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Long-term follow-up assessment of opioid use outcomes among individuals with comorbid mental disorders and opioid use disorder treated with buprenorphine or methadone in a randomized clinical trial

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Abstract

Aims—To investigate whether reduction in opioid use differs when treated by either buprenorphine–naloxone (BUP) or methadone (MET) among adults with comorbid opioid use disorder (OUD) and mental disorders.

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Author contributions

Yuhui Zhu: Formal analysis; investigation; methodology. **Zhe Fei:** Formal analysis; investigation; methodology. **Larissa Mooney:** Conceptualization; investigation; methodology; resources. **Elizabeth Evans:** Investigation; methodology; project administration; supervision. **Annemarie Kelleghan:** Conceptualization; data curation; investigation; methodology; validation. **Abigail Matthews:** Data curation; investigation; methodology; project administration; software. **Caroline Yoo:** Formal analysis; methodology. **Andrew Saxon:** Conceptualization; funding acquisition.

Clinical trial registration

The START Follow-up Study on ClinicalTrials.gov (NCT01592461).

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Design, Setting and Participants—In a randomized controlled trial, adults with OUD were randomized to 24 weeks of either BUP or MET treatment and were followed up in 3-yearly assessments. The present secondary analyses were based on 597 participants who completed all assessments.

Measurements—The outcome measure was the number of days of using opioids per month during the follow-up period. The Mini-International Neuropsychiatric Interview (MINI) was used to classify participants into three groups: life-time mood disorder (n = 302), life-time mental disorder other than mood disorder (n = 114) and no mental disorder (n = 181). Medication treatment (BUP, MET, no treatment) during the follow-up period was a time-varying predictor.

Findings—Based on zero-inflated Poisson (ZIP) mixed regression analysis, it was found that relative to no treatment, opioid use during the follow-up was significantly reduced by BUP [odds ratio (OR) = 0.12, 95% confidence interval (CI) = 0.07–0.21 for any use; risk ratio (RR) = 0.77, 95% CI =0.66–0.89 for days of use] and by MET [OR = 0.33, 95% CI = 0.25–0.45 for any use; RR = 0.78, 95% CI = 0.72–0.84 for days of use]. Relative to MET, BUP was associated with a lower likelihood of any opioid use among participants with mood disorders (OR = 0.52, 95% CI = 0.36–0.74) and for participants without mental disorder (OR = 0.37, 95% CI = 0.21–0.66) and fewer number of days using opioids (RR = 0.37, 95% CI = 0.25–0.56) among participants with other mental disorders.

Conclusions—Among adults with comorbid opioid use disorder and mental disorders, treatment with buprenorphine–naloxone produced greater reductions in opioid use than treatment with methadone.

Keywords

Buprenorphine; comorbidity; longitudinal; mental health disorder; methadone; opioid use disorder

INTRODUCTION

Mental disorders among individuals with opioid use disorder (OUD) are common [1,2]. The co-occurrence of a mental disorder with OUD (also referred to as comorbidity or dual diagnosis) presents well-established challenges in treatment for OUD [3]. The evidence is mixed in relation to the impact of the co-occurrence of these conditions on OUD treatment outcomes. Some studies report that comorbidity is associated with an elevated risk for opioid use relapse and other unfavorable outcomes [4,5]. Other studies report that comorbidity is associated with longer treatment retention [6,7] and lower relapse rates [8,9], or is not associated with continued opioid use [10,11] or treatment retention [12]. Conflicting findings are probably due, in part, to variation in study designs, most notably differences in the types of mental disorders [e.g. any psychiatric disorder, or one specific mental disorder such as depression, or posttraumatic stress disorder (PTSD)] and in medication treatment (i.e. methadone, buprenorphine) [13]. The discrepancy in findings underscores a need for studies that incorporate the complex factors involved in influencing outcomes of medication treatment for OUD (MOUD).

Buprenorphine and methadone are Food and Drug Administration (FDA)-approved medications for treating OUD. As opioid agonists, both medications are effective in

reducing opioid use. Opioid agonists have also been shown to act as psychotropic medicines in treating mental disorders, with beneficial effects in reducing mood, anxiety and psychotic symptoms [14,15]. Recently, there has been renewed interest in buprenorphine as a novel therapy for depression and other psychiatric disorders (PTSD) [16,17]. Buprenorphine, a partial μ-opioid receptor agonist and κ-opioid receptor antagonist, has shown antidepressant properties [16,18], although supportive data of its effectiveness for depression are scarce. Generally speaking, both buprenorphine and methadone have been shown to reduce opioid use and improve psychiatric symptomatology and quality of life among dual-diagnosis patients, but few of these studies have compared outcomes of buprenorphine and methadone treatment. One exception is an observational, non-randomized study that found reductions in psychopathological symptoms among patients on MOUD, but no statistically significant differences between buprenorphine and methadone regarding their effects [14]. Empirical evidence has suggested that dual-diagnosis patients may benefit from opioid agonist treatment (either methadone or buprenorphine) that not only targets their OUD but also effectively reduces severity of psychiatric symptoms. However, the relative effectiveness of buprenorphine versus methadone for patients with OUD and comorbid mental disorders has yet to be determined.

