment retention.[17] Integrated treatment is considered to be the gold standard for individuals with schizophrenia and substance use disorders, though treatment is rarely offered in this way.[18] In Ontario, Canada, where this study was conducted, opioid substitution therapy is largely provided in clinics that operate in a location separate from primary care and mental health services.

In summary, there is a paucity of data regarding the epidemiology of OUD in people with schizophrenia as well as a lack of controlled studies looking at the efficacy of opioid substitution therapy in this population. It is important to better understand these issues given the significant vulnerability and unique needs of this population. This study aims to explore the following questions:

1. What are the demographic and clinical characteristics of patients with psychotic disorders enrolled in methadone maintenance treatment for OUD, and do these characteristics differ between individuals with psychotic disorders versus other psychiatric comorbidity?
2. Is having a comorbid psychotic disorder, when compared with other psychiatric comorbidity, associated with higher illicit opioid use throughout 12 months of treatment?
3. Is there a difference in nonopioid substance use in patients with psychotic disorders compared with those with other psychiatric comorbidity?
4. Is there a difference in treatment retention in patients with psychotic disorders compared with those with other psychiatric comorbidity?

Methods

The data utilized for this study were collected as part of the Genetics of Opioid Addiction study (GENOA), a prospective cohort study conducted in Southern Ontario, Canada. Data were collected from June 2011 to April 2017 from 20 community-based outpatient methadone clinics across Southern Ontario, Canada. Ethics approval was obtained from the Hamilton Integrated Research Ethics Board (project ID 11–056), and written informed consent was obtained from each participant. Additional details regarding GENOA study methods have been previously described.[4,19,20] This study is reported in accordance with the *Strengthening the Reporting of Observational Studies in Epidemiology* (STROBE) guidelines.[21]

Participants

For study inclusion, participants were required to be males and females of ≥18 years old diagnosed with OUD as per the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV), and currently receiving methadone maintenance treatment for their OUD. Exclusion criteria included opioid substitution therapy other than methadone or if they were unable to communicate in English. A small number of participants (n = 82; 6%) were receiving treatment with buprenorphine–naloxone. Including these participants may reflect different treatments rather than effect of exposure, and thus these participants were excluded from the main analysis of the study (figure 1).

Data Collection and Instruments

Face-to-face interviews were conducted with all participants to obtain sociodemographic information, medical and psychiatric history, current medications, age at onset of opioid use, daily methadone dose, and length of time in treatment. In total, 681 individuals received the Mini-International Neuropsychiatric Interview (MINI) version 6.0,[22] administered by trained interviewers to identify psychiatric comorbidity. Individuals were identified as having a schizophrenia spectrum or other psychotic disorder if (1) they received a MINI diagnosis of lifetime psychotic disorder (schizophrenia, schizoaffective disorder, schizophreniform, brief psychotic disorder, delusional disorder, substance-induced psychosis, and psychosis not otherwise specified) or (2) they self-reported a previous diagnosis of a schizophrenia spectrum or other psychotic disorder or (3) their medical record indicated a prescription for clozapine. Clozapine was chosen as its sole indication is for treatment-resistant schizophrenia.[23] For the purposes of this study, we considered other nonpsychotic psychiatric disorders to include MINI diagnoses of anxiety disorders or mood disorders, including major depression and bipolar affective disorder.

Self-reported substance use was evaluated using the Maudsley addiction profile (MAP), which characterizes substance use in the past 30 days.[24] Illicit opioid use was measured using urine toxicology analysis. In all methadone maintenance therapy clinic sites, point-of-care-supervised urine drug screens for illicit opioids were performed weekly or biweekly. Urine screening was conducted using the iMDx Prep assay for morphine, oxycodone, fentanyl, methadone metabolite, and buprenorphine.[25] An illicit opioid-positive urine is defined by the detection of a non-methadone and nonprescribed opioid in the urine sample.

