Co-occurring Depression and Suicidal Ideation in Opioid Use Disorder:

Prevalence and Response During Treatment With Buprenorphine-Naloxone and Injection Naltrexone

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ABSTRACT

Objective: The concept of "deaths of despair" (suicide, overdose, and alcohol-related liver disease) highlights the importance of detecting and understanding the course of co-occurring depression in patients with opioid use disorder (OUD).

Methods: In a 24-week trial of 570 patients with *DSM-5*–defined OUD randomized to buprenorphine-naloxone (BUP-NX) or extended-release naltrexone (XR-NTX) from January 2014 to January 2017, the prevalence of depression (assessed with Hamilton Depression Rating Scale [HDRS]) was examined at baseline and after 4 weeks of treatment, and the association between depression and relapse to opioid use was explored using logistic regression.

Results: Among 473 patients who initiated medication, 14.2% (67/473) had moderate/severe depression (HDRS ≥ 17) and 34.9% (165/473) had mild depression (8 ≤ HDRS ≤ 16) at baseline. Patients with moderate/severe depression had more frequent histories of anxiety disorders and suicidal ideation. After 4 weeks of treatment, approximately two-thirds of participants with depression either responded (HDRS reduced ≥ 50% from baseline) or remitted (HDRS ≤ 7), with no significant differences between medication treatment groups. Those with moderate/severe depression were less likely to remit (52.8%; 28/53) compared to those with mild depression (76%; 98/129) at week 4 (OR = 0.43, 95% CI = 0.21–0.89, $P = .02$). Further, those who remitted at week 4 had lower, but not significantly different, risk of relapse to opioids compared to those who did not remit (OR = 0.55, 95% CI = 0.28–1.08, $P = .08$).

Conclusions: Depression is common among patients with OUD and often remits after initiation of BUP-NX or XR-NTX, although when it does not remit it may be associated with worse opioid use outcome. Depression should be screened and followed during initiation of treatment and, when it does not remit, specific depression treatment should be considered.

Trial Registration: ClinicalTrials.gov identifier: NCT02032433

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The opioid epidemic has been a national public health concern over the past two decades, with over 2 million individuals estimated to have an opioid use disorder (OUD)[1] and rising rates of opioid overdose deaths in the United States.[2] Numerous studies have reported high co-occurrence of depression, depressive symptoms, and/or depressive disorders with OUD.[3–5] However, only recently has it been documented and appreciated that some opioid overdose deaths, typically assumed to be unintentional, may have a suicidal component.[6,7] In addition, the concept of "deaths of despair" (deaths by suicide, overdose, and alcohol-related liver disease), in which hopelessness plays a role,[8] has re-emphasized the importance of detecting and understanding the course of co-occurring depressive symptoms in patients with OUD. Indeed, hopelessness has been found to be associated with more severe depressive symptoms and greater suicide risk.[9]

Previous research suggests that much of what presents as co-occurring depression among patients with substance use disorders improves when treatment for substance use disorder is initiated.[10–16] For example, several studies reported that symptoms of depression in patients with OUD tend to improve with medications for OUD (MOUD), including methadone,[11] buprenorphine,[12] and naltrexone.[13,17,18] However, to date, data comparing buprenorphine and naltrexone on patients with OUD are limited. Further, some clinical trials of antidepressant medications among patients entering methadone maintenance treatment have shown beneficial effects of antidepressant medication on both mood and opioid use outcomes,[19–21] while others have shown high placebo response rates.[22]

Previous studies on the association between co-occurring depression and treatment

Clinical Points

- Depression is common among people seeking medication treatment for opioid use disorder (MOUD).
- Two-thirds of those with co-occurring depression either remitted or responded within 4 weeks of initiating MOUD, and improvement did not differ between buprenorphine-naloxone and extended-release naltrexone.
- Those with moderate/severe depression were less likely to remit at week 4 compared to those with mild depression.
- Relapse to opioids was not associated with baseline depression and trended lower among patients whose depression remitted by week 4.

