Published in final edited form as:
J Subst Abuse Treat. 2014 ; 46(5): 546–552. doi:10.1016/j.jsat.2014.01.005.

A PLACEBO-CONTROLLED TRIAL OF MEMANTINE AS AN ADJUNCT TO INJECTABLE EXTENDEDRELEASE 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 40mg 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 three 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.

Keywords

Opiate dependence; Pharmacotherapy trials; Naltrexone; NMDA receptors; Memantine

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

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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 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 60mg/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 we 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, 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 40mg/day (or the maximum tolerated dose). XR-NTX (Vivitrol 380mg) 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 10mg 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 two 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 intent-to-treat principle. All statistical tests were two-tailed and employed an alpha significance level of 0.05, unless otherwise stated.

Safety of the treatment was evaluated based on reports of adverse events (AEs). The incidence of treatment-emergent AEs was defined as AEs that occurred after the first administration of study medication. The overall incidence of treatment-emergent AEs described as moderate or severe was compared between treatment arms using chi-square tests or Fisher's exact tests. A Data and Safety Monitoring Board met at the middle point of the study to review enrollment, overall treatment response, and medication tolerability.

3. Results

3.1. Sample description

We screened in person 557 individuals for eligibility and 88 were enrolled in the study (See Figure 1 for the CONSORT Flow Diagram). Of those who were screened, 197 individuals declined to participate (150 failed to complete the evaluation and were lost to follow-up, 43 were not interested in inpatient detox or treatment medications, and 4 wanted immediate treatment), and 173 individuals were not eligible to participate (76 had significant medical problems, 24 had significant psychiatric co-morbidities, 6 were taking other psychotropic medications, 52 were interested in agonist-based treatment and 15 were not eligible for other reasons). In addition, 105 participants entered other naltrexone treatment studies concurrently running at our clinic.

In summary, only 35% of patients initially interested in treatment, remained interested, eligible, and eventually entered treatment studies with XR-naltrexone. Lack of interest in antagonist-based treatment accounts for 53% of screening drop-outs. Based on our interviews with those participants it appears that that the major obstacle relates to alternatives that most individuals are very familiar with: 1) treatment with buprenorphine that does not involve inpatient stay, and 2) a widely shared belief that no medication for relapse prevention is needed once the person is detoxified. The second main reason for screening failure are research exclusion criteria, designed to minimize risk for exacerbation of the concurrent medical or psychiatric problem while undergoing detoxification (22% of screened participants). This most commonly includes participants with untreated/unstable hypertension, diabetes, or asthma but also psychotic or bipolar disorder. A rapid opioid detoxification poses a significant stress on the physiology and participants with pre-existing medical or psychiatric problems may become unstable and unable to complete the naltrexone induction.

A total of 82 individuals consented to the study and entered the inpatient unit. On average participants were 42 years of age (SD=17.0), mostly male (82%), and either White (48%) or Hispanic (33%). Participants reported using on average 9.8 bags of heroin per day (SD=6.6),

over half (52%) reported using heroin intra-nasally, and 15 participants (18%) used prescription opioids.

Twenty-seven (33%) of participants admitted to the hospital decided to withdraw from study participation during detoxification. Participants were stratified based on their age; 36 years and younger (younger users) vs. 37 years or older (older users), and their baseline level of opioid use; 5 or less bags/d (light use) vs. 6 or more bags/d (heavy use), clinical characteristics that were predictive of clinical outcome in previous studies (Sullivan et al., 2006). The stratification framework yielded four classification cells: older/heavy use (n=31), older/light use (n=15), younger/heavy use (n=26), younger/light use (n=10). Within each stratum participants were randomized 1:1 to two study arms; memantine 40mg (n=28) and placebo (n=27). Demographic characteristics of the randomized participants are presented in Table 1. There were significant differences between groups found in the following variables: Race/Ethnicity, baseline cocaine use, and baseline alcohol use.

3.2. Primary outcome: retention in treatment

Of the 55 randomized participants, 80% (n = 44) completed at least 4 weeks of treatment, and 56% (n = 31) completed all 12 weeks of the trial. The survival curves in Fig. 2 describe retention in treatment for the placebo and memantine groups along with 95% confidence limits. Retention to week 12 was higher in PBO (70%), compared to memantine (43%) group. A significant difference in survival was found between the treatment arm and placebo arm (Log-Rank Chi-Square 3.95, p = .047). The proportional hazards model shows that patients in the treatment arm were 2.3 times as likely to drop out compared to patients in the placebo arm (HR = 2.30, 95% CI = (0.98, 5.38), Chi-Square = 3.67, p = .056). Of the 28 patients randomized to memantine 96% (n=27) received the first XR-NTX injection, 64% % (n=18) received the second, and 46% (n=13) received the third. Among the 27 placebo patients, 96% (n=26) received the first XR-NTX injection, 70% (n=19) received the second, and 63% (n=17) received the third.

