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Longitudinal study of impact of medication for opioid use disorder on Hamilton Depression Rating Scale

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ABSTRACT

Objective: This study aimed to evaluate the longitudinal treatment effect on depression measured by Hamilton Depression Rating Scale (HAM-D) score in a randomized clinical trial for the treatment of opioid use disorder (OUD).
Methods: We conducted a secondary data analysis of data from the National Institute on Drug Abuse's Clinical Trials Network Protocol-0051. Patients with OUD ($N = 570$) were randomized to receive buprenorphine/naloxone (BUP-NX, $n = 287$) or extended-release naltrexone injection (XR-NTX, $n = 283$). The HAM-D score was completed at baseline and follow-up visit up to 36 weeks. A linear mixed model analysis was performed for log transformed HAM-D score and a generalized linear mixed model analysis was conducted for depression status.
Results: Compared with BUP-NX, subjects randomized to XR-NTX had higher HAM-D scores at weeks 1 and 3 ($p<0.05$). There were significant interactions between treatment and visit on HAM-D score and depression status during the first four weeks of treatments in individuals without lifetime major depressive disorder (MDD). Past year cocaine use was associated with HAM-D score and depression status just in individuals without MDD, whereas past year cannabis use was associated with HAM-D score and depression status just in individuals with MDD. Past year amphetamine use was associated with HAM-D score just in individuals without MDD, however, lifetime anxiety was associated with HAM-D scores regardless of MDD.
Conclusion: When prescribing XR-NTX, particularly in the first month of treatment, it is essential to monitor for depressive symptoms. Screening for depression and multiple substance abuse may help clinicians identify appropriate treatment.

1. Introduction

Opioid use disorder (OUD) is a significant public health problem and associated with mental health and substance use disorders, resulting in increased mortality, social and economic consequences (Blanco and Volkow, 2019). In the United States (U.S.), an estimated 1.6 million people had a past year OUD in 2019, 1.4 million people with a past year prescription pain reliever use disorder, and 10.1 million people misused opioids in the past year (SAMHSA, 2020). The estimated total economic burden of prescription opioid misuse alone in the U.S. is $78.5 billion per year, including the costs of healthcare, lost productivity, addiction treatment, and criminal justice involvement (Florence et al., 2016). In the past decade, opioid-related overdose resulted in more than 660,000 hospitalizations in the U.S. and more than $700 million healthcare dollars annually (Hsu et al., 2017; Stoicea et al., 2019). OUD has been reported to have multiple comorbidities including anxiety disorders, and depression or major depressive disorder (MDD), and other substance use disorders (SUDs such as tobacco, alcohol, cannabis, sedatives, opiates, cocaine), and chronic physical conditions (Vorspan et al., 2015; McHugh et al., 2017; Langdon et al., 2019; Malik et al., 2019; Onyeka

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et al., 2019; Sharma et al., 2019).

MDD is a common psychiatric disorder in U.S. adults (Hasin et al., 2018) and depression or MDD is highly co-morbid with OUD and other SUDs (Han et al., 2017; Kim et al., 2019; Hides et al., 2019; Rosoff et al., 2021). The presence of depression or MDD complicates treatment for SUDs; while co-occurrence of depression or MDD and SUDs exacerbates physical and mental health impairment, and poor treatment outcomes which contribute to higher morbidity, mortality, and healthcare cost (Blanco et al., 2012; Han et al., 2017). The Hamilton Depression Rating Scale (HAM-D) (Hamilton, 1960) is a useful instrument for monitoring changes in depression and suicidal ideation and in comparing the efficacy of various interventions, and it is one of the most commonly used observer-rated measures of depression. The HAM-D has been used in clinical trials for the treatment of anxiety (de Lima et al., 2019), chronic posttraumatic stress disorder (Ot'alora et al., 2018), as well as in studies of MDD (Fava et al., 2016; Richards et al., 2016; Cassano et al., 2018; Zajecka et al., 2019; Perlis et al., 2020; Rolle et al., 2020). One recent study reported that the HAM-D has good psychometric properties and sensitivity to detect depressive symptoms over time (Carrozzine et al., 2020).