outcomes of OUD have produced mixed results; some studies have found that a current diagnosis of depression was associated with worse outcome of OUD,[23,24] while others reported that depression was associated with better OUD treatment retention or outcome.[25] Of note, existing studies on depression in patients with OUD have examined depression scores averaged across patients,[17,18] resulting in a heterogeneous group of patients with and without significant depression at baseline, rather than separately examining subgroups with substantial depression. Further, they have been limited by small sample sizes.[11–13] The distinction between transient depressive symptoms and persistent syndromal depressive disorders in OUD remains salient to the field, along with the question of whether and when to treat depression in the context of treatment for OUD.

We therefore examined data from a large comparative effectiveness trial of buprenorphine-naloxone (BUP-NX) vs extended-release naltrexone (XR-NTX)[26–28] to explore the prevalence and early course of depressive symptoms after beginning MOUD, examining separately the subgroups with mild and with moderate/severe depression at the outset, and their associations with OUD and depression outcomes. First, we explored the association between severity of baseline depression and failure to initiate MOUD and relapse to opioid use during treatment. Then, among those who had baseline depression, we explored the potential associations between baseline depression and reduction or remission of depression during the first 4 weeks of treatment, overall and between treatment groups. Last, we examined the association between reduction or remission of depression at week 4 and relapse to opioid use during up to 24 weeks of treatment. We hypothesized that depressive symptoms would be prevalent in patients with OUD at baseline, and that a substantial proportion of those with baseline depression would experience reduction or remission of depression during the first 4 weeks of MOUD. We also hypothesized that baseline depression severity would be associated with failure to initiate MOUD and relapse to opioid use during treatment and that failure of depression to respond/remit at week 4 would be associated with greater risk of relapse to opioid use.

METHODS

Overview of the Parent Trial

This was a secondary exploratory analysis of data obtained from the X:BOT trial (CTN-0051; ClinicalTrials.gov: NCT02032433), a 24-week multisite, open-label, randomized trial of patients with OUD comparing the effectiveness of XR-NTX vs BUP-NX between January 2014 and January 2017. Full details of the methods and primary results of the study have been described previously.[26–28] Briefly, patients with OUD were recruited from inpatient units (detoxification and/or short-term residential treatment program) at 8 community-based treatment programs for substance use disorders. All sites provided short-term inpatient and follow-up outpatient treatment. Participants who were 18 years or older, were English-speaking, and met criteria for current OUD based on the *Diagnostic and Statistical Manual of Mental Disorders*—Fifth Edition (*DSM-5*) who used non-prescribed opioids within the past 30 days were included. Those who had other serious medical, psychiatric, or substance use disorders requiring a different or higher level of care; transaminase concentrations greater than 5 times the upper limit of normal; suicidal or homicidal ideation; allergy or sensitivity to XR-NTX or BUP-NX; methadone maintenance treatment (≥ 30 mg/d); chronic pain requiring opioids; or a legal status precluding study completion or who were not able to have safe intramuscular XR-NTX treatment were excluded from the study. Women who were pregnant, breastfeeding, planning conception, or unwilling to use birth control were also excluded. The institutional review boards of each site approved the study. All participants provided written informed consent prior to enrollment.

Eligible participants were randomized (1:1) to either BUP-NX or XR-NTX and were initiated on MOUD as soon as clinically possible. Altogether, 570 patients with OUD admitted to inpatient addiction treatment programs were randomized to either XR-NTX (n = 283) or BUP-NX (n = 287) for prevention of relapse across 8 sites. BUP-NX was initiated at any time after participants had been off opioids and showed substantial withdrawal symptoms. Once successfully inducted, BUP-NX was dispensed to participants at weeks 0, 1, 2, 3, 4, 6, 8, 10, 12, 14, 16, and 20 for self-administration at daily maintenance doses between 8 and 24 mg. XR-NTX was administered if a participant completed detoxification from opioids and subsequently had a negative urine toxicology result and passed a naloxone challenge. XR-NTX was administered by intramuscular injection approximately every 28 days.

