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Psychiatric comorbidity and treatment outcomes in patients with opioid use disorder: Results from a multisite trial of buprenorphine-naloxone and methadone

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Abstract

Background: Individuals treated for opioid use disorder (OUD) have high rates of psychiatric disorders potentially diminishing treatment outcomes. We examined long-term treatment experiences and outcomes by type of psychiatric disorder among participants who participated in the Starting Treatment with Agonist Replacement Therapies (START) study and its follow-up study.

Methods: We categorized the 593 participants who completed the Mini-International Neuropsychiatric Interview (MINI) during the START follow-up study into four mutually

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Contributors

All authors contributed to and approved the final manuscript.

Declaration of Competing Interest

Andrew J. Saxon reports receiving an honorarium for serving on an advisory board to Indivior, Inc. and receiving royalties from UpToDate, Inc.

Larissa J. Mooney received prior travel support and an honorarium for serving on an advisory board to Alkermes, Inc.

All other authors report no financial or other possible conflicts of interest.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.drugalcdep.2021.108996.

exclusive groups to indicate current psychiatric diagnosis: 1) bipolar disorder (BPD; n = 51), 2) major depressive disorder (MDD; n = 85), 3) anxiety disorder (AXD; n = 121), and 4) no comorbid mental disorder (NMD; n = 336). We compared participants' baseline characteristics and treatment outcomes.

Results: Groups with mental disorders had worse substance use outcomes and poorer psychosocial functioning than the NMD group. Participants with BPD had significantly more self-reported days using opioids (Mean: 8.6 for BPD vs. 3.4 days for NMD, $p < 0.01$) and heroin (Mean: 6.4 for BPD vs. 2.0 for MDD, 3.1 days for NMD, $p < 0.05$) in the 30 days prior to the final interview. Compared to patients without mental disorders, patients with MDD spent more time engaged with OUD pharmacotherapy during the ~16-month period between MINI and final interview (mean: 71.6 % vs. 50.6 %; $p < 0.001$).

Conclusions: Our results show that treatment outcomes in individuals with OUD vary by psychiatric comorbidity groups, which supports the need for mental health assessment and treatment for psychiatric conditions in the context of pharmacotherapy for patients with OUD.

Keywords

Opioid use disorder; Psychiatric comorbidity; Treatment outcomes; Methadone; Buprenorphine-naloxone; Prospective cohort study

1. Introduction

Opioid use disorder (OUD) is a public health concern in the United States, with an estimated 2.0 million Americans age 12 or older having this disorder in 2018 (Substance Abuse and Mental Health Services Administration, 2019). Emergency department visits for suspected opioid overdose increased 30 % from July 2016 to September 2017 (Vivolo-Kantor et al., 2018), and almost 50,000 people died from an opioid-involved overdose in 2019 (Mattson et al., 2021). Effective OUD pharmacotherapy include the opioid agonist methadone, the partial opioid agonist buprenorphine, and the opioid antagonist naltrexone (Schuckit, 2016), all of which may be delivered with adjunctive behavioral treatments.

Literature has reported a higher rate of comorbid psychiatric disorders among adults with OUD than those in the general population (Evans et al., 2020; Jones and McCance-Katz, 2019; Substance Abuse and Mental Health Services Administration, 2018). National reports on treatment-seeking patients with OUD indicate that 37.9 % have a current comorbid psychiatric diagnosis (Substance Abuse and Mental Health Services Administration, 2014). The most common psychiatric disorders among patients with OUD include major depression, anxiety, and bipolar disorder (Kidorf et al., 2004; Pettinati et al., 2013).

