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Withdrawal Severity and Early Response to Treatment in the Outpatient Transition From Opioid Use to Extended Release Naltrexone

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Background and Objectives: Long acting naltrexone has improved the therapy of opioid use disorder (OUD), and safe and effective withdrawal management during naltrexone induction may help advance treatment. Despite the uncertain role of opioid withdrawal in predicting successful outcomes, early symptom control may favor detoxification completion.
Methods: We explored withdrawal severity and early response to treatment, safety, and clinical measures in 35 adult patients with DSM-5 OUD during a 7-day office-based buprenorphine-naltrexone and ancillary medications transition to extended-release naltrexone (XR-NTX).
Results: Subjective and objective measures of withdrawal intensity improved consistently throughout treatment in the whole sample. Participants who went on to receive XR-NTX ($n = 27, 77\%$) reported a greater attenuation of symptoms by treatment day 2 ($r = .595$, $p = .001$), and were less likely to be injection drug users ($r = -.501$, $p = .004$). Adverse events (AEs) were recorded in 20% of participants: the majority ($n = 6, 85.7\%$) consisted of single episodes of increased withdrawal which were well controlled using ancillary medications. One serious AE was unrelated to treatment.
Conclusions and Scientific Significance: Early opioid withdrawal changes may be a useful indicator of treatment response, helping adjust the transition protocol to the individual patients' need and gather valuable information for a better understanding of the relationship between initiating and remaining in treatment. (Am J Addict 2018;27:471–476)

INTRODUCTION

Naltrexone is seemingly ideal to expand treatment options for the opioid epidemic as it blocks the intoxicating effects of opioid substances without inducing dependence, though the oral form has been met with poor adherence and acceptability by patients.[1,2] Oral naltrexone is less expensive than the long acting formulations and does not entail injection or implant procedures; however, it offers only 24-hour coverage compared to 4 weeks or longer. Prolonged medication exposure and behavioral incentives can help improve adherence and effectiveness,[3–5] yet problems of withdrawal management during detoxification and naltrexone induction persist.[6,7] Fear of discontinuing opioid agonist medications[8] and anticipation of severe withdrawal discomfort may variably influence treatment choice and outcome.[9] Additional concerns rise from reports of untimely or inappropriate use of naltrexone triggering heightened withdrawal to encompass delirium, agitation, and confusion during detoxification.[10,11] Thus, a definition and characterization of opioid withdrawal symptoms in relation to naltrexone administration is due.

Inpatient detoxification,[12,13] extended opioid tapering, lower baseline opioid use,[14,15] all favor treatment completion. The same cannot be said for a reduction of withdrawal discomfort.[16–18] However, studies suggest that better withdrawal control early into treatment may play a role in successful short-term detoxification completion.[19–21] If early response to treatment can be associated with successful naltrexone induction, anticipated gains include the possibility of delivering a safer and more efficient treatment, increasing feasibility, and acceptability. Few investigations have focused on predicting successful naltrexone induction through detoxification, and the role played by withdrawal symptoms has not been analyzed.[22–25]

To fill the knowledge gap, we explored characteristics of opioid withdrawal and early (day 2) response to treatment among 35 adults with OUD enrolled in a 7-day outpatient trial of induction onto extended-release naltrexone (XR-NTX), along with socio-demographic, clinical variables, and safety measures.

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METHODS

The screening process and treatment protocol are reported in detail elsewhere, together with the main outcomes of a preliminary group of 20 patients.[26]

Study Design

Participants were enrolled in an open-label, uncontrolled study (ClinicalTrials.gov NCT01690546) evaluating the feasibility of very low dose naltrexone-buprenorphine/naloxone-naltrexone outpatient transfer from drug use to XR-NTX injection in OUD. The treatment consisted of 7-day detoxification/induction, followed by day 8 XR-NTX injection and 4-week follow-up.