However, few studies have used the HAM-D in clinical trials of treatment for OUD. One study reviewed pharmacological treatment for depression during opioid agonist treatment (Pani et al., 2010), while another investigated patients with OUD (N = 34) treated with naltrexone and behavioral therapy by assessing HAM-D scores at baseline, and at 2- and 4-weeks after naltrexone induction (Mysels et al., 2011). Two recent studies used HAM-D scores to measure depressive symptoms at baseline in methadone maintenance (Huhn et al., 2019; Malik et al., 2019). However, the resutls of depression symptoms associated with naltrexone treatment of opioid-dependent patients are varied (Miotto et al., 1997; Krupitsky et al., 2004; Rea et al., 2004; Dean et al., 2006; Mysels et al., 2011). Specifically, there was no study focused on the longitudinal treatment effect of extended-release naltrexone (XR-NTX) versus buprenorphine/naloxone (BUP-NX) for OUD on depression among patients with OUD. The aims of this study are to (1) evaluate the longitudinal treatment effect of XR-NTX versus BUP-NX on depression severity as measured by HAM-D total scores and depression status based on a cut-off HAM-D score of clinically remission in treatment and (2) examine whether the impact of medication for opioid use disorder on HAM-D measures differed by lifetime MDD status.

2. Materials and methods

2.1. Study design

A secondary data analysis was conducted using data from the National Institute on Drug Abuse's (NIDA) Clinical Trials Network (CTN) Protocol CTN-0051. The primary objectives were to compare the efficacy of extended-release naltrexone injection XR-NTX to BUP-NX in a randomized, multisite clinical trial (Lee et al., 2016, 2018; Nunes et al., 2016). Participants were from eight study sites from CTN-affiliated community treatment programs with high volumes of opioid detoxification admissions and outpatient medical management capabilities. Inclusion criteria include having ages 18 years or older, with Diagnostic and Statistical Manual of Mental Disorders-5 opioid use disorder, and without using non-prescribed opioids in the past 30 days. Between 2014 and 2016, 570 participants were randomly assigned to receive extended-release naltrexone injection (XR-NTX, n = 283) and buprenorphine-naloxone (BUP-NX, n = 287). XR-NTX is administered by injection on an approximately every-four-week basis. If injections were missed and physical re-dependence was likely to have occurred, a repeat naloxone challenge or another detoxification program was required to reinitiate XR-NTX treatment. BUP-NX was provided for take-home daily sublingual dosing. BUP-NX was initially dispensed weekly, then every two weeks, then every four weeks. Medication compliance was ensured through weekly urine drug screen testing for buprenorphine. The CTN-0051 study was approved by the institutional review boards at participating sites, and participants provided written informed consent (Lee et al., 2016, 2018; Nunes et al., 2016). There was an Institutional Review Board exemption for the present study due to secondary data analysis using publicly accessed database.

2.2. Measurements

2.2.1. Demographic characteristics

Demographic characteristics included age (18–25 years, 26–34 years, 35–49 years and 50 years or older), gender (male and female), and race/ethnicity (non-Hispanic White, non-Hispanic African American, Hispanic, and other). Marital status was categorized as never married, married and other. Educational level was recorded as ≤ high School and more than high school and employment was recorded as working now and unemployed.

2.2.2. HAM-D scores

Several studies reported good psychometric properties and its sensitivity to detect clinically relevant depressive symptom changes in drug or psychotherapy trials (Huhn et al., 2019; Malik et al., 2019; Mysels et al., 2011; Pani et al., 2010). The HAM-D is a 21-item Likert-type scale, the scoring is based on the first 17 (Hamilton, 1960). Eight items are scored on a 5-point scale, ranging from 0 (not present) to 4 (severe) and nine items are scored from 0 to 2. Summing the scores from the first 17 items is associated with the following clinical categories: normal (≤7); mild depression (8–13); moderate depression (14–18); severe depression (19–22); and very severe depression (≥23). A score of ≤7 is widely thought to indicate remission (Frank et al., 1991; Lee et al., 2016; Trajković et al., 2011; Zimmerman et al., 2013). In the original trial, the HAM-D scores were assessed at baseline (screening) and follow-up visit at weeks 1, 2, 3, 4, 8, 12, 16, 20, 24, 28 and 36. For this study, depression status was recoded as binary, Yes (scores >7) and No (scores ≤7).