Research findings are mixed regarding the impacts of psychiatric disorders on treatment outcomes and psychosocial functioning in populations with OUD. Some studies have reported that psychiatric comorbidity in patients with OUD is associated with worse treatment outcomes, such as higher risks for a return to opioid use and nonadherence to pharmacotherapy treatment, poorer psychosocial or physical health status, and lower quality of life (Cacciola et al., 2001; Carpentier et al., 2009; Litz and Leslie, 2017). Conversely, other studies have found that individuals with comorbid opioid and psychiatric disorders

have equivalent or better treatment outcomes, such as improved negative urine drug assays, longer treatment engagement, and better medication adherence (Gelkopf et al., 2006; Griffin et al., 2014; Japanese Gastric Cancer Association, 2011; National Academies of Science Engineering and Medicine, 2017; Peckham et al., 2020; Trafton et al., 2006). These conflicting findings indicate treatment outcomes may be different by type of psychiatric condition and influenced by the duration of observation, which underscores the need for additional evidence on the impact of psychiatric comorbidities on treatment outcomes among patients with OUD. We aimed to address this gap in knowledge by examining a longitudinal cohort study of patients with OUD to assess different types of psychiatric disorders in relation to treatment experiences.

2. Methods

2.1. Study design

We conducted a secondary analysis of data provided by the Starting Treatment with Agonist Replacement Therapies study (START), which was conducted at nine federally licensed opioid treatment program (OTP) sites (i.e., methadone clinics) with 1269 participants randomized to buprenorphine (n = 740) or methadone (n = 529) from 2006 to 2009 (Saxon et al., 2013). All participants were tapered off their assigned study medications by 32 weeks post-randomization. Any OUD pharmacotherapy received during the follow-up interval was arranged by the participants themselves independent of the study and could change over time. Analyses also included data from a follow-up study of all randomized participants conducted from 2011 to 2016, nearly 2–8 (mean 4.5) years after randomization, performing three assessments 1 year apart (Hser et al., 2016). After participants provided written informed consent, face-to-face interviews and urine samples were collected at the first follow-ups at each site (Hser et al., 2016). The second and third follow-ups were conducted by research staff via phone interviews. Participants were compensated for each visit according to local site policies for study testing and assessments (Zhu et al., 2018). The parent study and the follow-up study were funded by the National Institute on Drug Abuse (NIDA) Clinical Trials Network (CTN). The studies were approved by the Institutional Review Boards (IRB) at each site, the State of California, and UCLA. A federal Certificate of Confidentiality was also obtained to protect participants' information further.

At the outset of the follow-up study, two sites were dropped, accounting for 189 participants due to small sample sizes and difficulties with conducting follow-ups. Hence, 1080 study participants were ultimately targeted for the three follow-up visits. At the first follow-up interview (Visit 1), conducted August 2011–April 2014, 965 participants were located, and 797 (73.7 % of the target population) were interviewed (Hser et al., 2016). At the second follow-up interview (Visit 2), conducted August 2012-June 2016, 723 participants from the group who completed Visit 1 (66.9 % of the target population) were administered the Mini-International Neuropsychiatric Interview (MINI); of these, 597 were again interviewed (55.3 % of the target population), from December 2013–June 2016, as the final follow-up interview (Visit 3). We omitted patients with eating disorders (n = 2) and psychotic disorders (n = 2) for the present paper, yielding a final analysis sample of 593 participants who completed all assessments. The mean length of the follow-up period among 593

participants was 6.5 years (min: 3.9–max: 9.4). The study flowchart provides additional details (Supplement Fig. 1).

2.2. Study variables

2.2.1. Psychiatric diagnoses—The MINI (Sheehan et al., 1998) was used at Visit 2 to assess psychiatric disorders according to DSM-IV criteria. The MINI includes modules on current diagnosis of different types of psychiatric disorders. We used indicators of current diagnoses to construct four mutually exclusive groups: 1) bipolar disorder (BPD; n = 51), 2) major depressive disorder (MDD; n = 85), 3) anxiety disorders (AXD; n = 121), and 4) no mental disorder (NMD; n = 336). Some participants had several mental health conditions (n = 114). Thus, drawing on prior research (Hser et al., 2015), we used the following hierarchy to categorize participants into one group based on diagnostic severity. First, those with any current BPD diagnosis were assigned to the BPD group, regardless of other non-SUD mental health diagnoses and the presence of psychotic features. The MDD and AXD groups were then similarly constructed. The remaining participants did not have any current non-SUD mental disorders and therefore were categorized to the NMD group. It is important to note that post-traumatic stress disorder (PTSD) was included as an anxiety disorder in this study, consistent with DSM-IV classification, given that the data collection was initiated before the publication of the DSM-5, at which time PTSD was recategorized.