The purpose of the present study was to investigate whether there were differential effects on opioid use among OUD patients with specific life-time psychiatric diagnoses (mood disorder, mental disorder other than mood disorder, none) who received MOUD with either methadone or buprenorphine. We focused upon mood disorder versus other mental disorders, because mood disorder is the most common mental disorder among this population and has been the most widely studied in relation to MOUD [16,17]. We hypothesized that OUD patients with mood disorder would have better outcomes (in terms of reductions in opioid use) if treated with buprenorphine, given its antidepressant effects associated with kappa antagonism, compared with outcomes of patients on methadone. We also examined the supposition that there would be no difference in opioid use reduction between the two medication treatments for participants with mental disorders other than mood disorder.

METHODS

Study design and participants

The present study utilized data collected by a large, multisite, prospective study that originally randomized 1269 participants with DSM-IV opioid dependence from nine federally licensed opioid treatment clinics during 2006–09 to receive either buprenorphine–naloxone (BUP) or methadone (MET) for 24 weeks. Following the assigned 24-week medication period, participants were referred or transferred to community treatment program, or were tapered off medication over ≤ 8 weeks if not transferred. Three-yearly follow-up assessments were conducted with 1080 participants during 2011–16. The parent study (Starting Treatment with Agonist Replacement Therapies; START), was a Phase IV study designed to compare the effects of BUP and MET on liver function [19]. Among the 1080 participants targeted for long-term follow-up, 797 completed follow-up interview one (visit 1), 728 completed interview two (visit 2), which included a structured psychiatric

interview (723 participants completed the psychiatric interview) and 647 completed interview three (visit 3). Among these participants, 597 participants had all relevant data from the three interviews for the present secondary analysis and constituted the analysis sample. The details of sample sizes and attrition at each stage are shown in the Consolidated Standards of Reporting Trials (CONSORT) diagram (Fig. 1). There were no differences in the demographic characteristics, history of substance use or randomization status of participants included and omitted from analysis, except for gender (36.2% versus 28.2%, $P = 0.005$) (Supporting information, Table S1).

Main measures

Opioid use was defined as the number of self-reported opioid use days per month during the present study's follow-up period, which was between the second and third follow-up interviews. The percentage of follow-up months with opioid use was calculated as the number of follow-up months with at least 1 day of opioid use divided by the total number of follow-up months, which varied for each participant (mean was ~16 months). The percentage of follow-up months with BUP or MET treatment was similarly calculated.

Concurrent treatment participation was the self-reported receipt of treatment with BUP or MET for each month during the follow-up period. Both were collected using the time-line follow-back (TLFB) method, aided by a calendar and other memory prompts [20]. During the follow-up, a participant could receive MET, BUP or no MOUD at any given month. The status of any MOUD was not randomized and could have changed over time; thus, MOUD during follow-up was a time-varying measure.

Mental disorder diagnoses were based on the Mini-International Neuropsychiatric Interview (MINI) version 6.0.0 [21], which was conducted at the second follow-up interview. The MINI is a brief structured interview consisting of 17 modules for assessing life-time and current psychiatric disorders according to DSM-IV and ICD-10 criteria. We used MINI diagnostic algorithms to define life-time mood disorders [major depressive episode, (hypo)manic episode and mood disorder with psychotic symptoms]. The algorithm establishes whether a participant has a major depressive disorder or a bipolar disorder (mutually exclusive) [22]. We composed three groups based on these mental disorder diagnoses (regardless of alcohol and drug dependence/abuse diagnosis): (1) mood disorder (mood; e.g. bipolar disorder, major depressive disorder), (2) mental disorder other than mood disorder (other; e.g. anxiety disorder, antisocial personality disorder) and (3) no mental disorder (none).

Statistical analysis

Using the complete data from our sample of 597 participants, group differences by mental disorder diagnosis were examined descriptively using χ^2 tests for categorical variables and analysis of variance (ANOVA) for continuous variables. All pairwise comparisons were Bonferroni-corrected for categorical variables, and mean values were compared using the Tukey–Kramer method.

Next, we examined the associations among opioid use, mental disorder diagnoses and treatment status during the follow-up period, with the primary outcome being the number

of opioid use days per month between the second and third follow-up interviews. Based on repeated measures of opioid use days over months and the high proportion of zero values in this primary outcome (see Table 3), we used PROC NLMIXED to fit a zero-inflated Poisson (ZIP) mixed model with random effects using the adaptive Gaussian quadrature method [23–25]. ZIP-mixed models consist of two portions. The first portion is a logistic regression for modeling a repeated dichotomous outcome (1 for any use, 0 for no use during each month), and the second portion is a Poisson regression for modeling repeated-count outcome (number of days using opioids during each month). The main independent variable is the mental disorder group (mood disorder, mental disorder other than mood disorder or no mental disorder). Time-invariant covariates were assessed at baseline and included randomization condition (BUP versus MET), age at randomization (in years), gender, race/ethnicity, cocaine use, injection drug use and study site. Monthly status of any MOUD (i.e. MET versus no MOUD, BUP versus no MOUD) between the second and third follow follow-up interviews was included as a time-varying predictor. A set of interaction terms between mental disorders and treatment status was included to examine the influence of mental disorders on the effect of treatment status on opioid use. The selection of these variables was based on a combination of clinical importance and statistical significance. The final ZIP-mixed model had a piece-wise linear slope for month with two knots at the first and 14th months based on the trajectory plot. Significance was defined as $P < 0.05$. SAS version 9.4 was used for all analyses. This analysis plan was not pre-registered and the results should be considered exploratory.