2.2.3. Baseline substance use and mental health problems

Baseline substance use in the past year was determined by the DSM-5 checklist (American Psychiatric Association, 2013). In this study substance use in the past year included alcohol, amphetamines, cannabis, cocaine, and sedative use. All these variables were recoded as binary (Yes or No). The psychiatric history was assessed at screening by study physician, participants were asked "Have you ever been treated for or have a history of…" various medical and mental health problems. The present study included lifetime anxiety disorder and MDD. The response option for these variables was binary (Yes/No).

2.3. Statistical analysis

The categorical variables were presented as raw values and percentage, while continuous variables were presented as mean ± SD. Because the HAM-D score was right-skewed, the log transformation using log (HAM-D + 1) was performed. The histogram of log transformed baseline HAM-D score was illustrated in Fig. 1. Chi-square was used to examine the associations of categorical variables across the two treatment groups, while independent t-test was used to determine HAM-D scores at each time point from baseline to 36 weeks between two treatment groups.

The linear mixed model (LMM) including treatment as fixed effect and individual as random effect was used to examine the longitudinal changes in log transformed HAM-D score as a continuous outcome variable adjusting for demographic factors (age, gender, race group, marital status, and education level), lifetime anxiety and MDD, and past year substance uses. The repeated measures longitudinal analysis for log transformed HAM-D score was performed using PROC MIXED (SAS 9.4). For binary depression status, the repeated measures generalized LMM (GLMM) was performed using PROC GLIMMIX (SAS 9.4) adjusting for

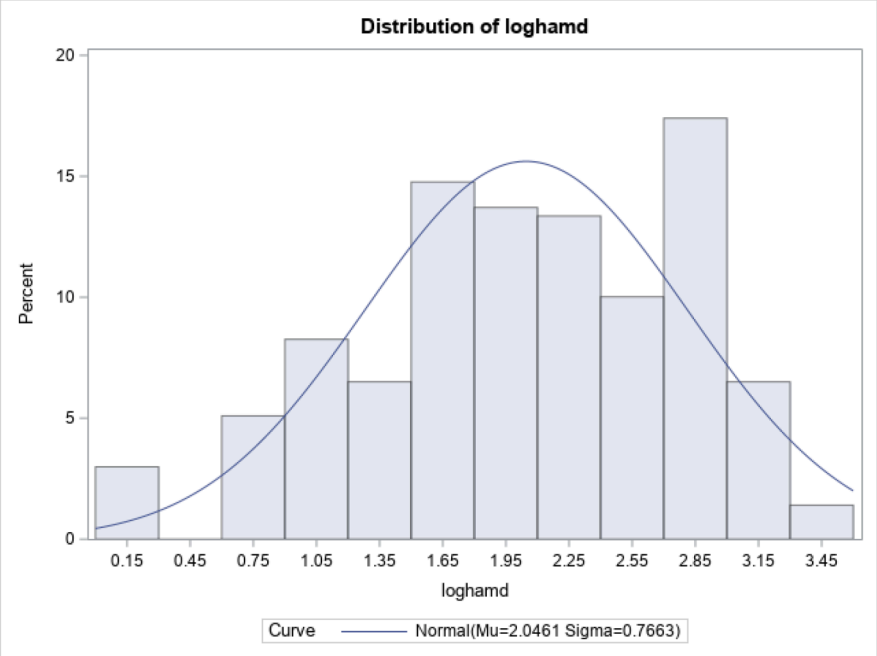

Fig. 1. Distribution of log transformed baseline HAM-D score.

the same baseline factors as the LMM analyses. The treatment by follow-up visit interaction was tested. In addition, the LMM and GLMM analyses were conducted stratified by lifetime MDD. p-values < 0.05 indicated statistical significance. All analyses were conducted using SAS 9.4 (SAS Institute, Cary, North Carolina, USA).

3. Results

3.1. Participant characteristics

There were no statistically significant group differences for demographic characteristics, lifetime anxiety and MDD, and past year substance uses. Notably, almost a third (31.4%) of the sample reported having lifetime MDD (Table 1).

3.2. Independent t-test

The overall mean HAM-D score was 8.94 (SD = 6.55) and the median was 7. The mean HAM-D scores of BUP-NX group consistently decreased over time from baseline through 16 weeks and then increased but not to the point of returning to baseline with Weeks 28 and 36 having a higher mean group HAM-D score than Week 1 of treatment (Fig. 2). The mean HAM-D scores of XR-NTX group did not consistently decrease until Week 4. After Week 4 mean group scores consistently decreased until Week 12 when the average group mean HAM-D increased but did not return to baseline. Furthermore, The XR-NTX group had higher HAM-D scores at weeks 1 and 3 compared with BUP-NX group ($p = 0.0341$ and 0.0269, respectively).

