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Baseline characteristics and treatment outcomes in prescription opioid dependent patients with and without co-occurring psychiatric disorder

Margaret L. Griffin[1,2,*], **Dorian R. Dodd**[1], **Jennifer S. Potter**[1,2,3], **Lindsay S. Rice**[1], **William Dickinson**[4], **Steven Sparenborg**[5], and **Roger D. Weiss**[1,2]

[1]Division of Alcohol and Drug Abuse, McLean Hospital, Belmont, MA 02478, USA

[2]Department of Psychiatry, Harvard Medical School, Boston, MA 02115, USA

[3]University of Texas Health Science Center San Antonio, San Antonio, TX 78229, USA

[4]Providence Regional Medical Center, Everett, WA 98201, USA

[5]Center for the Clinical Trials Network, National Institute on Drug Abuse, National Institutes of Health, Rockville, MD 20892, USA

Abstract

Background—Given the growing prevalence of prescription opioid dependence and the considerable rates of additional psychopathology in drug dependence, we examined the association between the presence of a co-occurring Axis I psychiatric disorder and sociodemographic and clinical characteristics in this secondary analysis of patients entering a treatment study for dependence on prescription opioids. Treatment outcomes were also compared.

Methods—Patients dependent on prescription opioids participated in a multi-site, two-phase, randomized, controlled trial to assess different lengths of buprenorphine-naloxone pharmacotherapy and different intensities of counseling (Clinicaltrials.gov identifier: NCT00316277). Among the 653 participants entering the first phase of the trial, 360 entered the second phase, receiving 12 weeks of buprenorphine-naloxone treatment; they are reported here. Half of those participants (180/360) had a current co-occurring psychiatric disorder in addition to substance dependence.

Results—Sociodemographic characteristics were similar overall between those with and without a co-occurring psychiatric disorder, but women were 1.6 times more likely than men to have a co-occurring disorder. On several clinical indicators at baseline, participants with a co-occurring disorder had greater impairment. However, they had better opioid use outcomes at the conclusion of 12 weeks of buprenorphine-naloxone stabilization than did participants without a co-occurring disorder.

Conclusions—Prescription opioid dependent patients with a co-occurring psychiatric disorder had a better response to buprenorphine-naloxone treatment despite demonstrating greater

[*]Corresponding author at McLean Hospital, Division of Alcohol and Drug Abuse, 115 Mill Street, Belmont, MA 02478, USA; telephone: 617-855-2242; mgriffin@mclean.harvard.edu.

Declaration of interest

Dr. Weiss has served as a consultant to Titan Pharmaceuticals and Reckitt Benckiser. Dr. Dickinson is a treatment advocate and speaker for Reckitt Benckiser.

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impairment at baseline. Additional research is needed to determine the mechanism of this finding and to adapt treatments to address this population.

The incidence of prescription opioid abuse and dependence in the United States has increased dramatically in recent years, becoming a major public health concern. Between 2002 and 2011, past-year prescription opioid abuse or dependence increased 20% from 1.5 million to 1.8 million, making opioid analgesics the most commonly abused illicit drugs other than marijuana in 2011 (1). The number of deaths due to opioid analgesic overdose more than quadrupled from 4,000 in 1999 (2) to 16,651 in 2010 (3).

Recent literature reviews of psychopathology in the general population agree that psychiatric disorders in drug dependent populations are common (4,5). National epidemiological surveys have recently reported that those with drug dependence are considerably more likely to have another psychiatric disorder than those without drug dependence (odds ratios=6.0 for anxiety and 8.5 for mood disorders) (6), with a prevalence rate for a co-occurring mental illness at 45.1% of those with past-year substance use disorder (7). Clinical research on drug dependence has reported similarly high rates of psychopathology: approximately half (47%) of opioid-dependent patients receiving methadone maintenance treatment had a lifetime psychiatric diagnosis other than substance dependence (8). Rates of psychiatric comorbidity in one study of those dependent on prescription opioids specifically were higher still: excluding heroin and methadone users, rates for a lifetime mood or anxiety disorder were 72.9% and 60.9%, respectively (9).