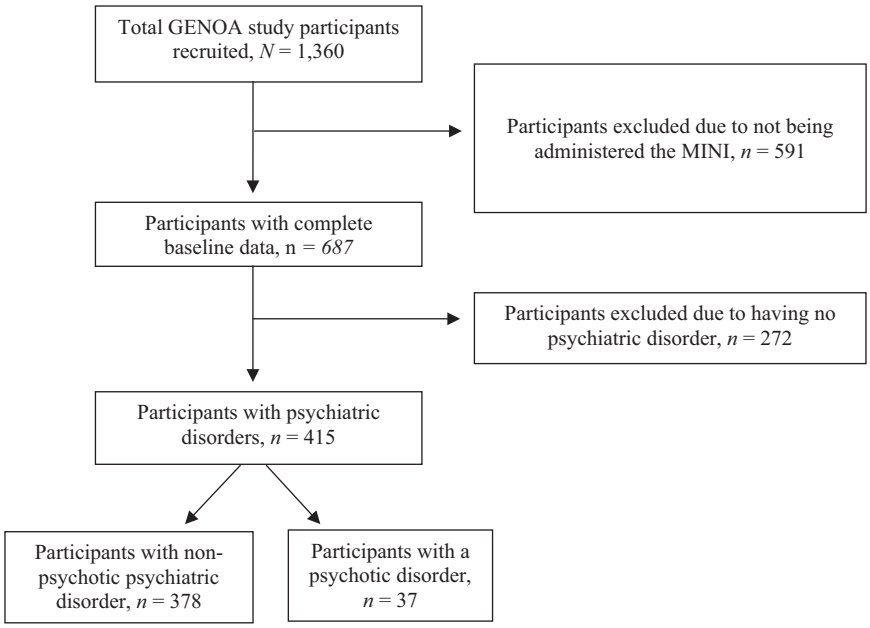

Fig. 1. Study flow diagram.

Retention in treatment is measured by availability of urine drug screen data, taken at 3-, 6-, 9-, and 12-month time points. All participants were followed for 12 months. So long as they remained patients at the methadone maintenance treatment (MMT) clinic sits, urine drug screen data was collected.

Primary Analysis and Outcome Measures

Our first objective was to better characterize individuals with psychotic disorders within this sample and to compare their characteristics, demographic and clinical, to those without psychotic disorders within the sample. This includes a comparison of demographic variables, age at first opioid use, methadone dose, length of time in treatment, medical comorbidities, psychiatric comorbidities, prescribed psychotropic medications, and self-reported recent substance use between the 2 groups. Our second objective was to compare illicit opioid use over 12 months in individuals with a psychotic disorder with those with other psychiatric disorders within the study sample. Therefore, the primary study outcome is defined as the percentage of illicit opioid-positive urine drug screens across 12 months. Illicit opioid use was selected as the primary outcome for this study as the main indication for MMT is to promote abstinence from illicit opioid use.[26] We hypothesized that individuals with psychotic disorders would have higher rates of illicit opioid use than individuals with other nonpsychotic psychiatric disorders. Finally, our third and fourth objectives were to examine differences between the 2 groups in nonopioid substance use and 12-month retention in treatment, respectively.

Statistical Analysis

Statistical analyses were conducted using STATA Version 15.1 (StataCorp LP), with the level of significance for hypothesis testing set at $\alpha = .05$ for all analyses. Categorical data are presented using percentages, normally distributed continuous data are described by mean and SD, and non-normally distributed continuous data are described by median and interquartile range (IQR). Demographic characteristics are presented by group: psychotic disorders versus other psychiatric disorders. Group differences were assessed using independent samples *t* tests or the Mann–Whitney *U* test for unequal variance for continuous variables and chi-square or Fisher's exact tests for categorical variables, as appropriate.

We constructed a multivariable logistic regression model to examine predictors of psychiatric disorder group status (psychotic disorder versus other psychiatric disorders). We included the following covariates in the model: age, sex, methadone dose, length of time in treatment, medications, percentage of opioid-positive urine drug screens, and 12-month treatment retention. Due to small numbers in the psychotic disorder group, and the rule of thumb for the number of events per variable for logistic regression analysis requiring more than 10 participants per covariate,[27] each variable was tested in the model independently, adjusted only for age and sex. Results are reported as odds ratio (OR) with 95% confidence intervals (CI). An OR greater than 1 is in favor of psychotic disorder status.

Results

Altogether, out of 1,360 participants recruited, 415 individuals fulfilled the present study inclusion criteria

and were included in the analyses (figure 1). Of these, 37 participants (9% of total study sample) were identified as having a comorbid lifetime psychotic disorder: 25 participants were identified by MINI diagnosis, 10 participants self-reported a psychotic disorder diagnosis, and 3 participants were identified due to treatment with clozapine. An additional 378 individuals (91%) were identified as having at least one nonpsychotic psychiatric disorder: 262 of these individuals had an anxiety disorder, 90 individuals had a diagnosis of bipolar affective disorder, and 190 individuals met criteria for a depressive disorder (data not shown).