RESULTS

Patient characteristics and life-time mental disorder diagnosis

Table 1 provides the patient characteristics at baseline for the three groups classified by the mental disorder diagnosis (mood disorder, mental disorder other than mood disorder and no mental disorder). Approximately half (50.6%) the study participants had mood disorder, 19.1% had mental disorder other than mood disorder and 30.3% did not have any comorbid mental health diagnoses. The three groups did not differ in demographics and other characteristics at the baseline.

Among participants with a mood disorder, 56.0% had bipolar disorder and 44.0% had major depressive disorder (Table 2), and many of them also had other mental health conditions, including 74.2% with anxiety disorders (e.g. 64.6% panic disorder, 37.8% obsessive–compulsive disorder, 26.8% social anxiety disorder, 17.2% PTSD), 31.8% antisocial personality, 7.6% psychotic disorder and 4.6% eating disorders. Among participants with mental health conditions excluding mood disorder, 69.3% had anxiety disorder (e.g. 52.6% panic disorder, 21.9% obsessive–compulsive disorder), 43% had antisocial personality disorder and 6.1% had psychotic disorder.

Opioid use and treatment participation during the follow-up period

As shown in Table 3, the mean number of months in follow-up between the second and third interviews was 16.0 months [standard deviation (SD) = 5.9]. The three mental disorder groups did not differ in opioid use (measured by either percentage time or number of

days per month) during the follow-up period. Participants with mood disorders had more percentage time of follow-up months of participation in MOUD (mean = 60.6% of time, SD = 42.2) than those with no mental disorders (mean = 49.9% of time, SD = 45.5); the difference was mainly due to BUP treatment (mean = 14.5% of time, SD = 32.4 for participants with mood disorders, relative to mean = 8.1% of time, SD = 24.8 for those with no mental disorders; $P < 0.05$). Figure 2 shows the percentage of participants receiving MOUD by the three mental disorder groups for each month since visit 2 when MINI diagnosis was assessed.

Opioid use outcomes according to differences in mental disorders by type of MOUD

The ZIP model results are shown in Table 4. In terms of having any opioid use or not (the logit portion where opioid use was modeled as a dichotomous variable), receiving treatment at a West Coast clinic [odds ratio (OR) = 1.72, 95% confidence interval (CI) = 1.46–2.03] and age (OR = 1.01, 95% CI = 1.00–1.02) were associated with a greater likelihood of opioid use. Randomization to BUP (versus MET) at baseline was associated with lower odds of opioid use (OR = 0.81, 95% CI = 0.69–0.95). We estimated the effects of receiving BUP or MET versus not receiving MOUD in the three groups: (1) among those with no mental disorder (BUP: OR = 0.12, 95% CI = 0.07–0.21; MET: OR = 0.33, 95% CI = 0.25–0.45; both P for interaction < 0.001); (2) among those with mood disorder (BUP: OR = 0.24, 95% CI = 0.17–0.34; MET: OR = 0.47, 95% CI = 0.37–0.58; both P for interaction < 0.001); and (3) among those with mental disorder other than mood disorder (not significant).

The Poisson portion of the ZIP model showed that injection use [risk ratio (RR) = 4.15, 95% CI = 1.44–11.94] and randomization to BUP (versus MET; RR = 3.14, 95% CI = 1.20–8.19) at baseline were associated with an increased number of opioid use days per month during the follow-up period. The time-varying effect showed that both treatments were associated with reduced opioid use among participants without mental disorder (BUP: RR = 0.77, 95% CI: 0.66–0.89; MET: RR = 0.78, 95% CI = 0.72–0.84) and those with mood disorder (BUP: RR = 0.80, 95% CI = 0.73–0.88; MET: RR = 0.72, 95% CI: 0.68–0.76) compared with those not receiving any MOUD treatment. Regarding the interaction of treatment status and mental health disorder group, only those who were on BUP showed a significant reduction of opioid use days among participants with comorbid mental disorders other than mood disorders (RR = 0.38, 95% CI = 0.25–0.56; P for interaction < 0.001) compared with those without treatment during follow-up. The estimated days of opioid use are plotted separately by the three mental disorder groups to show the interaction effects between mental disorders and treatment status during the follow-up period (Fig. 3).

In addition to separately comparing BUP participants and MET participants with the no-MOUD participants, we derived the differential treatment effects, specifically comparing BUP and MET on opioid use by mental disorder groups (Table 5). The logit portion showed that, relative to MET, BUP was associated with a lower likelihood of using opioids among participants with mood disorder (OR = 0.52, 95% CI = 0.36–0.74) and among those without mental disorder (OR = 0.37, 95% CI = 0.21–0.66). The Poisson portion showed that relative to MET, BUP was associated with a fewer number of opioid use days among those with mental disorder other than mood disorder (OR = 0.37, 95% CI = 0.25–0.56).