2.2.2. Outcome measures

2.2.2.1. Treatment participation.: The Timeline Follow-back (TLFB) approach (Sobell and Sobell, 1992) was used to collect self-reported use of prescribed buprenorphine or methadone dispensed from an OTP between Visit 2 and Visit 3. The mean of percentage of follow-up months in OUD pharmacotherapy (either buprenorphine or methadone) was calculated following prior reports (Evans et al., 2019; Hser et al., 2017).

2.2.2.2. Substance use.: We obtained self-reported days of substance use (including opioids, heroin, alcohol, cocaine, amphetamine, methamphetamine, and cannabis) using TLFB in the 30 days prior to Visit 3.

2.2.2.3. The Addiction Severity Index-Lite (ASI-Lite).: The ASI-Lite (Mclellan et al., 1992) is a structured interview that assesses problem severity in seven areas related to substance use disorders. The scores range from 0 to 1 with higher scores indicating greater severity. We used a weighting procedure to calculate composite scores at Visit 3 (McGahan et al., 1986).

2.2.2.4. Brief Symptom Inventory (BSI).: Conducted at Visit 3, the BSI assesses nine psychiatric symptom dimensions summarized into three global indicators of distress. The scale ranges from 0 to 4 with higher values indicating greater severity of symptoms (Derogatis and Melisaratos, 1983).

2.2.2.5. Medical Outcomes Study Short Form 36-Item Health Survey (SF-36).: The SF-36 is widely used to evaluate health-related quality of life (Ware and Sherbourne, 1992).

The SF-36 was conducted at Visit 3. We calculated the physical and mental component summary scores on a T-score metric with a mean of 50 and a standard deviation of 10.

2.2.3. Covariates—Participants' baseline characteristics were selected based on the original START study. Age, gender, race/ethnicity, randomization condition, urine drug test results, and injection drug use were included in analyses.

2.3. Data analysis

Chi-square test for categorical variables and ANOVA for continuous variables were used to compare group differences in baseline characteristics, treatment engagement measured from Visit 2 to Visit 3, substance use, ASI composite scores, BSI scale scores, and SF-36 physical and mental component summary scores at Visit 3. Also, pairwise comparisons were conducted using the Bonferroni correction ($\alpha = 0.05/6 = 0.0083$) for categorical variables and the Tukey-Kramer method for continuous variables. Except for pairwise comparisons, all other two-tailed tests with a p-value less than 0.05 were considered statistically significant. All data analyses were performed in SAS version 9.4 (SAS Institute, Cary, NC).

3. Results

3.1. Baseline characteristics

The baseline demographic and clinical characteristics of participants are shown in Table 1. More than half of the participants were male (63.6 %), white (72.3 %), originally randomized to buprenorphine (57.2 %), and injected drugs (65.5 %) at baseline. Those diagnosed with major depressive disorder were, on average, older than those with bipolar disorder and those without mental disorders (Mean: 41.8 for MDD vs. 36.5 for BPD, 37.0 years old for NMD; $p < 0.01$). The groups with mental disorders had more women than the NMD group (BPD: 43.1 %, MDD: 41.2 %, AXD: 45.5 % vs. NMD: 31.0 %; $p < 0.05$). The groups with mental disorders had more individuals who injected drugs (BPD: 78.4 %, MDD: 71.8 %, AXD: 68.6 % vs. NMD: 60.9 %; $p < 0.05$) and more individuals with a history of psychiatric disorders (BPD: 62.8 %, MDD: 63.6 %, AXD: 62.0 % vs. NMD: 39.9 %; $p < 0.001$). There were no baseline differences in remaining participant characteristics by psychiatric groups.