3.3. Linear mixed model analysis

The results based on the LMM analysis of the log transformed HAM-D score as a continuous outcome variable are presented in Table 2. The multivariable LMM revealed that lifetime anxiety and MDD, and past year amphetamine use were associated with increased HAM-D scores ($p = <0.0001$, 0.0040, and 0.0228, respectively), whereas past year cocaine use was associated with decreased HAM-D score ($p = 0.0076$) (Table 2). Furthermore, there was no overall treatment effect on HAM-D scores between XR-NTX and BUP-NX. However, the HAM-D scores were significantly lower at follow up visits compared with baseline (all p values <0.0001) and there was a significant interaction between treatment and visit in HAM-D scores at weeks 1, 3 and 4 ($p<0.0001$, 0.0009 and 0.0005, respectively) with increased HAM-D scores in the XR-NTX compared with BUP-NX. Stratified by lifetime MDD status, past year amphetamine and cocaine uses were associated with HAM-D score just in individuals without MDD, while there was a significant interaction between treatment and visit in HAM-D scores at weeks 1, 2, 3 and 4 in just in individuals without MDD. However, past year cannabis use was associated with increased HAM-D scores just in individuals with MDD.

3.4. Generalized linear mixed model analysis

The GLMM showed that lifetime anxiety and MDD were associated with depression status ($p = 0.0006$ and 0.0236, respectively). Furthermore, there was no overall treatment effect on depression status (Table 3). However, depression frequency was significantly lower at follow up visits compared with baseline (all p values <0.0001). Interestingly, there was significant interaction between treatment and visit in depression status at weeks 1, 2, and 3 ($p = 0.0053$, 0.0087 and 0.0008, respectively). Stratified by lifetime MDD status, past year cocaine use was negatively associated with depression status just in individuals without MDD, whereas past year cannabis use was positively associated with depression status just in individuals with MDD. Additionally, there was a significant interaction between treatment and visit in depression status at weeks 1, 2, and 3 just in individuals without MDD.

4. Discussion

To our knowledge, this is the first longitudinal study of the treatment effect of sublingual buprenorphine/naloxone and injectable naltrexone on log transformed HAM-D score and depression status. The XR-NTX treatment group had statistically significant higher HAM-D scores at weeks 1 and 3 compared with BUP-NX. Furthermore, there was significant interaction between medication treatment and follow-up visit in HAM-D scores at weeks 1, 3, and 4 when XR-NTX was associated with increased HAM-D scores. Moreover, there was also a significant interaction between treatment and visit in depression status based on HAM-D scores at weeks 1, 2, and 3. Additionally, past year amphetamine and

Table 1
Descriptive statistics at baseline ($N = 570$).

Variable	N (%)	XR-NTX group ($n = 283$)	BUP-NX group ($n = 287$)	χ^2/t value	P value
Gender					
Male	401(70.4)	195	206	0.5636	0.4528
Female	169(29.6)	88	81		
Age (year)					
18–25	111(19.5)	49	62	1.7979	0.6154
26–34	238(41.8)	120	118		
35–49	171(30.00)	89	82		
50+	50(8.7)	25	25		
Race					
Non-Hispanic White	387(67.9)	192	195	1.7468	0.6266
Hispanic	99(17.4)	45	54		
Non-Hispanic AA	60(10.5)	32	28		
Other	24(4.2)	14	10		
Marriage					
Never married	376(66.0)	187	189	0.0032	0.9550
Have been married/other	194(34.0)	96	98		
Education (year)					
≤ High school	132(23.2)	63	69	0.2538	0.6144
> High school	438(76.8)	218	220		
Employment					
Unemployed	465(81.6)	235	230	0.7972	0.3719
Working now	105(18.4)	48	57		
Lifetime anxiety					
No	313(54.9)	150	163	0.8271	0.3631
Yes	257(45.1)	124	133		
Lifetime major depressive disorder					
No	391(68.6)	190	201	0.5552	0.4562
Yes	179(31.4)	93	86		
Past year alcohol use					
No	211(37.0)	110	101	0.8266	0.3633
Yes	359(63.0)	173	186		
Past year amphetamines use					
No	391(68.6)	199	192	0.7733	0.3792
Yes	179(31.4)	84	95		
Past year cannabis use					
No	205(36.0)	106	99	0.5425	0.4614
Yes	365(64.0)	177	188		
Past year cocaine use					
No	280(49.1)	146	134	1.3690	0.2420
Yes	290(50.9)	137	153		
Past year sedative use					
No	290(50.9)	148	142	0.4532	0.5008
Yes	280(49.1)	135	145		
HAM-D Scores	8.94±6.55	8.58±6.45	9.28±6.63	1.28	0.2026

AA: non-Hispanic African American; SD: Standard deviation; p value is based on Chi-square test.