DISCUSSION

Our study findings showed that among patients treated for OUD, BUP appears to be more effective than MET for the three mental disorder groups, perhaps for different reasons. Relative to MET, BUP was associated with a higher likelihood of opioid abstinence among participants with mood disorder or without any mental disorder. BUP (relative to MET) was also associated with fewer days of opioid use among participants with mental disorder other than mood disorder. It should be noted that regardless of mental health condition type, participants treated with either BUP or MET had less opioid use than participants who were not treated with MOUD.

In addition to opioid use reductions elicited by MOUD, either buprenorphine or methadone would probably improve psychiatric symptomatology non-specifically and transdiagnostically. Methadone may exert effects on mood by blocking re-uptake of serotonin and norepinephrine in a similar fashion to many marketed antidepressants and by antagonism of the N-methyl [26], D-aspartate (NMDA) subtype of glutamate receptors in a similar fashion to ketamine, a marketed antidepressant [27]. In contrast, buprenorphine is postulated to improve mood via its antagonism of kappa-opioid receptors [28] and reduce anxiety-like behaviors via its agonism at nociception receptors [29]. Buprenorphine may also have more potent direct effects on anxiety-like symptoms than methadone, so that patients with anxiety disorders on buprenorphine are less driven to use illicit opioids in an attempt to ameliorate these symptoms. Indeed, in a study of patients with OUD and PTSD being treated with methadone no discernible improvements were seen in PTSD [30], whereas patients with OUD and PTSD treated with buprenorphine showed significant improvements in PTSD [31]. Comorbid mental disorders other than mood predominantly represent anxiety disorder in the overall sample, which could explain the finding that BUP was correlated with a significant reduction of opioid use days (compared to no treatment) during follow-up among participants with comorbid mental disorders other than mood disorder. For patients with OUD who have mood disorders, direct improvement in mood related to treatment with buprenorphine or methadone could lead to reductions in opioid use. It should also be noted that mood disorders may motivate some patients to seek and adhere to OUD treatment, as suggested by prior literature demonstrating improved outcomes on MOUD in individuals with depression [32], and consistent with study findings that participants with mood disorders had more time on MOUD than those with no mental disorders, particularly in the BUP group. In addition, mood and anxiety symptoms may also stem from intoxication/withdrawal states associated with opioid relapse, which are alleviated by buprenorphine and methadone.

The present study has several limitations. We did not have information on treatments or medications that these participants received for their psychiatric conditions. It is possible that additional care received for mental disorders was helpful in improving opioid use outcomes, even though such an effect has not been conclusively demonstrated [33]. Although medication conditions (BUP versus MET) were randomized during the initial study phase, medication received during the subsequent period was not. The analyses were based on the participants who had all relevant data, which were derived from self-report, and the study did not include mental health outcomes (e.g. symptoms of depression or

anxiety), which are important for this population [34]. Using the definition of 'lifetime' mood disorders instead of 'current' may have led to different results. Among study sites or regions (e.g. West Coast versus East Coast) there may be variability in post-trial treatment availability and/or availability of heroin and other opioids and these regional differences could influence variations in opioid use observed in the follow-up study, which should be further examined in future studies. Residual confounding is possible because other non-pharmacological factors, such as the structure of methadone programs, may also influence opioid use for participants who have mental disorder diagnoses. Finally, the clinical implications of the statistical significance found in the differences between groups (that combined several mental disorders in each group) need to be ascertained in future studies. Our study findings need to be replicated with a randomized trial to confirm that OUD patients with specific mental disorders (as opposed to mental comorbidities grouped together as done in the present study) have better outcomes when treated with BUP than with MET.

The present study documents the high prevalence of mental disorders among individuals with OUD seeking MOUD. MOUD (compared to no treatment) has been demonstrated to be effective in reducing opioid use, and the present study shows that these medications also reduced opioid use for individuals with mental disorders, perhaps by the effects of the medications on mental health symptom reduction, particularly buprenorphine. Many patients with OUD and mood disorders also have multiple other mental disorders and substance use disorders, representing a clinically complex population. Findings underscore the well-established need to assess and treat these conditions in a comprehensive and integrated approach [35].

This study confirmed that both BUP and MET are effective in reducing opioid use among individuals with comorbid mental disorders, which are highly prevalent among patients with OUD. It should be noted that participation in MOUD among the study sample was not optimal and was particularly low in BUP treatment during the follow-up period (e.g. treatment participation was almost four times more likely for MET than for BUP); it should be noted that the parent study was conducted more than a decade ago, when BUP treatment was less prevalent. In retrospect, the under-engagement of participants in BUP was unfortunate in light of our study finding that BUP is not only effective for OUD patients with mood disorder but even more effective than MET for those with other mental disorders (e.g. anxiety disorder). Strategies to expand access to and engagement in all types of MOUD, especially BUP, and to retain OUD patients in MOUD are essential to address OUD and comorbid mental health complications.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Declaration of interests