Participants were provided medical management for 24 weeks post-randomization. Additional voluntary psychosocial counseling was recommended and available at all study sites.

Measures

Self-report forms were completed at baseline and clinician-rated assessments of depression were conducted

at baseline and weeks 1, 2, 3, 4, 8, 12, 16, 20, and 24. Baseline assessments consisted of demographics and clinical characteristics including current severity and characteristics of opioid and other substance use, medical history, and psychiatric history.

Depression Assessment

Depression was assessed with the Hamilton Depression Rating Scale (HDRS),[29] a 17-item clinician administered assessment scale (range: 0–52). Consistent with standard cutoffs,[30] a score of 17 or higher was considered moderate/severe depression, scores between 8 and 16 were considered mild depression, and a score of 7 or less was considered not depressed. Following a convention used in clinical trials, "remission" of depression was defined as a score of 7 or less[31] at follow-up, and "response" was defined as a 50% or greater reduction from baseline score.[32]

Relapse. Relapse was defined as the return to regular use of non-study opioids any time after day 20 post-randomization (binary: yes/no) and operationalized as 4 or more consecutive weeks of any non-study opioid use by urine toxicology, self-report, or failure to provide a urine sample, or 7 or more consecutive days of self-reported non-study opioid use. This definition was consistent with the primary trial,[26] as well as other related ongoing trials,[33] and was chosen because prior studies showed that outcome of treatment with both injection naltrexone[34,35] and buprenorphine[36] tended to be binary—patients either stay on medication and do well or drop out and relapse. Participants were seen weekly during the trial, and self-reported substance use was collected via the Timeline Follow-back method,[37] and urine toxicology was conducted for opioids (buprenorphine, methadone, morphine [heroin, codeine, morphine], oxycodone) and other substances. Day 21 was defined as the start of the relapse-event observation period, because participants starting on MOUD were likely to "test" for blockade early in treatment, and those recently detoxified were likely to have positive urine samples for long-acting opioids prescribed as part of the detoxification regimen (non-study buprenorphine or methadone) for 2–3 weeks after being randomly assigned to a treatment arm.[27,28]

Suicidal ideation. Suicidal ideation was assessed at baseline by the study medical clinician using a single item (history of suicidal ideation: yes/no) from the medical and psychiatric history form used in the primary trial.[27]

Statistical Analysis

In preliminary analyses, among the intention-to-treat sample (N = 570), a logistic regression model was used to estimate the effect of baseline depression (none, mild, moderate/severe), and its interaction with treatment, on the odds of induction failure. Then, among the inducted sample, baseline participant characteristics were summarized using frequency and proportion for categorical variables and mean and standard deviation for continuous variables. Baseline differences across groups by severity of depression were compared using analyses of variance or χ^2 test, as appropriate. To maintain an overall significance level of 5%, a Bonferroni correction was applied to the analysis of differences in baseline characteristics (45 variables; test-specific significance level $\alpha = .05/45 = .001$).

First, among those with mild or moderate/severe depression at baseline that were successfully inducted onto study treatment (N = 232), logistic regression models were fit to estimate the odds of depression remission and response at week 4. An interaction model was fit that included the effects of treatment (XR-NTX vs BUP-NX), baseline depression (mild or moderate/severe), and their 2-way interaction. If the 2-way interaction was not significant, it was removed from the model and only main effects were assessed.

Second, among those who were successfully inducted (N = 473), logistic regression models were fit to estimate the odds of relapse. These models utilized the same approach as primary analyses, except that baseline depression was categorized as none, mild, and moderate/severe. Additionally, the association between depression remission and response at week 4 and relapse was assessed using logistic regression while controlling for baseline depression (mild, moderate/severe). All models controlled for site as a random effect, and all analyses tests were 2-tailed with a significance level of 5% unless specified differently. All analyses were conducted using SAS version 9.4.