Characteristics of Participants With Psychotic Disorders Versus Other Psychiatric Disorders

Participants with psychotic disorders had a median age of 35.5 years (IQR = 17) and 46% were female (table 1). The differences in these characteristics compared with participants with other psychiatric disorders did not reach statistical significance ($P = .069$ and $P = .224$, respectively). The majority of participants in both groups were unemployed: 81% of those with psychotic disorders and 71% of those with other psychiatric disorders ($P = .200$). Participants with psychotic disorders were in treatment for a mean length of 4.37 years (SD = 4.59) at the time of study entry, which did not differ from those without psychotic disorders (4.17 years; SD = 4.32; $P = .951$) (table 1). There was also no statistically significant difference between groups in age at first opioid use (24.91 vs. 24.58; $P = .972$) (table 2). Participants with psychotic disorders were receiving higher methadone doses than those without other psychiatric comorbidity, though this difference was not statistically significant (98.19 mg; SD = 75.58 vs. 77.09; SD = 42.81; $P = .138$).

There was no significant difference between the 2 groups with respect to HIV status, Hepatitis C status, liver disease, diabetes, or chronic pain, and the prevalence of these medical comorbidities was low overall (table 2). Some patients with psychotic disorders were also identified to meet MINI criteria for other psychiatric comorbidities, overall at similar rates to those identified in patients with other psychiatric disorders (table 2). However, the diagnosis of major depression was significantly less frequent in participants with psychotic disorders (24% vs. 48%, $P = .006$). Only 41% of participants identified as having a psychotic disorder were receiving a prescription for an antipsychotic medication (table 2). Of those on antipsychotic medication, 24% were on a single antipsychotic, 14% were on 2 antipsychotics, and 3% were on 3 antipsychotics. Individuals with psychotic disorders were significantly more likely to be prescribed antipsychotic medications (41% vs. 16%; $P < .001$) than those without a psychotic disorder. In addition, those with a lifetime psychotic disorder were significantly more likely to be on a prescribed antidepressant (51% vs. 33%; $P = .023$), benzodiazepine medication (46% vs. 26%, $P = .012$), and mood stabilizer (8% vs. 2%; $P = .038$) (table 2). Prescription of medication from each of these classes was associated with increased odds of being in the psychotic disorders group, adjusting for age and sex (table 4).

Treatment Outcomes: Illicit Opioid Use, Self-reported Recent Drug Use, and Retention in Treatment

Participants with psychotic disorders had a lower mean percentage of opioid-positive urine drug screens than participants with other psychiatric disorders (8% vs. 16%); however, the median percentage in both groups was similar (5% vs. 6%, $P = .115$; table 3). Using logistic regression analysis and adjusting for age and sex, we

Table 1. Demographic and Clinical Characteristics of Participants With Psychotic Disorders Versus Other Psychiatric Disorders ($N = 415$)

	Psychotic Disorder ($n = 37$)	Other Psychiatric Disorder ($n = 378$)	Test Statistic	*P* Value
Sociodemographic characteristics				
Age, median (IQR)	35.5 (17)	39 (18)	$z = -1.819$	0.069
Female sex, *n* (%)	17 (45.95%)	213 (56.35%)	$\chi^2 = 1.48$	0.224
Smoker, *n* (%)	33 (89.19%)	325 (85.98%)	$\chi^2 = 0.29$	0.588
Unemployment, *n* (%)	30 (81.08%)	269 (71.16%)	$\chi^2 = 1.65$	0.200
Age at first opioid use, median (IQR)	22.5 (12.5)	23 (12)	$z = -0.04$	0.972
Started opioid use by physician prescription, *n* (%)	20 (54.05%)	177 (47.07%)	$\chi^2 = 0.66$	0.417
Clinical characteristics				
Methadone dose (mg/d)				
Mean (SD)	98.19 (75.58)	77.09 (42.81)		
Median (IQR)	88 (77)	75 (55)	$z = -1.48$	0.138
Length of time in treatment (y)				
Mean (SD)	4.37 (4.59)	4.17 (4.32)		
Median (IQR)	2.13 (6.58)	2.84 (5)	$z = -0.06$	0.951

Note: IQR = interquartile range.