3.2. Treatment engagement and substance use

Compared to patients without mental disorders, patients with MDD spent more of the time from Visit 2 to Visit 3 engaged with OUD pharmacotherapy (Mean: 71.6 % vs. 50.6 % of follow-up months in OUD pharmacotherapy; $p < 0.001$) (Table 2). Compared to patients without mental disorders, patients with MDD spent more months on methadone (Mean: 60.0 % for MDD vs. 38.1 % for NMD; $p < 0.001$) and patients with BPD spent more months on buprenorphine (Mean: 22.0 % for BPD vs. 10.5 % for NMD, $p < 0.05$). In addition, patients with MDD spent more months on methadone than patients with BPD (Mean: 60.0 % for MDD vs. 35.1 % for BPD; $p < 0.001$).

In terms of substance use in the 30 days prior to Visit 3 (Table 3), participants with BPD had significantly more self-reported days of using opioids (Mean: 8.6 for BPD vs. 3.4 days for NMD, $p < 0.01$) and heroin (Mean: 6.4 for BPD vs. 2.0 for MDD, 3.1 days for NMD, $p < 0.05$). No statistical differences of other substance use by psychiatric groups were observed.

3.3. Substance-related issues, psychosocial functioning and psychiatric conditions

Table 4 presents the group differences in addiction severity (ASI composite scores), physical and psychiatric symptoms (BSI scale scores), and quality of life (SF-36 component summary scores) at Visit 3. Compared to the NMD group, each of the three psychiatric disorder groups had greater problem severity in 6 of 7 domains (as indicated by ASI composite scores: drug use, employment, social/family, legal, medical, and psychiatric), worse symptoms in all 10 measures of physical and psychiatric health, and poorer quality of life. Among three groups with mental disorders, participants with BPD had the worst physical and psychiatric symptoms.

In the sensitivity analysis, adding the excluded 2 participants with eating disorders and 2 with psychotic disorders in the AXD group as a new group did not change the results (data not shown). Attrition analysis revealed no statistically significant differences in the demographics of those interviewed (n = 593) and not interviewed (n = 487) except for gender (female: 36.4 % vs. 27.9 %, p < 0.01; Supplemental Table 1).

4. Discussion

This study aimed to characterize psychiatric disorders and their association with long-term treatment outcomes among individuals initially treated with methadone or buprenorphine for OUD in the START study. In our follow-up study, we found that the participants without mental disorders had the lowest proportion of females, injection drug use, and history of psychiatric disorders at baseline. During follow-up visits, those with MDD had a higher proportion of follow-up months with OUD pharmacotherapy than those without mental disorders. At the end of the follow-up, participants with BPD had significantly more days of using heroin and all opioids in the past 30 days. Furthermore, those with comorbid psychiatric disorders showed more severe substance-related conditions, psychosocial functioning, and psychiatric symptoms at the end of follow-up.

It has been well-established by previous studies that women are more likely than men to be diagnosed with a mental health condition (Evans et al., 2020; Grella et al., 2009; Griffin et al., 2014; Jones and McCance-Katz, 2019). We also found that the prevalence of injection drug use at baseline was higher among patients with OUD and comorbid psychiatric disorders. Other studies have reported that psychiatric and substance abuse comorbidity is highly prevalent among people who inject drugs (Mackesy-Amiti et al., 2012). Taken together, these findings replicate prior evidence and highlight the need to design treatments and other interventions that are sensitive to gender and infectious disease risk behaviors.

We also found that over 5 or more years of observation, patients with co-occurring opioid and major depressive disorders engaged with OUD pharmacotherapy for more months during follow-up than those without mental disorders. The continued high utilization of

pharmacotherapy among patients with OUD and comorbid psychiatric disorders compared to those without mental disorders is notable and may have several explanations. Findings from the literature on the association between psychiatric comorbidity and treatment engagement have been inconsistent (Astals et al., 2009; Gelkopf et al., 2006; Litz and Leslie, 2017). Possible reasons for inconsistent results include different outcome variables, multiple types of medication used, and different diagnostic criteria for psychiatric disorders. However, MDD diagnosis has been associated with improved opioid treatment outcomes in prior research, possibly related to greater engagement in treatment (Peckham et al., 2020), and that depression symptoms are associated with higher motivation to change opioid use (Morris et al., 2018).