Participants and Procedures

The study was approved by the Duke University Health System Institutional Review Board and it was conducted at the Duke Addictions Program (DAP). Participants were recruited among patients seeking treatment at DAP or were referred from other inpatient detoxification services and outpatient treatment programs in Durham County, North Carolina.

Individuals were eligible for the study if they were between the ages of 18 and 65 years with a primary DSM-5 diagnosis of OUD and reported current opioid use ($\geq$20 days in the last 30), were willing to switch to opioid antagonist treatment, and were not receiving methadone or buprenorphine therapy. Ineligibility included unstable medical or psychiatric conditions, other drug use disorder requiring treatment, pregnancy or breastfeeding, serum aminotransferases results over two times normal, and receiving opioids to treat medical problems.

Visits were scheduled on Days 1 through 9, then weekly through week 4 post-injection (last visit: Day 36). Each day, upon arrival at the study site participants were tested for drug use, assessed for vital signs and symptoms of withdrawal, and received scheduled study treatment (Day 1–8). Safety and withdrawal evaluations were repeated hourly, three or more times before visit completion.

Treatments

Naltrexone was administered daily for 7 days (increasing from .25 to 50 mg/day), initially in combination with a short buprenorphine taper (Day 1–3: 4, 2, and 2 mg), and then alone until Day-8 injection of XR-NTX 380 mg. Patients received psychoeducational support daily until injection and weekly after that, until Day 36. Non-opioid medications commonly used to help control withdrawal symptoms were offered at the study site and as take-home doses on as-needed basis (PRN), including the alpha-2-receptor agonist clonidine, trazodone, ibuprofen, acetaminophen, cyclobenzaprine, lorazepam, hydroxyzine, promethazine, and loperamide. Only one type of ancillary medication for any given symptom was to be dispensed on any treatment day and the dose range was determined in advance (a description of dosing and indications are reported by Mannelli et al.).[26]

Measures

Opioid Withdrawal

Symptoms and signs were self-rated by participants using the Subjective Opiate Withdrawal Scale (SOWS = 0–64)[27] and by a physician or a nurse using the Clinical Opiate Withdrawal Scale (COWS = 0–36).[28]

Biological Testing

Measures included instant urine toxicology for opioids, buprenorphine, and other main drugs of abuse (cocaine, amphetamine, methamphetamine, tetrahydrocannabinol, benzodiazepines, barbiturates, propoxyphene, phencyclidine); and a saliva strip for alcohol.

Drug Use

At admission, participants were asked about their opioid of choice (eg, heroin, prescription opioids), quantity of last 30-day use (equivalent of heroin bags per day), and modality of use (oral vs injection).

Adverse Events

An adverse event (AE) was defined as any reaction, side effect, or untoward event that occurred during the course of the clinical trial, whether or not the event was considered study related. AEs included new or worsening laboratory and clinical abnormalities as measured by vital signs (heart rate, blood pressure, skin temperature, and respiratory rate) performed three or more times daily during 4-hour treatment sessions, physical exams, laboratory parameters (cell blood count, complete metabolic panel and pregnancy test), and ECG at screen and last study visit.

If the severity of a subject's withdrawal symptoms required doses of an ancillary medication that exceeded the standing regimen, the condition being treated was noted as an AE. AEs included events reported by the participant, as well as those observed by the research staff at each visit. Pregnancy was not considered an AE, though it would require study discontinuation and determine follow-up observation as needed.

Data Analysis

Descriptive statistics (mean and SD, number, percent, and percent changes from baseline) were calculated for demographic and clinical features and efficacy measures. Successful induction was defined as no more than mild discomfort (COWS $\leq$12) recorded 1 hour and 1 day post-injection, as reported by other investigations of XR-NTX induction.[29]

Baseline SOWS and COWS withdrawal scores were compared with mean daily scores using paired Student's *t*-tests (two-tailed; alpha = .05). Drug use comparisons with baseline were analyzed using the McNemar's test.