Table 2. Comorbidities and Psychotropic Medication Use in Participants With Psychotic Disorders Versus Other Psychiatric Disorders ($N = 415$)

	Psychotic Disorder ($n = 37$)	Other Psychiatric Disorder ($n = 378$)	Test Statistic	*P* Value
Medical comorbidities, *n* (%)				
HIV	0	1 (0.26%)	Fisher's exact	1.0
Hepatitis C	1 (2.7%)	9 (2.38%)	Fisher's exact	1.0
Liver disease	0	0	—	—
Diabetes	0	1 (0.26%)	Fisher's exact	1.0
Chronic pain	3 (8.11%)	8 (2.12%)	Fisher's exact	.065
Psychiatric comorbidities, *n* (%)				
Major depression	9 (24.32%)	181 (47.88%)	$\chi^2 = 7.54$	.006
Bipolar disorder	7 (18.92%)	83 (21.96%)	$\chi^2 = 0.183$	.669
Social anxiety	8 (21.62%)	92 (24.34%)	$\chi^2 = 0.136$	.712
OCD	5 (13.51%)	71 (18.78%)	$\chi^2 = 0.626$	.429
PTSD	5 (13.51%)	67 (17.72%)	$\chi^2 = 0.417$	.519
Generalized anxiety	13 (35.14%)	122 (32.28%)	$\chi^2 = 0.126$	.723
Panic disorder	6 (16.22%)	98 (25.93%)	$\chi^2 = 1.692$	.193
Antisocial personality disorder	12 (32.43%)	99 (26.19%)	$\chi^2 = 2.492$	.114
Psychotropic medications, *n* (%)				
Antidepressant	19 (51.35%)	124 (32.8%)	$\chi^2 = 5.13$	.023
Benzodiazepine	17 (45.95%)	100 (26.46%)	$\chi^2 = 6.32$	.012
Mood stabilizer	3 (8.11%)	6 (1.59%)	Fisher's exact	.038
Stimulant	4 (10.81%)	21 (5.56%)	Fisher's exact	.263
Antipsychotic	15 (40.54%)	59 (15.61%)	$\chi^2 = 33.013$	<.001
Number of antipsychotics				
0	22 (59.46%)	319 (84.39%)		
1	9 (24.32%)	57 (15.08%)		
2	5 (13.51%)	2 (0.52%)		
3	1 (2.7%)	—		
Type of antipsychotic				
Aripiprazole	2	8		
Clozapine	3	0		
Fluanxol	1	0		
Haloperidol	0	0		
Invega Sustenna	1	0		
Methotrimeprazine	0	5		
Olanzapine	2	5		
Paliperidone	2	0		
Quetiapine	7	42		
Risperidone	4	1		

Note: OCD, obsessive compulsive disorder; PTSD, post traumatic stress disorder.

Table 3. Treatment Outcomes in Participants With Psychotic Disorders Versus Other Psychiatric Disorders ($N = 415$)

	Psychotic Disorder ($n = 37$)	Other Psychiatric Disorder ($n = 378$)	Test Statistic	*P* Value
Percentage of opioid-positive urine drug screens over 12 mo				
Mean (SD)	7.59 (10.65)	16.47 (24.2)		
Median (IQR)	4.71 (9.23)	5.76 (19.45)	$z = 1.58$	.115
12-Month retention in treatment	30 (81%)	316 (83.6%)	$\chi^2 = 0.154$	.695
Self-reported substance use last 30 d, *n* (%)				
Alcohol	12 (32.43%)	160 (43.13%)	$\chi^2 = 1.58$	.209
Amphetamine	4 (10.81%)	24 (6.35%)	Fisher's exact	.298
Cannabis	19 (51.35%)	198 (52.38%)	$\chi^2 = 0.014$	.905
Cocaine	6 (16.22%)	42 (11.38%)	Fisher's exact	.42
Illicit benzodiazepine	3 (8.11%)	47 (12.43%)	Fisher's exact	.6

Note: IQR = interquartile range.

Table 4. Characteristics Associated With Psychotic Disorder Status ($N = 415$)

Covariate[a]	OR	95% CI	*P* Value
Age	1.03	1.0, 1.06	.094
Sex	0.66	0.33, 1.30	.227
Methadone dose (mg/d)*	1.01	1.0, 1.01	.034
Length of time in treatment	0.98	0.91, 1.07	.691
Antidepressant treatment*	2.12	1.06, 4.22	.033
Antipsychotic treatment**	3.57	1.74, 7.32	.001
Mood stabilizer treatment *	6.61	1.51, 28.97	.012
Benzodiazepine treatment*	2.22	1.11, 4.43	.024
Percentage of opioid-positive urine drug screens*	0.97	0.95, 0.9996	.046
12-Month treatment retention	0.73	0.3, 1.77	.485
Constant	0.098	0.07, 0.14	.000

Note: CI = confidence interval; OR = odds ratio.
[a]Due to small numbers in the psychotic disorder group, each variable was tested in the model independently, adjusted for age and sex. Age and sex were each assessed independently in separate models. Constant reflects model with no covariates.
*$P < .05$, **$P < .01$.

identified that having a psychotic disorder was associated with less opioid-positive urine drug screens (OR = 0.97, 95% CI = 0.95, 0.99, $P = .046$; table 4).