Although most reports of treatment-seeking opioid users have found that psychiatric severity is related to worse substance use outcomes (8,10,11), data regarding the prognostic impact of co-occurring psychiatric illness in substance dependent patients are mixed. Some research reports indicate that psychiatric severity is not related to substance use treatment outcome (12,13), and other studies have shown mental health problems to be associated with better substance use treatment outcomes (14,15) in methadone-treated patients. However, none of these studies focused on patients dependent on prescription opioids.

Because the increased prevalence of prescription opioid dependence is a relatively recent phenomenon, previous research on the trajectory and treatment outcomes in opioid dependence has primarily examined heroin users. However, prescription opioid users differ from heroin users in substance use and psychiatric histories (16,17), drug use patterns, and other prognostic indicators (16). Therefore, the significance of the presence of a co-occurring psychiatric disorder other than a substance use disorder in patients dependent on prescription opioids is unknown. To understand this population better, the National Institute on Drug Abuse Clinical Trials Network conducted the multi-site Prescription Opioid Addiction Treatment Study (18), which treated prescription-opioid dependent participants with different lengths of buprenorphine-naloxone and different intensities of counseling. The current paper represents a secondary, exploratory examination of sociodemographic and clinical characteristics as well as substance use treatment outcome among study participants with and without a co-occurring psychiatric disorder.

Methods

Study design

The Prescription Opioid Addiction Treatment Study was a randomized, controlled trial, utilizing a two-phase adaptive treatment research design, conducted at ten sites across the United States; 653 participants were enrolled. The Institutional Review Board at each site approved the study, and participants provided written informed consent. Details of the study design have been reported elsewhere (19). To summarize briefly, in Phase 1, participants

received brief buprenorphine-naloxone treatment, which included induction, 2 weeks of stabilization, and a 2-week taper, with an 8-week post-medication follow-up. Participants who relapsed to opioid use during Phase 1 were invited to enter Phase 2, which consisted of 12 weeks of buprenorphine-naloxone stabilization, followed by a 4-week taper and an 8-week post-treatment follow-up. In each phase, participants were randomized to one of two counseling conditions: 1) Standard Medical Management (SMM) alone; or 2) SMM plus individual Opioid Dependence Counseling. At weekly SMM visits, buprenorphine-naloxone was dispensed to participants. Randomization to counseling condition in Phase 1 was stratified by 1) presence of current chronic pain and 2) lifetime history of heroin use. In Phase 2, randomization was stratified by Phase 1 treatment condition.

Successful outcome in the last four weeks of Phase 2 was the primary outcome measure in the trial, defined as abstinence from opioids during at least 3 of the final 4 weeks of buprenorphine-naloxone stabilization (weeks 9–12), including the final week, based on urine-confirmed self-report. Because the success rate in Phase 1 was so low (7%), this paper will examine data collected during Phase 2, for which the overall success rate was 49% (18). Success was not associated with counseling treatment condition (i.e., SMM-alone or SMM +opioid counseling) in either phase.

Inclusion and exclusion criteria

Study participants were at least 18 years old at the time of enrollment and met DSM-IV criteria for current opioid dependence. Study exclusion criteria included any of the following: heroin use on more than four days in the past month; a lifetime diagnosis of opioid dependence due to heroin use alone; a history of injection heroin use; pain requiring ongoing medical treatment with prescription opioids (according to the prescribing physician); and current participation in formal substance abuse treatment other than self-help groups. Participants receiving psychiatric medications could enter the trial unless they exhibited current psychosis, acute suicidal ideation, or psychiatric instability.

Treatments

Participants were inducted onto sublingual buprenorphine-naloxone. Depending on their initial response to the medication, participants received 4–12 mg during induction and once-daily doses ranging from 8–32 mg/day during stabilization. At each SMM visit, the study physician could adjust the dose by increments of up to 8 mg/week. Buprenorphine-naloxone treatment specifications in this study are described elsewhere (19). Study pharmacotherapy did not address co-occurring psychiatric disorders. However, appropriate referrals were made if a participant demonstrated a need for additional psychiatric treatment, including psychopharmacologic agents.