In the current study, we found higher utilization of methadone than buprenorphine by participants, which may be explained by methadone clinic procedures. Patients receiving methadone were required to attend a clinic daily to obtain medication following regulations regarding methadone dispensing and thus were more regularly in contact with the clinic personnel, which likely enhanced treatment engagement. Conversely, buprenorphine patients were not required to attend the clinic daily, given the nature of buprenorphine self-administration without supervision. Another explanation is that methadone treatment was more accessible to this group of individuals who were largely impoverished.

At the end of the follow-up, more than 5 years after baseline, participants with BPD had significantly more heroin and other opioid use in the past 30-days. This finding further supports the claim that some patients with OUD and comorbid psychiatric disorders may have higher rates of opioid use due to their greater psychiatric symptom severity (Quinn et al., 2017).

Consistent with previous studies (Carpentier et al., 2009; Havard et al., 2006), patients with OUD and comorbid psychiatric disorders reported poor functioning across multiple domains. Numerous significant group differences in components of ASI composite scores, BSI scale scores, SF-36 physical and mental component summary scores indicated higher problem severity across multiple problem areas in patients with OUD and different comorbid psychiatric disorders. Based on severity, participants with BPD had the poorest functional outcomes. Psychiatric treatment for patients with OUD can be combined with OUD pharmacotherapy and self-help groups. Since the 1970s and 80 s, a number of studies demonstrated that psychotherapy can be used effectively with individuals with SUDs (Woody et al., 1987, 1983, 1975). To reduce healthcare costs, however, support was reduced for these psychiatrically focused treatments. These findings point to an unmet need for medication and psychosocial therapies for patients with OUD and psychiatric comorbidity.

This study has several limitations. First, we assessed the type of psychiatric disorders at follow-up Visit 2. Although the question about the history of psychiatric disorders was included at treatment entry (in the parent START study), the pre-existing diagnosis patterns according to objective measures and the temporal relationship between OUD and psychiatric disorders are unknown. Second, attrition analysis showed that female participants had a higher follow-up rate, which might be overrepresented in this study, but the rates of treatment engagement in the present study were similar to an 11-year follow-up of the

Australian Treatment Outcome Study (ATOS) (Darke et al., 2015). Third, results are based on a sample of individuals treated for OUD in community-based, federally regulated OTP clinics, and thus findings may have limited applicability to patients treated in primary care clinics or other settings. Fourth, we did not include sedative use (e.g., benzodiazepines), which is common in individuals with OUD and did not collect information about participants' treatment for mental health disorders, both of which could have impacted treatment outcomes. Finally, substance use and treatment participation were self-reported and may be subject to recall bias. As for study strengths, this secondary analysis was conducted with a relatively large sample derived from a multi-site clinical trial and a follow-up prospective longitudinal study with a long duration to assess associations between OUD pharmacotherapy treatment outcomes and co-occurring psychiatric conditions. Our study sample has a similar rate of psychiatric disorders as has been reported in nationally representative data (Substance Abuse and Mental Health Services Administration, 2014).

5. Conclusions

In summary, participants with co-occurring OUD and psychiatric diagnoses were more likely to be female, people who inject drugs, and those with a history of psychiatric disorders. Participants with BPD had significantly more self-reported days of using opioids and heroin. MDD diagnosis is of clinical significance because it is associated with better engagement with OUD pharmacotherapy but poorer psychosocial functioning and health status. This study highlights the importance of mental health assessment and treatment for psychiatric conditions provided in conjunction with pharmacotherapy for patients with OUD. Future efforts should be directed toward improving screening and developing targeted treatment interventions for comorbid psychiatric disorders among patients with OUD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Baseline characteristics of participants by type of psychiatric disorder[†] (N = 593).