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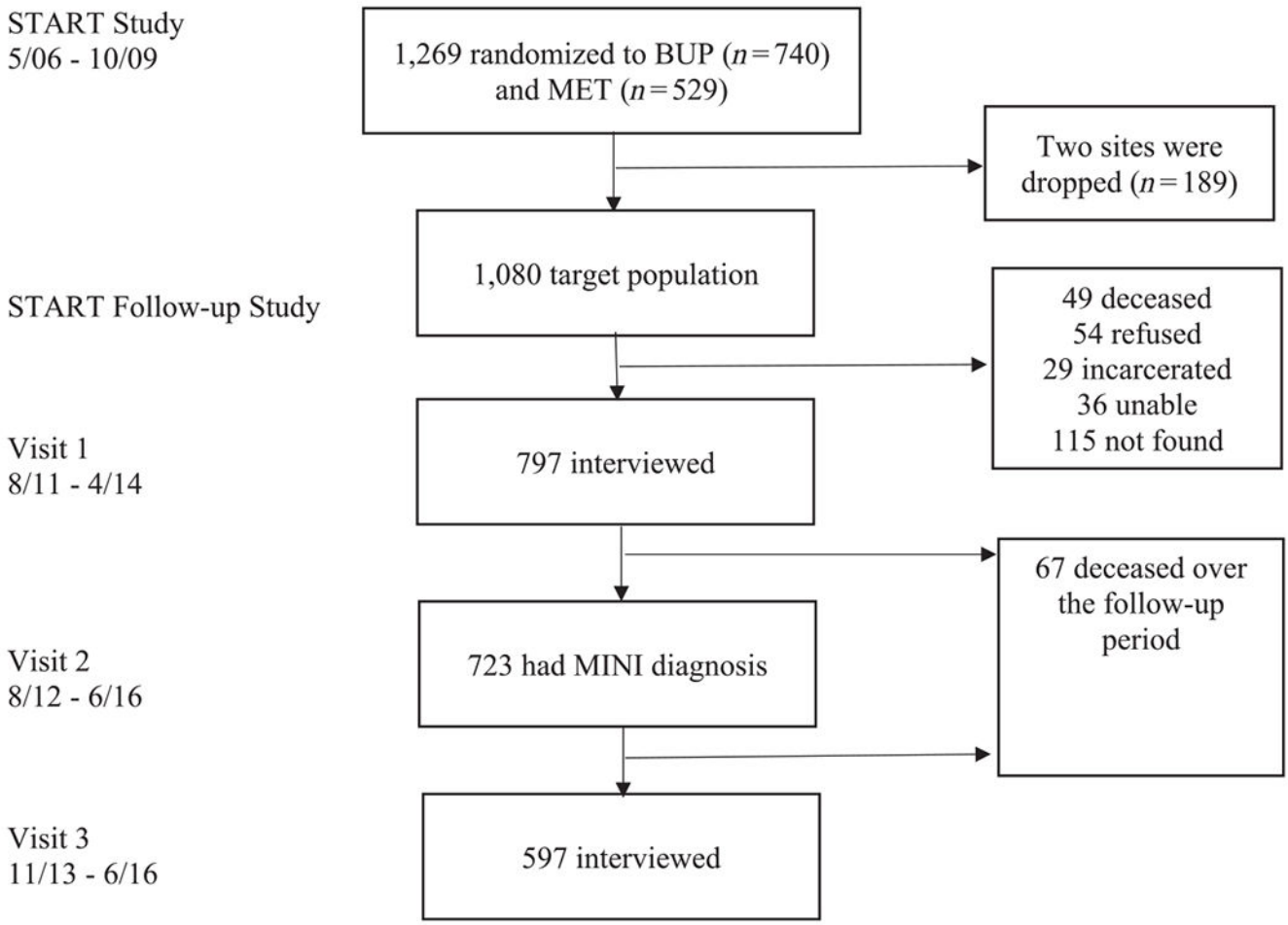

Figure 1.
Consolidated Standards of Reporting Trials (CONSORT) diagram: sample sizes and attrition at each stage