Variables of interest included socio-demographic and clinical characteristics that have shown to influence opioid withdrawal expression and/or naltrexone induction, including age, gender, injection drug use (IDU), daily quantity, and time from last use at admission.[22,23,30,31] Exploratory analyses were conducted by using Spearman correlation coefficients to

assess the nature of potential relationships between day-2 withdrawal changes, behavioral and biological variables, and induction onto XR-NTX. The level of significance was determined after applying the Bonferroni method of correction for multiple comparisons.

The safety population included all patients who took at least 1 dose of study medication. The observation was carried on for the duration of the study and included treatment and follow-up, for a total of 36 days. Incidence and timing of AEs were reported, each AE was summarized descriptively by severity and relationship to discontinuation.

RESULTS

Subjects

The sample included 26 men (74%) and 9 women (26%), the majority of whom were African American (74.3%), while the remaining participants were Caucasian. The average age was 40.1 years (range: 25–65) and the average education was less than high school (8.9 years), with 44% unemployment. Opioid use (average duration 9.7 years; range 7–18 years) involved heroin (57%) and prescription painkillers (43%) as drug of choice, 74% individuals used an equivalent of >6 bags of heroin per day, 26% reported using between 3 and 6 bags/day, last reported use was about 16 hours (range: 6–30) before treatment. Most of the participants reported smoking tobacco (91%) and a majority abused at least 1 substance in addition to opioids (69%), while 34% were injection drug users (IDUs). Participants had comorbid mood (34%) and anxiety (20%) disorders.

Twenty-seven participants received XR-NTX and returned for evaluation the following day. Eight individuals did not receive the injection: one of them discontinued the study after 2 days; two after 5 days; three others received treatment for 6 days; one for 7 days; and one for 8 days but refused the administration of XR-NTX. We contacted these participants to complete early termination visits. Each one of them reported lingering withdrawal and/or craving among the reasons for discontinuing treatment. The characteristics of the sample, stratified by XR-NTX administration are shown in Table 1.

TABLE 1. Characteristics of the sample ($n = 35$) stratified by injection completion

	Mean (SD) or *n*	
Independent variable	Inducted ($n = 27$)	Not inducted ($n = 8$)
Age (years)	41.8 (8.7)	39.6 (9.3)
Race (African American)	19	7
Gender (male)	21	5
Education (years)	8.9 (6.2)	8.7 (4.1)
Employed	9	4
Anxiety (self-reported)	6	1
Depression (self-reported)	9	3
Length of opioid use (years)	9.9 (6.6)	9.4 (7.1)
Daily use in the past 30 days (equivalent heroin bags)		
3–6	4	3
>6	23	5
Drug of choice		
Heroin	17	3
Prescription opioids	10	5
Other drug use (past 2 weeks)		
1 substance	19	5
>1 substance	9	2
Tobacco	26	8
Injection drug use*	4	8
Time from last opioid use on day 1 (hours)	17.6 (7.1)	19.1 (14.2)

*$p = .05$.

Withdrawal Severity, Drug Use, and XR-NTX Induction

There was a significant decrease of withdrawal intensity over the course of the study compared with baseline scores in the entire sample (Days 1-8; SOWS t [34] = 7.4, $p = .0001$; COWS t [34] = 6.4, $p = .001$). Withdrawal discomfort continued to be significantly lower following injection (Day 9; SOWS t [26] = 6.2, $p = .0002$; COWS t [26] = 4.4, $p = .001$). The proportion of opioid-positive urine drug screens reduced from 97.1% at baseline to 54% on Day 2 ($p = .0002$), and was 14.8% the day of the injection (Day 1 vs Day 8; $p = .0001$).