	Bipolar disorder (n = 51, BPD)	Major depressive disorder (n = 85, MDD)	Anxiety disorders (n = 121, AXD)	No mental disorder (n = 336, NMD)	Total (N = 593)
Age, n (%) [*e]					
18–24	9 (17.7)	7 (8.2)	21 (17.4)	52 (15.5)	89 (15.0)
25–34	13 (25.5)	19 (22.4)	32 (26.5)	122 (36.3)	186 (31.4)
35–44	16 (31.4)	16 (18.8)	27 (22.3)	61 (18.2)	120 (20.2)
45–54	12 (23.5)	35 (41.2)	32 (26.5)	76 (22.6)	155 (26.1)
55+	1 (2.0)	8 (9.4)	9 (7.4)	25 (7.4)	43 (7.3)
Mean (SD) [**a, e]	36.5 (10.2)	41.8 (10.6)	38.3 (11.6)	37.0 (11.4)	37.9 (11.3)
Gender, n (%) [*f]					
Male	29 (56.9)	50 (58.8)	66 (54.6)	232 (69.1)	377 (63.6)
Female	22 (43.1)	35 (41.2)	55 (45.5)	104 (31.0)	216 (36.4)
Race/ethnicity, n (%)					
Black	3 (5.9)	11 (12.9)	13 (10.7)	32 (9.5)	59 (10.0)
Hispanic	7 (13.7)	11 (12.9)	11 (9.1)	36 (10.7)	65 (11.0)
White	37 (72.6)	54 (63.5)	87 (71.9)	251 (74.7)	429 (72.3)
Other race	4 (7.8)	9 (10.6)	10 (8.3)	17 (5.1)	40 (6.8)
Randomized conditions, n (%)					
Buprenorphine	32 (62.8)	48 (56.5)	60 (49.6)	199 (59.2)	339 (57.2)
Methadone	19 (37.3)	37 (43.5)	61 (50.4)	137 (40.8)	254 (42.8)
Baseline urine drug screen positive for, n (%)					
Opioids	49 (96.1)	80 (94.1)	110 (90.9)	315 (93.8)	554 (93.4)
Cocaine	20 (39.2)	31 (36.5)	43 (35.5)	94 (28.0)	188 (31.7)
Methamphetamine/amphetamine	3 (5.9)	8 (9.4)	12 (9.9)	21 (6.3)	44 (7.4)
Cannabis	9 (17.7)	13 (15.3)	24 (19.8)	72 (21.4)	118 (19.9)
Alcohol (positive breathalyzer)	10 (19.6)	30 (35.3)	41 (33.9)	101 (30.2)	182 (30.7)
In past 30 days, injected drugs n (%) [*]	40 (78.4)	61 (71.8)	83 (68.6)	204 (60.9)	388 (65.5)
Any history of psychiatric disorders (excluding drug), n (%) [***a,e,f]	32 (62.8)	54 (63.5)	75 (62.0)	134 (39.9)	295 (49.8)

	Bipolar disorder (n = 51, BPD)	Major depressive disorder (n = 85, MDD)	Anxiety disorders (n = 121, AXD)	No mental disorder (n = 336, NMD)	Total (N = 593)
Any medical diseases, n (%)	41 (80.4)	69 (81.2)	93 (76.9)	253 (75.3)	456 (76.9)

Group comparison based on Chi-squared test for categorical variables and ANOVA test for continuous variables (*p<0.05, **p<0.01, ***p<0.001).

All pairwise comparisons are the Bonferroni correction for categorical variables; Tukey-Kramer method was used for continuous variables (a=BPD vs. MDD, b= BPD vs AXD, c= BPD vs NMD, d= MDD vs. AXD, e = MDD vs. NMD, f=AXD vs. NMD).

†All variables were conducted in the initial START trial.

Table 2

Engagement in OUD pharmacotherapy from the MINI (Visit 2) to the end of follow-up (Visit 3) by type of psychiatric disorder.

