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A placebo-controlled trial of memantine as an adjunct to injectable extended-release naltrexone for opioid dependence

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ABSTRACT

There is preclinical support for using NMDA receptor glutamatergic antagonists to aid in naltrexone-based treatment of opioid dependence. We hypothesized that adding memantine will improve efficacy of extended-release (XR) naltrexone to prevent relapse. In this double blind study opioid-dependent participants ($N = 82$) underwent inpatient detoxification and naltrexone induction. During naltrexone initiation participants were randomized to receive memantine 40 mg or placebo and continued treatment for 12-weeks with XR naltrexone and relapse-prevention therapy. Sixty eight percent of participants completed detoxification and received the first dose of XR naltrexone. Rates of trial completion were significantly greater in participants receiving placebo than memantine (70% vs. 43%, $p < 0.05$). Severity of opioid withdrawal symptoms during the first 3 weeks of the trial appeared to be lower in the group receiving memantine ($p = 0.07$). Adding memantine does not appear to increase the effectiveness of injectable XR naltrexone as a relapse prevention strategy in opioid dependence and may lead to an increase in treatment drop-out.

1. Introduction

Rates of prescription opioids and heroin use and related morbidity continue to grow at an alarming rate (CDC, 2012; SAMHSA, 2013). Of those individuals that needed treatment for an illicit drug use problem less than 20% received treatment at a specialty medical facility (SAMHSA, 2013). Therefore, increasing access to specialty treatment for opioid dependent individuals and expanding available treatment options are important public health priorities (CASA Columbia, 2012).

An agonist-based strategy, particularly treatment with buprenorphine, is a most commonly used medical treatment approach. However agonists are not effective for all patients, as many individuals continue using opioids or drop out of treatment (Mattick, Kimber, Breen, & Davoli, 2008). Agonists are most effective when used as a long-term maintenance strategy but many, particularly younger patients and those with a brief history of opioid use, do not find this plan acceptable. Additional problems with unsupervised use of buprenorphine include medication non-compliance as well as misuse and diversion. Therefore, it is imperative to develop an alternative pharmacological approach to complement agonists in a response to the current epidemic of opioid dependence.

In 2012 FDA approved injectable, extended-release naltrexone (XR-NTX) to prevent relapse to opioid dependence, after opioid detoxification and therefore may be used as an alternative to maintenance treatment with opioid agonists; methadone and buprenorphine (SAMHSA, 2012). XR-NTX may be particularly useful for patients that are detoxified and have a high level of motivation for abstinence, those who are not interested in agonist treatment or had a poor response to treatment with agonists, as well as youth and patients with a brief history of opioid dependence (SAMHSA, 2012). However, due to clinical difficulties initiating naltrexone, very few patients are at present able to benefit from it (Sigmon et al., 2012).

It is difficult to induce patients with physiological opioid dependence onto XR-NTX because its antagonism at mu-opioid receptors can precipitate opioid withdrawal. To optimize the likelihood of compliance with XR-NTX, it is best to start naltrexone at the completion of the acute phase of opioid withdrawal. This is preferably done in the inpatient setting to minimize treatment drop-out and to assure close monitoring while aggressively treating residual opiate withdrawal. However, the effectiveness of this approach is limited by persistent opiate withdrawal symptoms that do not sufficiently respond to standard medications and often result in treatment dropout. Following XR-NTX administration and discharge to outpatient care, some patients continue to struggle with protracted withdrawal and craving during the first weeks of treatment. Such patients typically do not return for subsequent injections and eventually relapse. Therefore a medication that targets signs and symptoms emerging during early phase of treatment may further improve the outcome of this antagonist-based strategy to prevent relapse.

One of the candidate medications is memantine, an antagonist at the glutamatergic NMDA receptor. Effects of memantine in animal

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models of opioid dependence suggests that it may be effective in reducing opiate withdrawal and preventing relapse in opiate-dependent individuals (Harris, Rothwell, & Gewirtz, 2008; Popik, Wrobel, & Bisaga, 2006). Similarly, positive results were obtained in human laboratory models (Bisaga et al., 2001; Comer & Sullivan, 2007) and in a small controlled clinical trial (Krupitsky et al., 2002) (Krupitsky et al., 2002). Subsequently we conducted a randomized, placebo-controlled trial of memantine (30 or 60 mg/d) combined with oral naltrexone 50 mg/d and weekly individual therapy as a relapse prevention strategy for opioid-dependent individuals who completed detoxification. We found no significant difference in treatment retention, heroin use or craving between memantine and placebo groups (Bisaga et al., 2011). In this earlier trial there was a substantial dropout during the inpatient phase and first month of outpatient treatment, which limited the duration of exposure to study medication. Because of the abundance of preclinical evidence supporting effectiveness of memantine we have decided to replicate the study using an optimized study design. We used an extended-release injectable naltrexone, which improves treatment retention as compared to oral naltrexone (Krupitsky et al., 2012) and we used a single target dose of memantine (40 mg/d) and started it earlier during naltrexone induction. We hypothesized that patients treated with XR-NTX in combination with memantine would remain in treatment longer and will have less opioid use than patients receiving XR-NTX in combination with placebo.