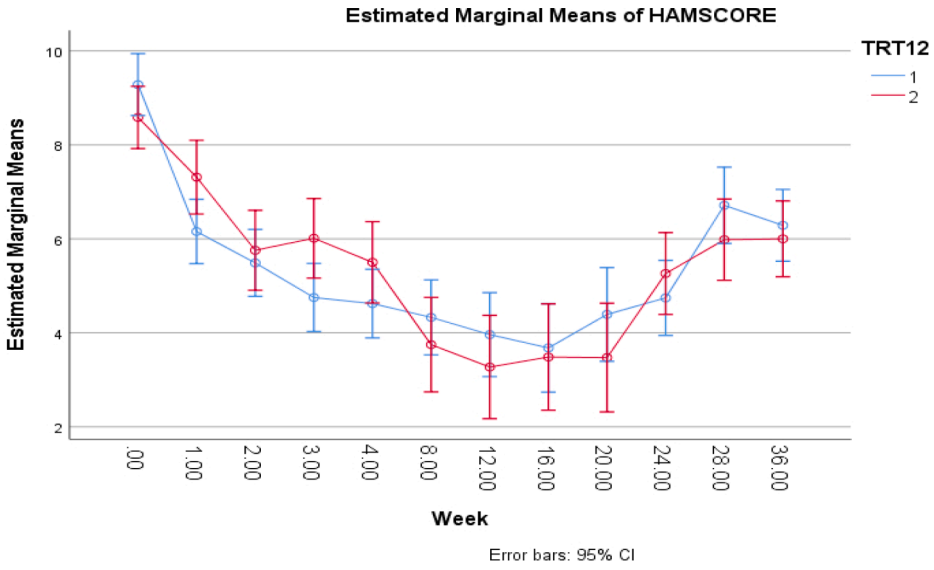

Fig. 2. Mean values of HAM-D score by week and treatment. 1 refers to BUP-NX and 2 refers to XR-NTX.

Table 2
Linear mixed model analyses of HAM-D scores.

Variable	β ± SE[1]	p	β ± SE[2]	p	β ± SE[3]	p
Lifetime major depressive disorder (ref=No)						
Yes	0.17±0.06	0.0040	–	–	–	–
Lifetime anxiety (ref=No)						
Yes	0.26±0.06	<0.0001	0.21±0.07	0.0025	0.32±0.11	0.0043
Past year alcohol use (ref=No)						
Yes	−0.01±0.06	0.9182	−0.02±0.07	0.8259	−0.02±0.10	0.8748
Past year amphetamines use (ref=No)						
Yes	0.13±0.06	0.0228	0.14±0.07	0.0406	0.12±0.10	0.2623
Past year cannabis use (ref=No)						
Yes	0.06±0.06	0.3334	−0.05±0.07	0.5099	0.36±0.10	0.0006
Past year cocaine use (ref= No)						
Yes	−0.14±0.05	0.0076	−0.18±0.06	0.0039	−0.13±0.09	0.1463
Past year sedative use (ref= No)						
Yes	−0.14±0.05	0.0076	0.08±0.06	0.3698	−0.05±0.09	0.5729
Treatment (ref=BUP-NX)						
XR-NTX	−0.08±0.06	0.2097	−0.04±0.08	0.6384	−0.12±0.11	0.3118
Visit (ref=baseline)						
Week 1	−0.45±0.05	<0.0001	−0.53±0.07	<0.0001	−0.28±0.09	0.0019
Week 2	−0.54±0.06	<0.0001	−0.66±0.07	<0.0001	−0.28±0.09	0.0014
Week 3	−0.70±0.07	<0.0001	−0.80±0.07	<0.0001	−0.53±0.11	<0.0001
Week 4	−0.75±0.06	<0.0001	−0.85±0.07	<0.0001	−0.52±0.10	<0.0001
Week 24	−0.72±0.07	<0.0001	−0.81±0.07	<0.0001	−0.53±0.11	<0.0001
Week 28	−0.40±0.07	<0.0001	−0.42±0.07	<0.0001	−0.36±0.11	0.0010
Week 36	−0.51±0.07	<0.0001	−0.52±0.07	<0.0001	−0.48±0.11	<0.0001
Interaction (ref=baseline)						
Treat*Week1	0.32±0.08	<0.0001	0.37±0.10	0.0002	0.21±0.13	0.1067
Treat*Week2	0.16±0.08	0.0602	0.21±0.11	0.0463	0.03±0.13	0.8408
Treat*Week3	0.29±0.09	0.0009	0.37±0.11	0.0007	0.10±0.14	0.4885
Treat*Week4	0.30±0.08	0.0005	0.35±0.11	0.0009	0.18±0.15	0.2169
Treat*Week24	0.06±0.09	0.5581	0.02±0.12	0.8689	0.11±0.16	0.4929
Treat*Week28	−0.04±0.10	0.6591	−0.13±0.12	0.2883	0.12±0.16	0.4620
Treat*Week36	0.01±0.10	0.9307	−0.13±0.12	0.2836	0.27±0.16	0.0933