Assessments

Before admission into the study, participants received a comprehensive medical and psychiatric examination to determine whether eligibility criteria were met. Study physicians identified a number of health issues, including current and lifetime Axis I psychiatric diagnoses of major depressive disorder, post-traumatic stress disorder, attention deficit hyperactivity disorder, panic or other anxiety disorder, bipolar disorder, and other psychiatric disorder. Participants received a battery of assessments at baseline and throughout the study, including the measures described below. Data reported in this paper were collected at baseline, other than results for treatment outcome.

The Composite International Diagnostic Interview (CIDI; 20) is a structured interview that was used to diagnose opioid dependence (required for study inclusion) and other substance use disorders. Co-occurring current Axis I psychiatric diagnoses included in this paper were

determined by combining the CIDI assessment of major depressive disorder and post-traumatic stress disorder (PTSD) with the physician's baseline report for psychiatric diagnoses. As a validity check, given the use of two different measures for co-occurring psychiatric diagnoses, we considered the possibility that the CIDI diagnoses might be more objective than the physician diagnoses, resulting, for example, in a differential likelihood of diagnosing major depressive disorder in women. We therefore sorted the participants with co-occurring psychiatric disorders into those diagnosed by CIDI vs. physician only. Results reported below were similar regardless of diagnostic methodology and therefore support combining all participants with a co-occurring diagnosis, regardless of measure used.

The Pain and Opiate Analgesic Use History is a self-report inventory developed for this study to delineate opioid use and pain histories. *The Fagerstrom Test for Nicotine Dependence* (21) is a 6-item measure that provides a nicotine dependence severity score (0–10) in smokers, with higher scores indicating greater severity; scores for nonsmokers were set to zero. Drug craving was assessed with the 3-item *Craving Scale* (22). Response options on a visual analog scale ranged from 0 for "no desire/likelihood of use" to 10 for "strong desire/likelihood of use." The composite score is a mean of these items, ranging from 0 to 10. *The Addiction Severity Index-Lite* (ASI; 23) is a semi-structured interview that measures the severity of substance abuse-related problems across seven different domains: alcohol, drug, legal, medical, psychiatric, family/social, and employment. ASI composite scores range from 0 to 1, with higher scores indicating greater problem severity. *Opioid use* was assessed weekly during treatment and biweekly during follow-up via self-report and corroborated by urine drug screens. *The Beck Depression Inventory* (BDI) (24) is a 21-item self-report measure to determine the severity of depressive symptoms (range=0–69, with higher scores indicating greater severity). Quality of life was measured by the self-administered Medical Outcome Study *Short Form-36 (SF-36) Health Survey* (25). Subjects respond to 36 Likert-scaled items for the past four weeks; Physical and Mental Component Summary scores are then computed, with higher scores indicating better quality of life.

Data analysis

Bivariate analyses compared participants with and without co-occurring psychiatric diagnoses. Continuous variables were assessed with independent *t*-tests, and dichotomous variables with chi-square tests.

Results

Sample background

Of the original 653 participants enrolled in Phase 1, 360 entered Phase 2. Half of those (n=180) had a current psychiatric diagnosis in addition to substance dependence: major depressive disorder (n=111), panic disorder or another anxiety disorder other than PTSD (n=81), PTSD (n=52), attention deficit hyperactivity disorder (n=15), bipolar disorder (n=10), and/or another psychiatric disorder (n=17). A single co-occurring disorder was most common (57.2% of the 180 participants with co-occurring psychiatric illness), but some participants had 2 disorders (29.4%) and the remainder had 3 or 4 disorders (13.4%); the mean number of co-occurring disorders was 1.6 (sd=0.8).

As shown in Table 1, participants with and without a co-occurring psychiatric diagnosis did not differ on race, age, years of education, marital status, or current employment status. However, women were about 1.6 times more likely than men to have a co-occurring psychiatric diagnosis ($\chi^2(1)=19.18$, $p<.001$; N=360). Primary reason for first use of prescription opioids did not vary by co-occurring psychiatric diagnosis, with most participants reporting pain (64.7%), followed by using to get high (28.6%).