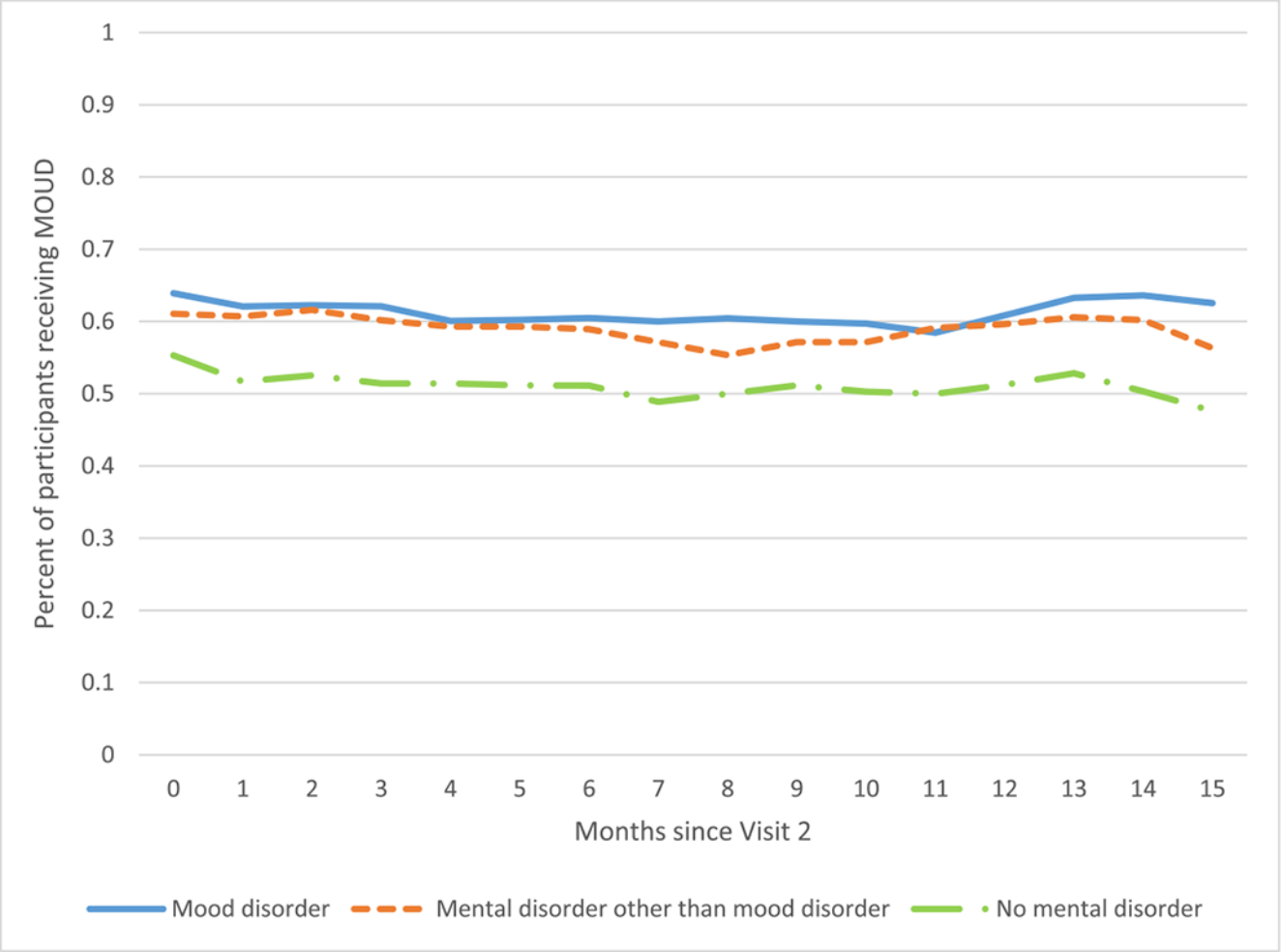

Figure 2.

Percentage of participants receiving medication treatment for opioid use disorder (MOUD) during the follow-up period by mental disorder group [Colour figure can be viewed at wileyonlinelibrary.com]

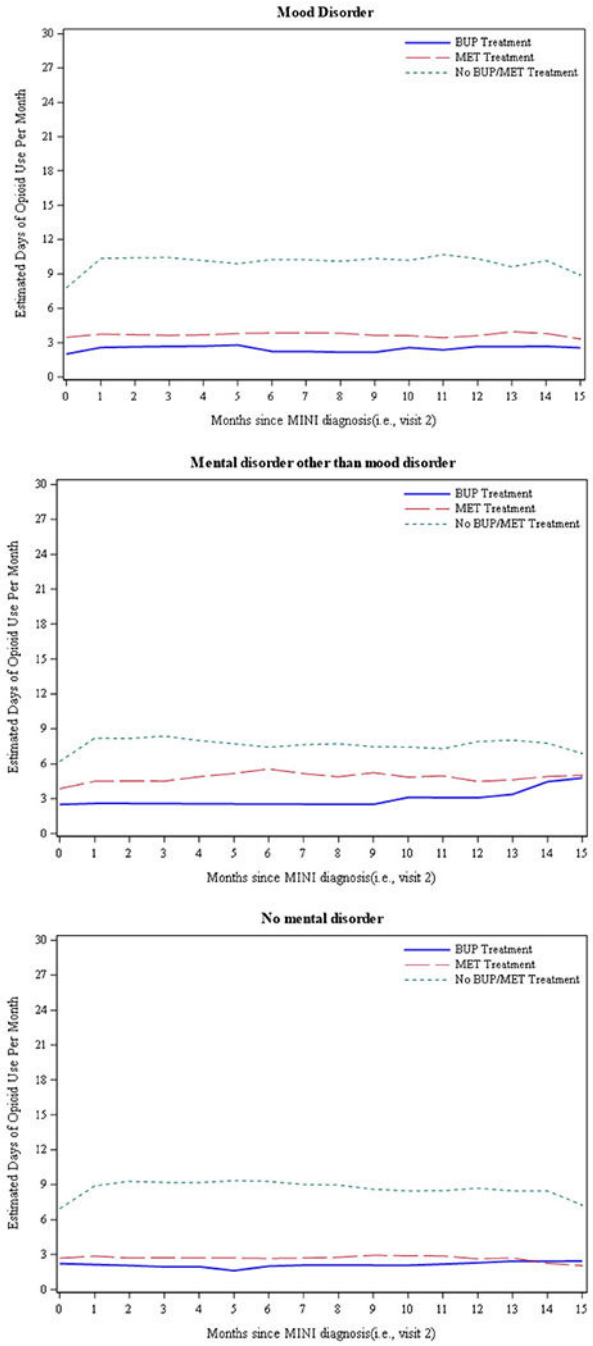

Figure 3.