β is adjusted regression coefficient; SE is standard error; p value is based on t-test in linear mixed model.
[1] Linear mixed model for the whole sample.
[2] Linear mixed model for non-major depressive disorder sample.
[3] Linear mixed model for major depressive disorder sample. All models adjusted for demographic variables (age, gender, race/ethnicity, marital status, educational level, and employment).

cocaine uses were associated with HAM-D score just in individuals without lifetime MDD, while past year cocaine use was negatively associated with depression status just in individuals without lifetime MDD, whereas past year cannabis use was associated with HAM-D scores and depression status just in individuals with lifetime MDD.

One-third (31.4%) of participants being treated for OUD had a history of MDD and 45.1% a history of anxiety, and many had other concurrent substance uses (63.0% alcohol, 31.4% amphetamines, 64.0% cannabis, 50.9% cocaine, and 49.1% sedatives). The 31.4% prevalence of lifetime MDD is somewhat lower compared to previous studies that reported prevalence rates of 44%−54% in OUD (Mysels et al., 2011; Pani et al., 2010). One earlier study reported 26%–54% of treatment-seeking patients with OUD had comorbid depression (Hollister et al., 1981). Another study estimated that approximately 54% of patients in treatment for OUD had a lifetime diagnosis of MDD (Brady et al., 2003). One Australian OUD treatment study reported that 25.8% of patients met criteria for MDD (Teesson et al., 2005). However, in 2017, the estimated prevalence of MDD in the general U.S. adult population was 7.1% (NIMH, 2017).

While our study found that there was no overall treatment effect of XR-NTX vs BUP-NX on HAM-D scores, we did find that there were significant differences in HAM-D scores at weeks 1 and 3 between XR-NTX vs BUP-NX. Consistent with a previous study (Mysels et al., 2011), we found a time effect of treatment with HAM-D scores decreasing over time, and this decrease persisted from baseline to 36 weeks. Several previous studies have reported that there were no or small improvements in depression symptoms associated with naltrexone treatment of opioid-dependent patients (Dean et al., 2006; Krupitsky et al., 2004; Miotto et al., 1997; Mysels et al., 2011; Rea et al., 2004). For example, in an uncontrolled cohort study using 81 patients received naltrexone for opioid dependence, depressive symptoms improved during the treatment, however, patients exhibited higher than expected rates of overdose and suicide (Miotto et al., 1997). Another study found there was no difference between methadone and buprenorphine groups in depressive symptoms measured by Beck Depression Inventory (Dean et al., 2004), while in a randomized controlled trial using 80 patients, depressive symptoms were found to be lower while on naltrexone compared with continued methadone maintenance (Dean et al., 2006). Furthermore, our study further demonstrated that there was significant treatment x follow-up time interaction in the first 4 weeks (Table 2). Our findings support that naltrexone treatment was associated with reduced depressive symptoms measured by HAM-D over time (Dean et al., 2006; Mysels et al., 2011). However, as suggested, it would be prudent to monitor depression and anxiety symptoms in patients receiving naltrexone at regular stages throughout treatment (Dean et al., 2006). As expected, at week 24 which was the end of the treatment intervention, HAM-D scores increased significantly in both groups. Transitions of care are predictably stressful for patients and a time when relapse risk is elevated (Manuel et al., 2017; Johannessen et al., 2020). Patients were referred to outpatient treatment the following the study intervention, but this still marks a transition to a new clinical team for services.