We assessed the nature of potential relationships between early (Day 2) in-treatment changes of withdrawal measures, sociodemographic and clinical measures of interest, and induction onto XR-NTX (Table 2). Higher subjective withdrawal score changes from baseline after receiving treatment on the second day were associated with induction onto naltrexone injection ($r = .595, p = .001$) while IDUs were less likely to receive XR-NTX ($r = -.501$, $p = .004$). Subjective and objective measures of withdrawal intensity were strongly correlated with each other ($r = .919, p = .0001$) and were not associated with other potential covariates. In particular, change of withdrawal severity was not associated with differences in time elapsed from last opioid use at treatment admission or use of opioids during treatment. Figure 1 shows the distribution of individuals inducted onto XR-NTX based on score reduction by end of treatment Day 2.

Adverse Events

Safety data were available for 35 subjects. All subjects reported symptoms of opioid withdrawal at different times after leaving the treatment site, similar to those documented on their withdrawal assessments. Six participants described the occurrence of more intense discomfort; each one of them reported a single episode lasting a few hours after leaving the clinical site on Days 3, 4, 6 (2 episodes), and 7 (2 episodes), which required the use of PRN take home ancillary medications in excess of the standing regimen. Events were

defined as moderate intensity, treatment-related AEs, and were not associated with acute opioid use or study discontinuation. A seventh participant with undisclosed history of comorbid schizoaffective disorder and prolonged non-compliance with psychopharmacologic treatment, experienced a non-treatment related SAE consisting of psychomotor agitation after 2 weeks from injection, and required a few days of hospitalization. Following behavioral stabilization, the participant was discharged and was able to complete the study. There was no AE following XR-NTX administration. In particular, no clinical, behavioral, or injection site reactions were recorded at the follow-up visits. Overall, no overdose episodes were recorded and there were no clinically significant shifts in hematology, chemistry, or urinalysis values over time. No clinically significant changes in vital signs or in physical examination results were recorded during treatment.

DISCUSSION

In this office-based study of transitioning from opioid use to extended release naltrexone therapy, early withdrawal response to treatment was significantly associated to XR-NTX induction. In particular, individuals who showed larger reductions of discomfort by the end of the second day of treatment were more likely to receive naltrexone injection. The clinical corollary is that individuals should initiate induction after the phase of more intense withdrawal symptoms has subsided. This way they may be able to experience early relief of discomfort and overcome negative expectations once they are in treatment.

Early withdrawal responses indicative of completion were previously observed in other opioid detoxification trials of comparable length and using similar medications, including buprenorphine taper, alpha-2-adrenergic receptor agonists, and symptomatic ancillary drugs.[13,19,20] The use of very low doses of naltrexone has been associated with reduced withdrawal expression in combination with clonidine during methadone detoxification,[32] and upon buprenorphine discontinuation and XR-NTX administration in OUD patients.[29] However, no improvement in completion rates has been recorded. A relationship between initial response and treatment outcome has been determined in psychiatric[33] and substance use disorders,[34,35] leading to the formulation of clinician guidelines to optimize intervention and prevent patient drop-out.[36]

IDU was negatively associated with treatment completion. Using injection drugs is a relevant risk behavior often associated with disease severity and the presence of comorbidity[37] which has been linked with reduced likelihood of completing naltrexone induction in OUD patients.[22]

The administration of oral naltrexone in combination with buprenorphine was well tolerated, it was safely continued after buprenorphine termination, and the majority of the participants were able to transition to XR-NTX. Although all the AEs but one were found to be withdrawal related, symptoms were managed using PRN medications and did not require further interventions. Interestingly, residual use of opioids during treatment did not affect outcome or trigger additional safety issues.

Taken together, our results underscore the importance of performing systematic baseline evaluation and quantitative monitoring of withdrawal discomfort using subjective (SOWS) and objective (COWS) measures performed by patient and provider to safely deliver XR-NTX transition treatment.