RESULTS

Among the 570 participants who were randomized to receive XR-NTX (n = 283) or BUP-NX (n = 287), 474 participants were successfully inducted onto study medication (n = 204 for XR-NTX and n = 270 for BUP-NX). Baseline depression did not significantly moderate the effect of medication treatment on induction failure ($P = .11$), and when assessing main effects only, there were no significant differences in the odds of induction failure for those with mild (OR = 1.24, 95% CI = 0.69–2.24, $P = .48$) or moderate/severe (OR = 0.88, 95% CI = 0.35–2.20, $P = .78$) baseline depression compared to those with no baseline depression adjusting for treatment.

Participant Characteristics

Among the 473 participants who were successfully inducted, 14.2% (67/473) met the HDRS threshold for moderate/severe depression and 34.9% (165/473) met mild depression criteria.

At baseline, participants were predominantly White, male with average age in the early 30s, and unemployed. Approximately 25% were homeless. Details of the sociodemographic characteristics of the participants were reported previously.[26] There were no statistically significant differences in sociodemographic variables among depressed and non-depressed groups.

Table 1 presents baseline characteristics of participants by severity of depression. Depressed and non-depressed groups did not differ significantly on measures of OUD

Table 1. Baseline Clinical Characteristics by Severity of Depression (N = 473)[a,b]

	Moderate/severe depression (n = 67, 14.2%)	Mild depression (n = 165, 34.9%)	No depression (n = 241, 50.9%)	*P* value
Opioid use				
Primary opioid heroin, n (%)	57 (85.1)	134 (81.7)	186 (77.5)	.31
Primary opioid cost ($/d), median (IQR)	65.0 (45.0–100.0)	80.0 (50.0–130.0)	70.0 (50.0–100.0)	.07
Age at onset of opioid use, mean (SD), y	20.5 (6.9)	20.5 (7.9)	21.8 (6.6)	.14
Duration of opioid use, mean (SD), y	14.8 (10.1)	12.9 (9.5)	11.7 (8.3)	.04
Intravenous use, n (%)	43 (64.2)	112 (67.9)	167 (69.3)	.73
Other substance use, n (%)				
Current tobacco smoker	56 (83.6)	134 (81.2)	216 (89.6)	.05
Cannabis	42 (62.7)	75 (45.5)	98 (40.8)	<.01
Amphetamine-type stimulants	35 (52.2)	76 (46.1)	142 (59.2)	.03
Sedatives/benzodiazepine	23 (34.3)	48 (29.1)	67 (27.9)	.59
Other *DSM-5* substance use disorder, n (%)				
Alcohol use disorder	22 (32.8)	52 (31.5)	62 (25.7)	.33
Amphetamine use disorder	16 (23.9)	32 (19.4)	46 (19.1)	.67
Cannabis use disorder	27 (40.3)	50 (30.3)	64 (26.6)	.09
Cocaine use disorder	17 (25.4)	51 (30.9)	84 (34.9)	.31
Benzodiazepine/sedative use disorder	21 (31.3)	43 (26.1)	64 (26.6)	.69
Psychiatric/medical history, n (%)				
Major depressive disorder	30 (44.8)	49 (29.7)	74 (30.7)	.06
Anxiety disorder	45 (67.2)	75 (45.5)	100 (41.5)	**<.001**
ADHD	18 (26.9)	32 (19.4)	37 (15.4)	.09
Bipolar disorder	9 (13.4)	25 (15.2)	36 (14.9)	.94
Suicidal ideation	23 (34.3)	26 (15.8)	34 (14.1)	**<.001**
Suicidal behavior	11 (16.4)	18 (10.9)	31 (12.9)	.52
Psychotic episodes	3 (4.5)	6 (3.6)	4 (1.7)	.26
Prior mental health treatment	4 (6.0)	12 (7.3)	23 (9.5)	.55
Psychiatric hospitalizations	13 (19.4)	44 (26.7)	56 (23.3)	.48
Chronic pain for 6 mo	24 (35.8)	44 (26.7)	59 (24.5)	.18
Chronic medical problems	13 (19.4)	28 (17.0)	25 (10.4)	.06
Physical abuse	28 (41.8)	76 (46.3)	91 (37.8)	.23
Sexual abuse	22 (33.3)	48 (29.3)	63 (26.3)	.50