Substance use

In general, participants with a co-occurring psychiatric disorder were more likely to have a drug dependence diagnosis in addition to opioid dependence, both lifetime ($\chi^2(1)=19.33$, p<.001) and past-year ($\chi^2(1)=14.78$, p<.001). They were also more likely to meet criteria for lifetime ($\chi^2(1)=12.46$, p<.001) and past-year ($\chi^2(1)=4.19$, p<.05) alcohol dependence (N=360). Participants with a co-occurring psychiatric diagnosis reported greater opioid craving ($t(358)=3.15$, p<.01) and higher scores on the Fagerstrom Test for Nicotine Dependence ($t(358)=2.08$, p<.05) at baseline. Heroin use was similar in the two groups, as was age of onset for opioid dependence.

ASI composite scores were more severe for participants with a co-occurring psychiatric diagnosis in the following domains: drug ($t(358)=4.67$, p<.001), medical ($t(353)=2.92$, p<.01), psychiatric ($t(350)=10.13$, p<.001), family/social ($t(325)=4.34$, p<.001), and employment ($t(353)=2.19$, p<.05). No differences were seen in medical or alcohol composite scores.

Other clinical characteristics

Participants with a co-occurring diagnosis reported higher depression severity scores ($t(358)=7.16$, p<.001) and worse overall quality of life, both physically ($t(358)=2.06$, $p<.05$ and mentally ($t(358)=6.77$, p<.001) compared to those without a co-occurring psychiatric disorder. No differences were reported for prior treatment or chronic pain.

Treatment outcome

Although the data reported above indicate generally greater problem severity at baseline among those with a co-occurring psychiatric diagnosis, those participants were 1.6 times more likely to have a successful opioid use outcome while receiving buprenorphine-naloxone treatment at week 12 of Phase 2, adjusted for treatment condition and site (OR=1.62, CI=1.05–2.51, N=357), p<.03); this was the primary outcome measure in the main study. This difference was not maintained at follow-up (week 24 in Phase 2), when <9% of participants overall had a successful opioid use outcome. Comparison of the most common co-occurring diagnoses showed little variation in rates of successful opioid use outcomes at the end of treatment: 58.6% for major depressive disorder, 58.0% for anxiety disorder, and 53.8% for PTSD. Since it could be hypothesized that improvements in treatment methods for psychiatric disorders in recent years have reduced the negative impact of a co-occurring psychiatric disorder on treatment outcomes, we compared treatment outcome in participants according to whether or not they were taking medication or reported ongoing psychosocial treatment for their co-occurring disorders during the treatment portion of Phase 2 (i.e., weeks 1–12). We found that, among those with a co-occurring diagnosis, participants receiving treatment for their psychiatric disorder were no more likely to have successful opioid use outcomes than participants not receiving treatment (54% (n=53/99) vs. 58% (n=46/80); $\chi^2(1)=.28$, p<.60).

Discussion

The results of the present study are consistent with previous findings that psychiatric comorbidity is common in opioid-dependent patients (8,9). Participants with a co-occurring Axis I psychiatric diagnosis in the present study were similar to those without a psychiatric diagnosis on sociodemographic variables other than gender: women were more likely than men to have a co-occurring diagnosis; this gender difference is consistent with results from a large epidemiological study of lifetime comorbidity (9), but contradicts the finding of no gender association in a study of patients with opioid use disorder (8). Our population of prescription opioid users with and without co-occurring psychiatric disorders differed on

several substance use and other clinical characteristics at baseline. Specifically, participants with co-occurring diagnoses had a greater number of substance dependence diagnoses, more self-reported impairment as a result of their substance use, and greater opioid craving and nicotine dependence severity. Quality of life was also worse, both physically and mentally, and, not surprisingly, depressive symptom scores were higher. These group differences at baseline were expected (8,13); they may reflect a greater overall vulnerability to the deleterious effects of substance use disorders among those with a co-occurring psychiatric disorder (26).

A greater likelihood of successful opioid use outcomes in Phase 2 despite enrolling in the study with more apparent barriers to success was an unexpected finding. Perhaps more severe problems and worse quality of life lead to greater motivation to seek treatment, as suggested by Rounsaville and colleagues (27). They found that opioid users entering treatment had higher rates of depression than those not entering treatment, suggesting that greater psychopathology may act as an incentive to pursue treatment. The level of distress and poorer quality of life associated with greater psychopathology may also motivate patients to take a more active role in their treatment, becoming more willing to make the major life changes necessary to reduce their opioid use. Alternatively, perhaps the study medication relieved psychiatric symptoms, hence reducing the desire to use opioids, as has been suggested in a study of opioid dependent patients receiving methadone maintenance treatment (15). This explanation warrants consideration, given that buprenorphine treatment may reduce some depressive symptoms (28,29). We cannot evaluate this potential medication effect, since all study participants received buprenorphine.