The design of this study excluded evaluation and follow-up of repeated XR-NTX injections. XR-NTX treatment has shown to be clinically useful and to safely provide relapse prevention support for 6 months, and up to 18 months.[3,38]

TABLE 2. Correlations assessing the relationship between withdrawal measures, behavioral and biological independent variables of interest, and naltrexone injection among 35 trial participants (Bonferroni correction for multiple comparisons, p significance = .005)

Rho value[a]	1	2	3	4	5	6	7	8	9	10
1. Naltrexone induction	–									
2. Sows changes Day 2	.595**	–								
3. COWS changes Day 2	.454	.919***	–							
4. Time of last use	.248	.320	.290	–						
5. Daily opioid quantity	.159	−.045	.251	.012	–					
6. Injection drug use	.501*	.320	.290	.310	.070	–				
7. In-treatment opioid use	.208	.184	.115	.103	.301	.193	–			
8. Age	−.389	.201	.306	.110	.302	.106	.230	–		
9. Gender (male)	.281	.291	.101	.150	.195	.095	.293	.245	–	
10. Race (African American)	−.185	.045	.016	.113	.192	.205	.182	.143	.333	–

[a]The Rho coefficient is a measure of the strength of the correlation between variables. The range of values is from +1, indicating a maximum positive association, to −1.

*$p = .004$.

**$p = .001$.

***$p = .0001$.

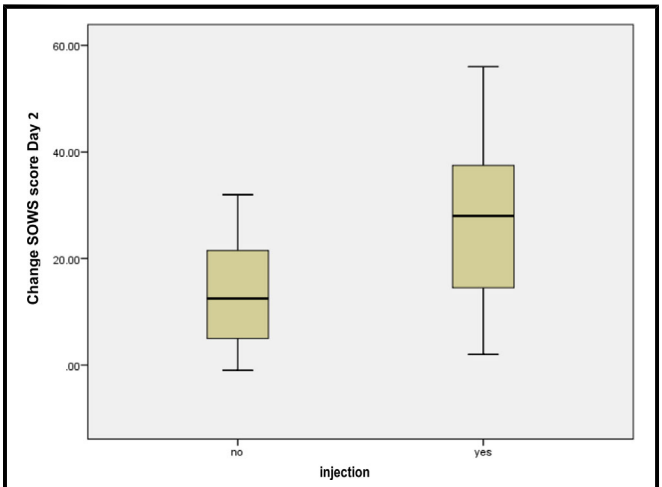

FIGURE 1. Boxplot of the distribution of participants' day 2 change of SOWS scores stratified by XRNTX injection completion (completion: Yes $n = 27$, No, $n = 8$).

Further investigation is needed to identify effective methods of retention in treatment.

We chose not to complete a predictor analysis due to the small sample size. The relatively low statistical power may also explain a lack of significance in the case of potentially important factors, including type of opioid substance, daily quantity used, and time of last use. It should be also noted that indicators of outcome strongly depend on the study population and are influenced by rates of positive outcome; therefore, their validity may vary in samples with greatly different rates of successful outcome. Inclusion/exclusion criteria and self-selection may further limit generalizability, although participant's demographics, characteristics of drug use, and psychiatry comorbidity were comparable with those of large samples of OUD individuals entering treatment,[39] as well as with OUD populations receiving naltrexone induction and XR-NTX treatment.[22,23,25] Given the limitations, the results of this study assume primarily an exploratory pilot significance. Despite all, this exploratory analysis is the first to indicate a relationship between measures of withdrawal severity and naltrexone and XR-NTX induction. Future research should consider these findings, address the optimal use of different methods of induction including its duration, and examine the predictive role of early withdrawal severity among patients requesting to transition from high levels of physiological dependence such as those on opioid maintenance therapy. Optimal withdrawal management is of particular importance among populations at risk such as medical and psychiatric comorbid patients, to provide a safe transition tailored to individual needs.

In sum, the development of clinical algorithms of early withdrawal management can expand the use of antagonist formulations in OUD and further the understanding of the relationship between initiating and remaining in treatment.

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Declaration of Interest

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