Estimated days of opioid use per month during follow-up by mental disorder groups [Colour figure can be viewed at wileyonlinelibrary.com]

Note: BUP: Buprenorphine-naloxone; MET: Methadone. Since treatment status is a time-varying covariate, the number of participants in each treatment type varies for each month. Across the follow-up period, on average, 11.5% of the participants were in BUP treatment, 42.5% in MET treatment, and 43.2% in neither treatment.

Table 1

Baseline characteristics.

	Mood disorder (n = 302)	Mental disorder other than mood disorder (n = 114)	No mental disorder (n = 181)	All (N = 597)
Age (years)				
18–24	48 (15.9)	16 (14.0)	26 (14.4)	90 (15.1)
25–34	92 (30.5)	45 (39.5)	50 (27.6)	187 (31.3)
35–44	62 (20.5)	18 (15.8)	41 (22.7)	121 (20.3)
45–54	83 (27.5)	22 (19.3)	51 (28.2)	156 (26.1)
55+	17 (5.6)	13 (11.4)	13 (7.2)	43 (7.2)
Mean (SD)	37.5 (11.1)	37.5 (12.2)	38.7 (11.2)	37.9 (11.3)
Male (versus female)	182 (60.3)	73 (64.0)	126 (69.6)	381 (63.8)
Ethnicity				
Black	23 (7.6)	10 (8.8)	26 (14.4)	59 (9.9)
Hispanic	32 (10.6)	14 (12.3)	20 (11.1)	66 (11.1)
White	223 (73.8)	83 (72.8)	126 (69.6)	432 (72.4)
Other	24 (8.0)	7 (6.1)	9 (5.0)	40 (6.7)
West Coast site (versus East)	189 (62.6)	74 (64.9)	103 (56.9)	366 (61.3)
Drug injection	208 (68.9)	74 (64.9)	107 (59.4)	389 (65.3)
Cocaine use	90 (29.8)	44 (38.6)	54 (29.8)	188 (31.5)
Randomized to BUP (versus MET)	175 (58.0)	58 (50.9)	110 (60.8)	343 (57.5)

BUP = buprenorphine–naloxone; MET = methadone; SD = standard deviation.

Group comparison based on χ^2 test for categorical variables and analysis of variance (ANOVA) for continuous variables; no group difference was significant for measures.

Table 2

Life-time mental disorder diagnosis.

	Mood disorder (n = 302)	Mental disorder other than mood disorder (n = 114)	No mental disorder (n = 181)	All (N = 597)
Bipolar disorder ***ab,ac	169 (56.0)	0 (0.0)	0 (0.0)	169 (28.3)
Major depressive disorder ***ab,ac	133 (44.0)	0 (0.0)	0 (0.0)	133 (22.3)
Any anxiety disorder ***ac,bc	224 (74.2)	79 (69.3)	0 (0.0)	303 (50.8)
Panic disorder/agoraphobia ***ac,bc	195 (64.6)	60 (52.6)	0 (0.0)	255 (42.7)
Social anxiety disorder ***ab,ac,bc	81 (26.8)	6 (5.3)	0 (0.0)	87 (14.6)
Obsessive–compulsive disorder ***ab,ac,bc	114 (37.8)	25 (21.9)	0 (0.0)	139 (23.3)
Posttraumatic stress disorder ***ab,ac	52 (17.2)	0 (0.0)	0 (0.0)	52 (8.7)
Generalized anxiety disorder ***ac,bc	37 (12.3)	9 (7.9)	0 (0.0)	46 (7.7)
Psychotic disorder ***ac,bc	23 (7.6)	7 (6.1)	0 (0.0)	30 (5.0)
Eating disorder ***ab,ac	14 (4.6)	0 (0.0)	0 (0.0)	14 (2.4)
Antisocial personality disorder ***ac,bc	96 (31.8)	49 (43.0)	0 (0.0)	145 (24.3)

BUP = buprenorphine–naloxone; MET = methadone; SD = standard deviation.

Group comparison based on χ^2 test for categorical variables and analysis of variance (ANOVA) for continuous variables; all pairwise comparisons are Bonferroni-corrected for categorical variables; the Tukey–Kramer method was used for continuous variables ([a]mood disorder, [b]mental disorder other than mood disorder, [c]no mental disorder).

***$P < 0.001$.

Table 3

Cumulative opioid use and receipt of treatment between the second and third follow-up interviews.

	Mood disorder (n = 302)	Mental disorder other than mood disorder (n = 114)	No mental disorder (n = 181)	All (N = 597)
Follow-up months, mean (SD)	15.9 (6.2)	16.6 (5.7)	15.8 (5.4)	16.0 (5.9)
Percentage time of follow-up months with opioid use	26.8 (37.2)	27.5 (38.0)	25.2 (38.4)	26.4 (37.7)
Percentage time of follow-up months with no opioid use	73.2 (37.2)	72.5 (38.0)	74.8 (38.4)	73.6 (37.7)
Opioid use days per month, mean (SD)	5.4 (9.0)	5.5 (9.0)	5.6 (9.9)	5.5 (9.3)
Percentage time of follow-up months received any MOUD *ac	60.6 (42.2)	58.0 (44.1)	49.9 (45.5)	56.8 (43.8)
Percentage time of follow-up months received BUP *	14.5 (32.4)	9.1 (27.2)	8.1 (24.8)	11.5 (29.4)
Percentage time of follow-up months received MET	43.8 (45.2)	43.8 (46.0)	39.3 (46.1)	42.5 (45.6)

BUP = buprenorphine–naloxone; MD = mood disorder; MET = methadone; SD = standard deviation, in parentheses; MOUD = medication treatment for opioid use disorder.