Previous studies have shown the two medications are from different classes (a mu opioid receptor antagonist, XR-NTX vs. a partial agonist, BUP-NX). For example, agonists may maintain physical tolerance, have withdrawal signs and symptoms, and raise a significant diversion risk, whereas antagonists block opioid effects without producing physical tolerance, may not have physiological consequences of stopping antagonist treatment and abuse potential (Lee et al., 2016). Another study found that XR-NTX had more difficulty in induction and greater relapse events than BUP-NX, while both medications had similar effectiveness

Table 3
Generalized linear mixed model analyses of depression status.

Variable	β ± SE[1]	p	β ± SE[2]	p	β ± SE[3]	p
Lifetime major depressive disorder (ref=No)						
Yes	0.39±0.17	0.0236	–	–	–	–
Lifetime anxiety (ref=No)						
Yes	0.57±0.17	0.0006	0.51±0.20	0.0102	0.57±0.35	0.0979
Past year alcohol use (ref=No)						
Yes	−0.01±0.16	0.9841	−0.03±0.20	0.8777	−0.05±0.30	0.8779
Past year amphetamines use(ref=No)						
Yes	0.27±0.16	0.0965	0.34±0.20	0.0825	0.11±0.32	0.7234
Past year cannabis use (ref=No)						
Yes	0.19±0.17	0.2393	−0.09±0.20	0.6465	0.92±0.32	0.0040
Past year cocaine use (ref= No)						
Yes	−0.25±0.15	0.0921	−0.50±0.19	0.0081	−0.01±0.27	0.9782
Past year sedative use (ref= No)						
Yes	−0.25±0.15	0.0921	0.17±0.19	0.3731	−0.01±0.28	0.9682
Treatment (ref=BUP-NX)						
XR-NTX	−0.39±0.22	0.0765	−0.37±0.27	0.1652	−0.19±0.41	0.6370
Visit (ref=baseline)						
Week 1	−1.18±0.20	<0.0001	−1.63±0.26	<0.0001	−0.33±0.36	0.3528
Week 2	−1.47±0.22	<0.0001	−1.76±0.26	<0.0001	−0.91±0.38	0.0152
Week 3	−1.92±0.23	<0.0001	−2.18±0.29	<0.0001	−1.43±0.39	0.0003
Week 4	−1.88±0.23	<0.0001	−2.43±0.31	<0.0001	−1.01±0.38	0.0083
Week 24	−1.62±0.24	<0.0001	−1.85±0.30	<0.0001	−1.14±0.40	0.0047
Week 28	−0.92±0.23	<0.0001	−1.04±0.27	0.0002	−0.60±0.39	0.1236
Week 36	−1.08±0.22	<0.0001	−1.07±0.27	<0.0001	−1.01±0.38	0.0076
Interaction (ref=baseline)						
Treat*Week1	0.83±0.30	0.0053	1.25±0.37	0.0008	0.06±0.52	0.9154
Treat*Week2	0.84±0.32	0.0087	0.93±0.40	0.0206	0.65±0.55	0.2417
Treat*Week3	1.11±0.33	0.0008	1.35±0.42	0.0012	0.65±0.56	0.2401
Treat*Week4	0.56±0.35	0.1070	0.82±0.46	0.0756	0.09±0.55	0.8732
Treat*Week24	0.46±0.35	0.1799	0.56±0.44	0.1981	0.19±0.59	0.7431
Treat*Week28	0.10±0.32	0.7643	0.03±0.41	0.9465	0.11±0.57	0.8428
Treat*Week36	0.48±0.31	0.1270	0.03±0.39	0.9390	1.16±0.54	0.0318

β is adjusted regression coefficient; SE is standard error; p value is based on t-test in generalized linear mixed model.
[1] Generalized Linear mixed model for the whole sample.
[2] Generalized Linear mixed model for non-major depressive disorder sample.
[3] Generalized Linear mixed model for major depressive disorder sample. All models adjusted for demographic variables (age, gender, race/ethnicity, marital status, educational level, and employment).

and safety once treatment was initiated. However, the risk of XR-NTX induction failure is one concern in clinical practice, and agonist treatments should be encouraged for the individuals who are unable to complete detoxification (Lee et al., 2018).