Mean (SD)	Bipolar disorder (n = 51, BPD)	Major depressive disorder (n = 85, MDD)	Anxiety disorders (n = 121, AXD)	No mental disorder (n = 336, NMD)	Total (N = 593)
# Follow-up months	14.5 (3.6)	16.0 (6.5)	16.3 (6.5)	16.1 (5.7)	16.0 (5.8)
# Follow-up months, median (IQR)	15.0 (2.0)	15.0 (2.0)	15.0 (2.0)	15.0 (2.0)	15.0 (2.0)
% Follow-up months received any OUD pharmacotherapy*** e	60.1 (38.0)	71.6 (39.1)	62.4 (41.8)	50.6 (45.3)	56.9 (43.8)
% Follow-up months received buprenorphine c	22.0 (37.4)	9.4 (25.9)	11.6 (30.0)	10.5 (28.6)	11.6 (29.5)
% Follow-up months received methadone***a,e	35.1 (40.8)	60.0 (45.1)	45.2 (45.8)	38.1 (45.3)	42.4 (45.6)

Notes: IQR: interquartile range; SD: standard deviation.

Group comparison at each visit based on ANOVA test for continuous variables (*p < 0.05, **p < 0.01, ***p < 0.001).

All pairwise comparisons: Tukey-Kramer method was used for continuous variables (a = BPD vs. MDD, b = BPD vs AXD, c = BPD vs NMD, d = MDD vs. AXD, e = MDD vs. NMD, f = AXD vs. NMD).

Table 3

Number of days of substance use in the 30 days prior to the end of follow-up (Visit 3) by type of psychiatric disorder.

Mean (SD)	Bipolar disorder (n = 51, BPD)	Major depressive disorder (n = 85, MDD)	Anxiety disorders (n = 121, AXD)	No mental disorder (n = 336, NMD)	Total (N = 593)
Opioids *,**,c,∞	8.6 (12.5)	5.9 (11.3)	4.4 (10.0)	3.4 (9.1)	4.4 (10.0)
Heroin *,a,c	6.4 (11.4)	2.0 (5.9)	3.7 (8.7)	3.1 (8.2)	3.3 (8.4)
Cannabis	5.9 (11.0)	3.9 (9.2)	6.3 (10.8)	4.0 (9.4)	4.6 (9.9)
Alcohol	2.4 (6.8)	2.3 (6.6)	3.2 (7.5)	3.0 (6.7)	2.9 (6.8)
Methamphetamine	1.3 (4.2)	0.9 (3.6)	0.9 (4.0)	0.9 (4.0)	0.9 (3.9)
Amphetamine	1.2 (5.9)	0.7 (4.6)	1.3 (6.0)	0.4 (3.1)	0.7 (4.3)
Cocaine	1.3 (4.0)	0.3 (1.3)	0.9 (3.7)	0.5 (2.9)	0.7 (3.0)

Group comparison at each visit based on ANOVA test for continuous variables (*p < 0.05, **p < 0.01, ***p < 0.001).

All pairwise comparisons: Tukey-Kramer method was used for continuous variables (a = BPD vs. MDD, b = BPD vs AXD, c = BPD vs NMD, d = MDD vs. AXD, e = MDD vs. NMD, f = AXD vs. NMD).

∞Self-reported opioids include heroin, Demerol, Codeine, Dilaudid.

Table 4

Problem severity, psychiatric symptoms, and psychosocial functioning at the end of follow-up (Visit 3) by type of psychiatric disorder.