Group comparison based on analysis of variance (ANOVA) for continuous variables; all pairwise comparisons are Bonferroni-corrected for categorical variables; the Tukey–Kramer method was used for continuous variables ([a]mood disorder, [b]mental disorder other than mood disorder, [c]no mental disorder).

*$P < 0.05$.

Table 4

Zero-inflated Poisson (ZIP) mixed regression predicting the number of opioid use days per month during follow-up.

	Logit Portion[b]		Poisson portion	
Covariates	**OR (CI)**	**P**	**RR (CI)**	**P**
Mental disorders (versus no mental disorder)				
Mood disorder	1.07 (0.85, 1.34)	0.58	0.76 (0.26, 2.26)	0.62
Mental disorder other than mood disorder	0.83 (0.62, 1.11)	0.21	0.38 (0.09, 1.50)	0.17
Randomized to BUP (versus MET)	**0.81 (0.69, 0.95)**	**0.01**	**3.14 (1.20, 8.19)**	**0.02**
Age (years)	**1.01 (1.00, 1.02)**	**0.001**	1.00 (0.96, 1.05)	0.98
Male (versus female)	0.94 (0.79, 1.11)	0.44	1.30 (0.48, 3.48)	0.61
White (versus non-white)	0.94 (0.79, 1.12)	0.50	1.87 (0.63, 5.59)	0.26
West Coast sites (versus East)	**1.72 (1.46, 2.03)**	< **0.001**	1.69 (0.61, 4.70)	0.31
Injection use at baseline	1.03 (0.86, 1.24)	0.74	**4.15 (1.44, 11.94)**	**0.009**
Cocaine use at baseline	0.97 (0.83, 1.15)	0.76	1.95 (0.70, 5.42)	0.20
Slope (months since MINI)[c]				
Months 0–1	0.90 (0.66, 1.23)	0.50	**1.28 (1.22, 1.34)**	< **0.001**
Month 1	1.12 (0.81, 1.54)	0.49	**0.78 (0.74, 0.81)**	< **0.001**
Month 14	1.09 (0.75, 1.57)	0.65	**0.88 (0.84, 0.92)**	< **0.001**
Time-varying covariates				
BUP treatment (versus no treatment)	**0.12 (0.07, 0.21)**	< **0.001**	**0.77 (0.66, 0.89)**	< **0.001**
MET treatment (versus no treatment)	**0.33 (0.25, 0.45)**	< **0.001**	**0.78 (0.72, 0.84)**	< **0.001**
Interaction of time-varying treatment and mental health disorder group				
BUP treatment in mood disorder[a]	**0.24 (0.17, 0.34)**	< **0.001**	**0.80 (0.73, 0.88)**	< **0.001**
BUP treatment in mental disorders other than mood disorder[a]	1.52 (0.69, 3.34)	0.30	**0.38 (0.25, 0.56)**	< **0.001**
MET treatment in mood disorder[a]	**0.47 (0.37, 0.58)**	< **0.001**	**0.72 (0.68, 0.76)**	< **0.001**
MET treatment in mental disorders other than mood disorder[a]	0.97 (0.67, 1.42)	0.89	0.38 (0.10, 1.53)	0.17

BUP = buprenorphine–naloxone; MET = methadone; CI = confidence interval; MINI = Mini-International Neuropsychiatric Interview; RR = risk ratio; OR = odds ratio.

Confidence intervals not including the value 1 are highlighted in bold type, which indicates significance.

[a]Reference group = no treatment with same mental health status;

[b] models the probability of opioid use (ref: no use) during the follow-up;

[c] three spline-time indicators (i.e. a slope indicator at months 0–1 and two slope-change indicators at months 1 and 14).

Table 5

Differential treatment effect (BUP versus MET) on opioid use by mental disorder groups.[a]

	Logit portion[b]		Poisson portion	
Treatment effect of BUP versus MET	**OR (CI)**	**P**	**RR (CI)**	**P**
Mood Disorder	**0.52 (0.36, 0.74)**	< **0.001**	1.11 (1.00, 1.23)	0.04
Mental disorder other than mood disorder	1.56 (0.69, 3.50)	0.28	**0.37 (0.25, 0.56)**	< **0.001**
No mental disorder	**0.37 (0.21, 0.66)**	< **0.001**	0.99 (0.83, 1.17)	0.86

BUP = buprenorphine–naloxone; MET = methadone; CI = confidence interval; RR = risk ratio; OR = odds ratio.

Statistical significance was determined by Bonferroni adjustment (0.05/6 = 0.008) given the multiple tests (i.e. six tests). Confidence intervals not including the value 1 are highlighted in bold type, which indicates significance.

[a]Calculations were based on the parameters from the ZIP-mixed model;

[b]models the probability of opioid use (ref: no use) during the follow-up.