Buprenorphine acts as a mu-opioid partial agonist and also as a kappa-opioid antagonist, while naltrexone acts as a mu-opioid antagonist and also, to a lesser degree, a delta- and kappa-opioid antagonist (Cameron et al., 2021; de Laat et al., 2019; Serafini et al., 2018). The antagonism of the kappa-opioid system may have an effect on depression, while buprenorphine mono-product has been explored as a treatment for depression, but research is needed on the impact of the combination product BUP-NX (Serafini et al., 2018). Low-dose naltrexone in combination with pro-dopamine antidepressant medication has been shown in a small study to improve treatment of MDD (Mischoulon et al., 2017), however, research on naltrexone alone for the treatment of depression is lacking. Potential non-pharmacological impacts of treatment may also contribute to improved mood during treatment including regained sense of control, decrease or relief of withdrawal symptoms and increased focus on self-care.

MDD is a common comorbidity among individuals with OUD. Previous study revealed that history of depression was predictive of the overall total HAM-D score throughout the 4-week period studied (Mysels et al., 2011). In the present study, we found that lifetime MDD was associated with HAM-D scores as a continuous trait. Furthermore, the present results added that lifetime MDD was associated with depression status. Moreover, lifetime anxiety, past year amphetamine and cocaine use were associated with HAM-D scores, while lifetime anxiety and MDD were associated with HAM-D status. Additionally, stratified by lifetime MDD status, past year amphetamine and cocaine use were associated with HAM-D score just in individuals without lifetime MDD, while past year cocaine use was negatively associated with depression status just in individuals without lifetime MDD, whereas past year cannabis use was associated with both HAM-D scores and depression status just in individuals with lifetime MDD. These findings suggest that baseline lifetime MDD is associated with HAM-D scores or depression status in OUD treatment, while the associations of lifetime anxiety and past year substance uses with HAM-D score or depression status may differ by lifetime MDD status.

4.1. Strengths and limitations

This study has several strengths. First, the sample size is relatively large (N = 570). Second, this is the first longitudinal study of the treatment effect of sublingual buprenorphine/naloxone and injectable naltrexone on HAM-D scores and depression status. The LMM has been used to examine correlated HAM-D scores in clinical trials in treatment of depression (Ballard et al., 2015; Driessen et al., 2015; Lam et al., 2017; Park et al., 2020); however, no study has focused on the treatment effects on HAM-D scores in OUD using a LMM for HAM-D score as a continuous or GLMM for depression status as a binary variable. Although some of our results are consistent with Mysels et al. (2011), the present study has important differences with respect to sample size (n = 34), study design and treatment duration.

Several limitations exist. First, the baseline data about mental health problems such as lifetime anxiety and MDD were self-reported, making responses prone to social desirability and recall bias. Meanwhile, lack of data on when anxiety and MDD were active. Second, the present study could not adjust the potential influence of antidepressants (or drugs for depression). Third, patient adherence or drop-out may influence the interaction, however, due to relatively large sample size of this study,

the influence of patient adherence or drop-out on the interaction should be small. In addition, the study participants were receiving specific medications for OUD and the results may not generalizable to all individuals with OUD.

5. Conclusion

Although buprenorphine/naloxone and extended-release naltrexone did not show overall treatment effect on HAM-D scores and depression status in patients with OUD, the two treatments have treatment by visit interactions on HAM-D scores or depression status during the first four weeks of treatment. This suggests that when starting XR-NTX treatment, it is essential to monitor for changes in depressive symptoms. Furthermore, lifetime anxiety disorder, past year amphetamine, cocaine and cannabis uses were associated with HAM-D score or depression status dependent on lifetime MDD status. Screening for depression and concurrent substance use disorders may help clinicians identify appropriate treatment for the individual.

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Declaration of Competing Interest

The authors declared no conflicts of interest.

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Ethical approval

The original CTN-0051 study (Extended-Release Naltrexone vs. Burpenorphine for Opioid Treatment) was approved by the institutional review boards at participating sites, and participants provided written informed consent. The present study was reviewed by the West Virginia University Institional Review Board and there was an Institutional Review Board exemption due to secondary data analysis using publicly accessed database.

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