The current study has several limitations. It represents a secondary analysis: the main POATS trial did not primarily aim to examine psychiatric comorbidity. Therefore, psychiatric disorders other than major depressive disorder and PTSD were assessed by study physician report. Our measure of psychiatric disorder was binary rather than continuous, so we cannot assess variation within diagnostic categories. Administering a comprehensive psychiatric assessment instrument was not performed in an effort to reduce participant burden. Given the exploratory nature of the current study and the fact that statistical power for the current analyses was not considered a priori, multiple tests of significance may be allowed. Nevertheless, most tests (17/29) were significant, which is greater than would be expected by chance. Since regular heroin users were excluded from this study, generalizability is limited, by design, to a subset of prescription opioid users with minimal or no heroin use. As the first large-scale randomized, controlled trial of prescription opioid patients, this study represents an important effort to understand this rapidly growing population.

The present study shows that within the population of treatment-seeking patients dependent on prescription opioids, those with a co-occurring psychiatric disorder form a distinct subgroup with important differences in baseline severity and response to treatment. This finding emphasizes the importance of conducting psychiatric assessments in substance dependence treatment settings so that clinicians are best able to understand and serve this unique population. While several explanations are proposed for the differences found between those with and without co-occurring psychiatric diagnoses, the current study design does not allow for a clear determination of why these differences exist. Additional research is needed to determine the causal mechanisms that account for differences between prescription opioid users with and without co-occurring psychiatric disorders, and, further, to determine how best to adapt treatments for this specific population.

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Table 1

Baseline characteristics of prescription opioid dependent patients by current co-occurring psychiatric disorder (N=360)

	Co-occurring psychiatric disorder		
	Yes (180)	**No (180)**	**p**
Sociodemographic characteristics			
Female, %	53.3	30.6	.001
White, %	91.7	89.4	ns
Age, mean, sd	33.2, 9.4	31.9, 9.9	ns
Years education, mean, sd	12.9, 2.1	12.9, 2.3	ns
Never married, %	46.1	53.9	ns
Employed full-time, %	57.8	62.8	ns
Substance use			
Heroin use ever, %	25.0	27.2	ns
Age of onset for opioid dependence (357), mean, sd	28.7, 8.9	28.2, 9.4	ns
First source of prescription opioids (357), %			.02
Legitimate prescription from an M.D.	62.4	47.5	
Given by someone	17.4	27.9	
Any prior opioid treatment, %	34.4	35.6	ns
Any drug dependence diagnosis, excluding opioids, %			
Lifetime	52.2	29.4	.001
Past year	23.9	8.9	.001
Alcohol dependence diagnosis, %			
Lifetime	36.1	19.4	.001
Past year	6.7	2.2	.041
Opioid craving score, mean, sd	8.3, 2.0	7.6, 2.3	.002
Nicotine dependence score, mean, sd	3.8, 2.9	3.1, 2.8	.038
Other clinical characteristics			
Addiction Severity Index composite scores, mean, sd			
Alcohol (338)	.05, .10	.05, .08	ns
Drug	.35, .07	.32, .07	.001
Legal (337)	.06, .14	.05, .13	ns
Medical (355)	.26, .20	.16, .28	.004
Psychiatric (352)	.25, .20	.07, .13	.001
Family/social (325)	.20, .23	.11, .17	.001
Employment (355)	.42, .29	.35, .28	.029

	Co-occurring psychiatric disorder		
	Yes (180)	**No (180)**	**p**
Chronic pain, %	45.6	37.2	ns
Beck Depression Inventory, mean, sd	27.3, 11.9	18.9, 10.5	.001
Quality of life score			
Physical	47.5, 10.3	49.7, 9.7	.040
Mental	33.5, 12.8	42.0, 11.0	.001
Lifetime abuse, %			
Physical	39.4	18.9	.001
Sexual	28.9	10.6	.001