Individuals with and without psychotic disorders reported similar rates of alcohol (32% vs. 43%; $P = .209$), cocaine (16% vs. 11%; $P = .42$), illicit benzodiazepine (8% vs. 12%; $P = .6$), cannabis (51% vs. 52%; $P = .905$), and amphetamine (11% vs. 6%; $P = .298$) use in the previous 30 days (table 3).

At 12 months, 30 (81%) out of the initial 37 patients with psychotic disorders remained in treatment (table 3). Of the 10 patients in MMT for less than 1 year at the time of study entry, 8 (80%) remained in treatment at 12 months (data not shown). Among participants with other psychiatric disorders, 316 (84%) remained in treatment at 12 months (table 3). Of 92 patients with other psychiatric disorders in MMT for less than 1 year at the time of study entry, 68 (74%) remained in treatment at 12 months (data not shown). Twelve-month retention in treatment was not associated with psychotic disorder group status in the logistic regression (OR = 0.73, 95% CI = 0.3, 1.77, $P = .485$; table 4).

Discussion

In this large prospective study of patients receiving MMT for OUD, individuals with a lifetime diagnosis of a schizophrenia spectrum or other psychotic disorder *did not differ* in their rate of illicit opioid use or treatment retention when compared with those with other psychiatric disorders. In fact, having a psychotic disorder was associated with decreased odds of higher opioid-positive urine screens. These findings are in contrast with commonly held beliefs that patients with psychotic disorders have worse treatment outcomes. Our findings also raise questions about the routine exclusion of persons with psychotic disorders from trials of opioid substitution therapy, which may not be warranted or helpful.[28] The results of this study suggest that individuals with psychotic disorders should not be routinely excluded from studies that include patients with other psychiatric comorbidity.

There is little other literature on outcomes of MMT in patients with psychotic disorders with just 2 small studies specifically examining outcomes in this population.[16,17] A retrospective study of 206 participants with a variety of psychiatric diagnoses, including 13 individuals with a diagnosis of schizophrenia-examined retention in treatment.[16] At 12 months, only 1/13 (7.7%) people with schizophrenia remained in treatment, a retention rate markedly lower than the rate of retention among all other psychiatric comorbidities.[16] Another prospective study of 85 individuals receiving MMT for heroin use disorder included 25 individuals with chronic psychosis and 60 participants without.[17] This study did not find significant difference in rates of treatment retention between the 2 groups.[17]

Beyond treatment outcomes, we attempted to explore other clinical differences in this population that might highlight the unique needs of patients with psychotic disorders. We did not identify a statistically significant difference in methadone dose between our 2 study groups; however, we note that the mean methadone dose for individuals with psychotic disorders fell within a high-dose range, whereas the mean dose for those with other psychiatric disorders is considered within the moderate-dose range.[29] MMT is not without risks and this finding has important safety implications.[30] Methadone is metabolized by the cytochrome P450 enzyme system[31] and is susceptible to drug interactions (eg, medications, smoking), which may explain the higher doses prescribed for patients with psychotic disorders. Furthermore, individuals with psychotic disorders, in addition to being prescribed more antipsychotic medication, were also

more likely to be on prescription antidepressant, benzodiazepine, and mood-stabilizing medications. This is particularly concerning given the known safety risks, mainly related to multidrug toxicity, due to the QTc-prolonging and sedating effects of these medications when combined with methadone.[32–34] Less than 50% of individuals with psychotic disorders in our sample were prescribed antipsychotic medication. This is comparable to rates of antipsychotic medication adherence reported in the literature[35,36] (though prescription of medication does not imply adherence). As many patients identified to have a psychotic disorder were not receiving antipsychotic treatment, this raises questions about whether their treatment follows clinical guidelines. It is possible that lack of antipsychotic prescription reflects lack of recognition or identification of psychotic disorders in this OUD population. Some individuals in our sample had a diagnosis of substance-induced psychosis for which long-term antipsychotic medication may not have been indicated; however, the low rate of prescription of antipsychotic medications may also point to unmet diagnostic or treatment needs. With respect to those people in the other psychiatric disorder group who were prescribed antipsychotic medication, this is likely due to the use of atypical antipsychotics to augment treatment of major depressive disorder[37] as well as quetiapine being commonly prescribed to treat insomnia. Our study data identify that the majority of prescribed antipsychotics in the nonpsychotic disorders group were quetiapine, followed by aripiprazole. Both olanzapine and methotrimeprazine are often used off-label for their sedative properties.