[a]Sociodemographic measures are not presented. Bonferroni correction was applied. Test-specific significance level was $P < .001$ (presented in bold).
[b]Moderate/severe depression: HDRS ≥ 17, mild depression: 8 ≤ HDRS ≤ 16, no depression: HDRS ≤ 7.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, HDRS = Hamilton Depression Rating Scale, IQR = interquartile range, SD = standard deviation.

severity or co-occurring substance use, with the exception that those with depression had longer duration of opioid use, more current cannabis use, and less current stimulant use. These differences were small, and none met the Bonferroni-adjusted significance level (α = .001).

Prior histories of major depressive disorder, anxiety disorders, suicidal ideation, and psychiatric hospitalizations and histories of chronic pain, chronic medical conditions, and physical and sexual abuse were common and did not differ significantly between groups with the exceptions of anxiety disorders and suicidal ideation. The moderate/severe depression group showed higher rates of a self-reported history of anxiety disorders (67.2%) and suicidal ideation (34.3%) compared to the mildly depressed (anxiety disorders 45.5%; suicidal ideation 15.8%) and no depression (anxiety disorders 41.5%; suicidal ideation 14.1%) groups.

Changes in Depression Status During the Initial Course of Treatment

Among the 232 participants with depression at baseline, 182 participants completed the HDRS at week 4. Among these participants, 52.8% (28/53) and 76.0% (98/129) achieved remission (HDRS ≤ 7) in the moderate/severe and mild depression groups, respectively, after 4 weeks of MOUD, and 64.2% (34/53) and 64.3% (83/129) showed response (≥ 50% reduction in HDRS).

There was no significant difference in the odds of depression response at week 4 between baseline depression groups (OR = 1.20, 95% CI = 0.58–2.48, $P = .62$). However, those with moderate/severe baseline depression were less likely to achieve remission at week 4 compared to those with mild baseline depression (OR = 0.43, 95% CI = 0.21–0.89, $P = .02$). The effect of baseline depression on depression outcomes did not significantly differ between treatment groups (remission: $F_{1, 172} = 2.03$, $P = .16$; response: $F_{1, 172} = 0.04$, $P = .83$). Further, there were no significant differences in the odds of depression remission nor in the odds of response at week 4 between the BUP-NX and XR-NTX treatment groups (remission: OR = 1.04, 95% CI = 0.53–2.06, $P = .91$; response: OR = 0.78, 95% CI = 0.41–1.47, $P = .44$).

Associations Between Depression and Relapse to Opioids During Treatment

The effect of baseline depression on the odds of relapse did not significantly differ between treatment groups ($F_{2, 460} = 0.08$, $P = .93$). For main effects of baseline depression, there were no significant differences in the odds of relapse to regular opioid use between groups with moderate to severe

depression at baseline (58.2%, 39/67), mild depression at baseline (52.7%, 87/165), and no depression at baseline (53.5%, 129/241) (mild vs none: OR = 0.96, 95% CI = 0.63–1.47, $P = .86$; moderate/severe vs none: OR = 1.11, 95% CI = 0.61–2.02, $P = .74$; moderate/severe vs mild: OR = 1.07, 95% CI = 0.53–2.15, $P = .85$) (overall: $F_{2,462} = 0.11$, $P = .90$) when adjusting for treatment.