2. Methods

2.1. Participants

Treatment-seeking individuals were evaluated at Columbia University's Substance Treatment and Research Service (STARS) outpatient clinic. Clinical screening included the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) (SCID Axis I/P version; (First, Spitzer, Gibbon, & Williams, 1995) and a clinical interview assessing substance abuse severity. Individuals between 18–60 years old, who met DSM-IV criteria for current dependence on heroin or prescription opioids, completed a psychiatric evaluation and medical assessments. Medical evaluations included history, laboratory tests, electrocardiogram (ECG), and a physical examination. Individuals with unstable medical or psychiatric disorders were excluded. Other exclusion criteria were: 1) history of opioid overdose; 2) ongoing treatment with prescription opioids for chronic pain or medical illness; 3) regular use of methadone; 4) physiological dependence on alcohol or sedative-hypnotics; 5) current participation in another psychotherapy or substance abuse treatment program or currently prescribed psychotropic medications; 6) pregnancy, lactation, or failure to use adequate contraceptive methods in women as detoxification procedure may pose risk to a fetus and the effect of naltrexone or memantine treatment has not been determined. Enrolled participants provided informed consent, and all study procedures were in accord with the standards of the New York State Psychiatric Institute IRB.

2.2. Study procedures

Participants were admitted to an inpatient unit at the New York State Psychiatric Institute for the purpose of medically assisted opioid withdrawal and initiation of treatment with XR-NTX. We used a brief course of buprenorphine followed by a slow naltrexone induction procedure. Participants were stabilized on buprenorphine for 1–2 days, followed by a washout period of 1 day, then given an increasing daily dose of naltrexone (3.125 mg, 6.25 mg, and 25 mg), while precipitated withdrawal symptoms were treated with clonidine, clonazepam, and other adjuvant medications (Sigmon et al., 2012).On the second day of naltrexone induction, participants started receiving placebo or memantine with the target dose of 40 mg/day (or the maximum tolerated dose). XR-NTX (Vivitrol 380 mg) was administered intra-muscularly on the fourth day of the naltrexone induction. Participants were discharged with small supplies of, and tapering schedules for adjunctive medications that they had been receiving in the hospital (clonidine, trazodone, and zolpidem).

Participants continued outpatient treatment for 12 weeks, attending the clinic three times per week and continuing with XR-NTX and study medication (memantine or placebo). All participants received two additional doses of XR-NTX at weeks 4 and 8. Throughout the 12 weeks of the study, participants received two medication capsules twice daily, each containing memantine 10 mg or placebo, and encapsulated with 25 mg of riboflavin. Randomization schedule was prepared by a research pharmacy while participants and study personnel were blind to study medication assignment.

During each visit, participants gave an observed urine specimen and completed self-report measures of drug and alcohol use, craving, and mood. All urine specimens were tested on-site for a full toxicology panel including morphine and oxycodone, and two samples per week were sent to the laboratory for quantitative toxicology levels. Urine samples were observed under UV light for riboflavin fluorescence, indicating compliance with study medication. Pregnancy status was assessed with serum test before beginning treatment, and a urine test monthly thereafter. Blood was drawn monthly for memantine serum levels. A research nurse obtained vital signs, collected safety measures to assess for side-effects, and recorded medication compliance. Participants met with a research psychiatrist once per week to monitor their progress in treatment, and review medication safety and adherence. Participants were reimbursed $15 in vouchers for transportation and completion of research assessments at each visit. Participants who missed at least six consecutive visits, thereby stopping memantine/placebo for at least 2 weeks, were classified as study drop-outs.

All participants met individually with a therapist once a week for a manualized therapy that included motivational and cognitive–behavioral elements adopted from behavioral naltrexone therapy (BNT) (Rothenberg et al., 2002). Therapy sessions were audio-taped for supervisory and adherence purposes, in addition to weekly supervision sessions to prevent therapeutic drift.

2.3. Outcome measures and data analyses

The primary outcome of the study was the retention in the 12-week trial (time to drop out in weeks). Secondary outcomes were: weekly proportion of participants who used opiates (dichotomous), weekly proportion of participants who were rated as asymptomatic on Clinical Global Impression (CGI) severity score (dichotomous), weekly proportion of participants who had cravings (defined as any craving score >0 during the week; dichotomous), weekly ratings of opiate withdrawal symptoms (SOWS: Subjective Opiate Withdrawal Scale: continuous), and weekly ratings of depression symptoms (HAM-D 21: Hamilton rating scale for depression: continuous), controlling for baseline HAM-D.

Retention rates were compared using Kaplan–Meier Curves and log-rank statistics. A cox proportional hazards model was used to obtain hazard ratio estimates between the two treatment arms. Longitudinal secondary outcomes were analyzed using mixed effect models (fixed and random effects) with appropriate link functions. The mixed effects model is an available-case method of analysis that provides accurate estimates of treatment effects when dropout and missing data are present. The two-way interaction between treatment and time (i.e., week) was assessed and was retained in the final models if found to be significant. All interaction terms were evaluated at a significance level of 15%. PROC GLIMMIX in SAS was used to conduct these analyses. All analyses were conducted based on the