Strengths and Limitations

To our knowledge, this is one of very few studies to detail the characteristics and outcomes of individuals with psychotic disorders receiving MMT for OUD. The study is strengthened by its large sample size, multicenter design, and use of a validated standardized interview for the identification of psychiatric disorders. Our study compared individuals with psychotic disorders with individuals with other psychiatric disorders; therefore, conclusions about how these patients fare in treatment compared with individuals without psychiatric comorbidity is not addressed. Psychiatric comorbidity, in general, may adversely affect outcomes in OUD treatment[38–40]; therefore, the focus of this study was to examine whether individuals with psychotic disorders have characteristics and outcomes that are comparable to individuals with other psychiatric comorbidity—not to compare them with patients with OUD alone. This study, like most others, is limited by healthy user and volunteer biases and participants with less severe psychiatric comorbidity may have been more likely to participate. We recognize that the findings in our study may not be generalizable to all patients with comorbid OUD and psychotic disorders. Our findings probably apply to individuals who are agreeable to participate and be followed in a research study and, moreover, to participants who have been in MMT for long periods of time (an average of 4 years within both study groups). These findings therefore may not be generalizable to all patients with psychotic disorders, and specifically those newly starting treatment. The long average length of treatment in this study may have also resulted in a healthy adherer bias.[41] Interestingly, in this sample, the rate of retention for those in treatment for less than 1 year was the same for those in treatment for more than 1 year. This study cannot comment on rates of retention in treatment for either group for individuals undergoing MMT initiation.

The group of individuals we identified as having psychotic disorders is probably quite heterogeneous, as persons with a lifetime diagnosis of any psychotic disorder were combined due to methodological limitations. It may very well be that individuals with schizophrenia have different characteristics and outcomes than individuals with a history of substance-induced psychosis. In addition, the number of people with active psychotic symptoms at the time of study entry or during the study itself is not known. It is also likely that we did not capture all individuals with psychosis, given diagnostic limitations of the MINI, and self-report rates of psychotic disorders were quite low. In total, 9% of our sample of participants with comorbid psychiatric disorders were identified to have a psychotic disorder. Based on the prevalence of OUD in patients with psychotic disorders (in one study estimated at about 5% for heroin use disorder and about 7% for nonheroin OUD), the number of these individuals enrolled in our study appears to be quite small.[11] This may reflect a lack of willingness to participate in the study, inability to provide informed consent, or perhaps, undertreatment of OUD in patients with psychotic disorders.[42] The small number of participants in the psychotic disorder group also limited the statistical power available to detect group differences. Larger studies will be required in the future.

This study only looked at outcomes with MMT. There is an extreme paucity of data in the literature regarding outcomes for persons with a psychotic disorder and comorbid OUD on buprenorphine/naloxone, which is particularly troubling given its superior safety profile and recent emergence as first-line therapy for OUD.[43] More studies are needed to understand outcomes in treatment of OUD in patients with psychotic disorders, and any unique needs or considerations in this population. How the treatment of psychotic disorders, or lack thereof, influences OUD outcomes is outside of the scope of this study but is a critical avenue for future research. Future research should explore outcomes in patients newly initiating treatment and patients receiving treatment with buprenorphine. Future studies should also avoid excluding patients based on the presence of psychiatric comorbidity.

Conclusions

This study adds important information to the sparse literature on characteristics and outcomes of individuals with psychotic disorders and OUD-receiving MMT. Rates of retention in treatment and opioid use are particularly encouraging and are in stark contrast to the widely held belief that these individuals do more poorly in treatment. Higher methadone doses and higher rates of coprescription of sedating and QTc-prolonging medications in this group pose unique safety concerns. Controlled studies of individuals with psychotic disorders *initiating* methadone and buprenorphine/naloxone for OUD are desperately needed.

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