Association Between Depression Persistence at Week 4 and Relapse

Relapse to opioid use did not differ significantly between patients who showed depression response after 4 weeks of treatment (41.0%; 48/117 relapsed) compared to among those who did not show response after 4 weeks of treatment (47.7%; 31/65 relapsed) (OR = 0.73, 95% CI = 0.39–1.36, $P = .31$). Relapse to opioid use trended lower among patients who achieved depression remission after 4 weeks of treatment (38.9%; 49/126 relapsed) compared to those whose depression did not remit (53.6%; 30/56 relapsed), although the difference was not statistically significant when controlling for treatment and baseline depression (OR = 0.55, 95% CI = 0.28–1.08, $P = .08$).

DISCUSSION

In a sample of treatment-seeking patients with OUD admitted to inpatient treatment programs, 34.9% had an HDRS score between 8 and 16, consistent with mild depression at baseline, and 14.2% had an HDRS score greater than 16, consistent with moderate/severe depression. Approximately two-thirds of these patients with baseline depression reached standard criteria for depression response (at least 50% reduction in depressive symptom severity by HDRS) or remission (HDRS ≤ 7) after 4 weeks of treatment with either BUP-NX or XR-NTX. Those with mild depression were more likely to remit compared to those with more severe depression. There was no difference in response of depression between BUP-NX vs XR-NTX, both medications being associated with substantial reduction in depression. Relapse to opioid use over the 24-week trial was not associated with baseline depression and trended lower among patients whose depression remitted by week 4 compared to those who did not remit, although this difference did not reach significance.

The substantial rates of depressive symptoms observed at baseline and of baseline depression improving or remitting after initiation of treatment for substance use disorder are consistent with prior studies in treatment seeking samples.[5,10,14–16] To our knowledge, our study is the largest study to date to investigate the initial course of depression in patients with OUD receiving MOUD, and we focus on patients meeting criteria for depression at baseline. Possible mechanisms may be that MOUD promotes abstinence from opioids and other drugs, which may improve depression by reducing direct effects of substances on mood or by improving social functioning and reducing stress associated with active drug use.

Buprenorphine has been hypothesized to be an antidepressant due to κ receptor antagonism, although antidepressant effects observed in clinical trials have been small.[38,39] Improvement in depression has been reported during treatment with both buprenorphine and naltrexone.[12,13,17] A recent study of 159 patients with OUD randomized to 12 weeks of either XR-NTX or BUP-NX reported no overall significant differences in outcome of anxiety or depression between treatments, but significantly lower insomnia scores in the XR-NTX group.[18]

Although our study did not conduct a structured diagnostic assessment of depression, relying instead on a cross-sectional measure of depression severity (the HDRS), depression that persists after 4 weeks of abstinence would be considered, according to *DSM-5*, to be an independent depression warranting specific depression treatment. The trend toward a higher rate of relapse to opioid use among patients whose depression did not remit over the first 4 weeks of MOUD provides further impetus to follow and treat persistent depression among patients with OUD. The distinction between independent and substance-induced depression is difficult to make before abstinence is established, though our findings suggest that greater severity of depression at baseline may be a marker of a depression that will persist and warrant intervention. Depression that resolves with treatment of OUD would be categorized as substance-induced under *DSM-5*. *DSM-5* asserts that substance-induced depression "warrants clinical attention." Particularly relevant for the opioid overdose epidemic, a study in a mixed sample of patients with substance use disorders showed that both *DSM-IV* independent and substance-induced depression at baseline assessment were associated with a history of suicide attempts.[40]

Of interest, depression level at baseline was not significantly associated with relapse. Some previous studies have shown co-occurring diagnosis of major depressive disorder to be predictive of worse outcomes in substance use disorder treatment,[41–43] including opioid use,[23,24] while some show depression associated with better outcome.[25] As suggested in previous studies, it is possible that for some participants, depression at baseline may have provided more motivation to adhere to substance use treatment.[25,44] Studies that utilized depressive symptoms measured by cross-sectional scales such as the Beck Depression Inventory or HDRS, as in the present study, have shown inconsistent association with treatment outcome.[5,45] Future research with cohorts deliberately enriched for co-occurring depression may help with further exploration of the prognostic implications of depression. In addition, diagnosis of depression with a clinical history and/or structured diagnostic interview, would be preferable to a symptom scale such as the HDRS.