	Bipolar disorder (n = 51, BPD)	**Major depressive disorder (n = 85, MDD)**	**Anxiety disorders (n = 121, AXD)**	**No mental disorder (n = 336, NMD)**	**Total (N = 593)**
Addiction Severity Index Lite (ASI)[€]					
Alcohol	0.06 (0.2)	0.05 (0.1)	0.07 (0.2)	0.06 (0.1)	0.06 (0.1)
Drug[***c,e,f]	0.23 (0.2)	0.18 (0.1)	0.18 (0.1)	0.12 (0.1)	0.15 (0.1)
Employment[***c,e,f]	0.70 (0.3)	0.74 (0.3)	0.64 (0.3)	0.54 (0.3)	0.60 (0.3)
Social/Family[***c,e,f]	0.18 (0.2)	0.15 (0.2)	0.12 (0.2)	0.07 (0.1)	0.10 (0.2)
Legal[**c]	0.10 (0.2)	0.05 (0.1)	0.08 (0.2)	0.05 (0.1)	0.06 (0.1)
Medical[***e,f]	0.35 (0.4)	0.44 (0.4)	0.36 (0.3)	0.23 (0.3)	0.30 (0.4)
Psychiatric[***b,c,e,f]	0.40 (0.2)	0.32 (0.2)	0.27 (0.2)	0.10 (0.2)	0.19 (0.2)
Brief Symptom Inventory (BSI)[λ]					
Somatic[***b,c,d,e,f]	1.6 (0.9)	1.3 (0.9)	0.9 (0.8)	0.5 (0.6)	0.8 (0.8)
Obsessive[***b,c,d,e,f]	2.0 (1.0)	1.7 (1.0)	1.3 (0.9)	0.8 (0.8)	1.1 (1.0)
Interpersonal sensitivity[***a,b,c,e,f]	1.6 (1.1)	1.2 (1.0)	1.0 (0.9)	0.5 (0.6)	0.8 (0.9)
Depression[***b,c,d,e,f]	1.7 (1.1)	1.4 (1.1)	1.0 (0.9)	0.6 (0.7)	0.9 (0.9)
Anxiety[***a,b,c,d,e,f]	1.9 (1.1)	1.4 (1.1)	1.1 (0.8)	0.5 (0.7)	0.9 (0.9)
Hostility[***a,b,c,e,f]	1.3 (1.1)	0.9 (0.8)	0.7 (0.7)	0.4 (0.5)	0.6 (0.7)
Phobic anxiety[***a,b,c,e,f]	1.3 (1.1)	1.0 (0.9)	0.8 (0.7)	0.3 (0.5)	0.6 (0.8)
Paranoid ideationAnxiety[***a,b,c,d,e,f]	1.7 (1.0)	1.3 (0.9)	0.9 (0.8)	0.6 (0.7)	0.9 (0.9)
PsychoticismAnxiety[***a,b,c,d,e,f]	1.5 (1.0)	1.1 (1.0)	0.8 (0.7)	0.4 (0.5)	0.7 (0.8)
GlobalAnxiety[***a,b,c,d,e,f]	1.6 (0.9)	1.3 (0.8)	1.0 (0.6)	0.5 (0.5)	0.8 (0.7)
Psychosocial functioning[£]					
SF-36 Physical Component	42.1 (12.5)	42.1 (12.0)	45.2 (12.6)	48.5 (11.2)	46.4 (12.0)
SummaryAnxiety[***c,e,f]					

	Bipolar disorder (n = 51, BPD)	Major depressive disorder (n = 85, MDD)	Anxiety disorders (n = 121, AXD)	No mental disorder (n = 336, NMD)	Total (N = 593)
SF-36 Mental Component SummaryAnxiety***b,c,d,e,f	34.3 (14.4)	36.6 (15.7)	41.6 (11.6)	50.7 (10.7)	45.4 (13.6)

Group comparison at each visit based on ANOVA test for continuous variables (*p < 0.05, **p < 0.01, ***p < 0.001).

All pairwise comparisons: Tukey-Kramer method was used for continuous variables (a = BPD vs. MDD, b = BPD vs AXD, c = BPD vs NMD, d = MDD vs. AXD, e = MDD vs. NMD, f = AXD vs. NMD).

€ASI scores range from 0 to 1 with higher scores indicating greater severity.

λBSI scores range from 0 to 1 with higher scores indicating greater severity.

£SF-36 component summary scores on a T-score metric that gives a mean of 50 and standard deviation of 10.