This study has limitations. First, the focus of the parent trial was treatment of OUD, not depression. Thus, assessment of depression was not based on a structured clinical diagnostic interview, but instead relied on a clinician administered scale measuring current severity of symptoms of depression. We followed evidence-based cutoffs of the

HDRS score for categories of mild depression and moderate to severe depression from validation studies, which have demonstrated both high sensitivity and specificity for diagnosing major depression by symptom severity.[30] Second, elevated depression scores in our participants could reflect opioid withdrawal symptoms given the large overlap between opioid withdrawal and depressive symptoms (eg, fatigue, insomnia, anxiety, depressed mood, irritability, and loss of appetite). Third, our analyses were limited to the first 4 weeks of MOUD, before substantial dropout has occurred and when opportunity for intervention is greatest. Future research should examine trends in depression over long-term course of treatment. Last, suicidal ideation was assessed based on a single-item measure rather than using a specific psychometric instrument measuring suicidality.

Implications for clinical practice from this study include that patients presenting for treatment of OUD should be screened for depression and require monitoring of depressive symptoms during initiation of medication treatment and that depression that does not resolve with initiation of MOUD should be considered for specific antidepressant treatment. Depression should be screened first with a cross-sectional scale, such as the HDRS, Beck Depression Inventory, or the Patient Health Questionnaire-9. If a patient with OUD screens positive for depression, a thorough clinical history should be obtained to assess current and lifetime depression and other psychiatric comorbidity prevalent among patients with OUD and often co-occurring with depression (eg, anxiety or posttraumatic stress disorders). More severe depression combined with a history of independent depression may warrant depression treatment at the outset, almost concurrent with MOUD. Mild depression may be closely monitored given that they are more likely to remit with MOUD. The substantial prevalence of suicidal ideation at baseline in this sample, particularly among the patients with moderate to severe depression, taken together with studies on the role of suicidal intent in opioid overdoses,[6,7] highlights the importance of screening for depression and suicidal ideation in the effort to combat the opioid overdose epidemic.

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Potential conflicts of interest: **Dr Fishman** has been a consultant for Alkermes, Drug Delivery LLC, and Verily Life Sciences and received research support from Alkermes. **Dr Rotrosen** has been a principal investigator or co-investigator on studies for which support in the form of donated or discounted medication and/or funds has been, or will be, provided by Alkermes, Inc. (Vivitrol, extended-release injectable naltrexone) and by Indivior, Inc. (formerly Reckitt-Benckiser; Suboxone, buprenorphine/naloxone combination). In addition, studies in planning are anticipating support from Alkermes, Indivior, and Braeburn Pharmaceuticals, Inc. (extended-release injectable buprenorphine). He recently served in a non-paid capacity as a member of an Alkermes study steering committee. He has no relevant equity, intellectual property, paid consulting, travel, or other arrangements with any of these entities. **Dr Nunes** has been an investigator on studies for which support in the form of donated or discounted medication and/or funds has been, or will be, provided by Alkermes, Inc. (Vivitrol, extended-release injectable naltrexone), Indivior, Inc. (formerly Reckitt-Benckiser; Suboxone, buprenorphine/naloxone combination), and Braeburn-Camurus. In addition, studies in planning are anticipating support from Alkermes, Indivior, Braeburn Pharmaceuticals, Inc. (extended-release injectable buprenorphine), and Pear Therapeutics. He has served as a non-paid consultant to Alkermes, Camurus, and Pear Therapeutics. He has no relevant equity, intellectual property, paid consulting, travel, or other arrangements with any of these entities. **Dr Na** and **Ms Scodes** report no competing interests.

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