Among the 24 randomized participants who dropped out of the trial, one left prior to completing detoxification, 18 stopped attending the clinic appointments and most likely resumed opiate use, 3 continued heroin use over prolonged period of time and were referred to the agonist-based treatment, one stopped taking study medication citing ongoing withdrawal symptoms, one moved out of state, and one was removed by investigators after hospitalization for psychiatric worsening. There were no differences between those who completed the trial and those who dropped in demographic or clinical characteristics, except for completers having more years of education (t(50)=2.89, p=0.035).

3.3. Secondary outcomes

3.3.1. Opiate use—Approximately 64% of participants used opiates at least once during the month following the first injection, and 43% used opiates during the month following the second injection. The proportions of participants who used opiates during the trials were not significantly different across the two treatment groups (p = 0.11). A significant time effect (p = 0.002) suggests that the proportion of participants who used opiates decreased in both arms over the 12-week trial. This decrease was comparable across treatments, as no

significant interaction between treatment and time was found. Early opiate use was explored as a predictor of retention to end of study, but no significance was found. Of participants who used opiates during the first month of treatment, 36% completed treatment as compared to 23% rate of treatment completion among participants who did not use during the first month of treatment (p=0.37). Of participants who used opiates during the second month of treatment 32% of those who used after the 2nd injection completed treatment as compared to 46% of treatment completers who did not use and also completed treatment (p=0.21). Overall, the median of the percent of positive urines for the subjects in the memantine group was 9% (IQR = 3%–40%), and for the subjects in placebo group was 10% (IQR = 0%–19%).

3.3.2. Withdrawal symptoms—Figure 3 displays the weekly mean severity of self-reported withdrawal symptoms in both groups. The withdrawal severity decreased over the duration of the trial. There was a significant interaction between treatment and week (p = . 006), suggesting the pattern of improvement was different between the two groups. The interaction appears to be due to the memantine group displaying lower withdrawal scores in the first 3 weeks of the study, and higher withdrawal scores during the remaining weeks compared to the placebo group (a crossover effect see figure 2). Contrast between the groups was investigated for the first 3 weeks of the trial, which showed a marginally significant p-value (p=0.07).

3.3.3. Craving and Depression—No significant difference in craving was observed across the two treatment arms (p = 0.81), although a significant time effect (p= 0.007) suggests that the proportion of individuals with any level of craving intensity decreased considerable for both treatment groups throughout the course of the trial. No significant time-by-treatment interaction was found. HAM-D depression scores did not differ between individuals in the treatment group and individuals in the control group throughout the trial (p = 0.62). A significant time effect (p <0.0001) suggests that HAM-D improved in individuals in both treatment arms over the 12-week trial. No significant interaction was found.

3.3.4. Clinical Global Impression (CGI)—CGI severity scores did not differ between the treatment groups (p = 0.54). There was, however, a statistically significant time effect (p = 0.002), indicating that the CGI severity scores improved over time over time in both groups, suggesting that patients remaining in treatment had lower severity of disease. No significant treatment by time interaction was found.

3.4. Medication adherence

Compliance with oral medication was assessed at each visit using a structured calendar-based interview to record the number of capsules taken, and confirmed using a visual inspection of urine samples for riboflavin fluorescence. Medication compliance was quantified as the proportion of days with compliance of 80% or more capsules taken. The median rate (and interquartile range) of medication adherence was 86% (34–100%) for the placebo group, and 80% (41–91%) for the memantine group. There were no significant differences in medication adherence between the two groups (p = .48). Blood samples were collected at weeks 4, 8, and 12 as an additional assessment of memantine levels. Memantine

levels were measured in 71% of participants that remained in treatment at week 4. No memantine was detected in participants randomized to receive placebo. The mean memantine blood level, measured in 64% of the memantine group was 62.3 ng/ml (SD 39.0; range 5 to 164) confirming that although participants were generally compliant with memantine, there was a wide range of compliance.

Blood level was also obtained for naltrexone and its active metabolite 6-beta-naltrexol (Table 3). The mean concentration for naltrexone was always above 2 ng/mL, which is considered to sufficient for its therapeutic effects (Comer, Sullivan, & Hulse, 2007). There was no significant difference in the mean serum levels of NTX and 6BN between memantine and placebo treated individuals and mean levels of naltrexone and 6BN were no different for study completers vs. those that dropped out prior to study completion.

3.5. Medication tolerability, and adverse effects

The mean maximum tolerated dose of memantine (of the maximum 4 capsules per day, each containing memantine 10mg or placebo) was 3.3 ± 1.5 capsules/day in the memantine group, 3.8 ± 0.5 capsules/day in the placebo arm. Seven participants required dose reductions, with two from the placebo group, and five from the memantine group. This was not a significant difference (p=.25). One participant was discontinued from study medications in the memantine group due to ongoing withdrawal effects. The most frequent reasons given for dose reductions were insomnia, fatigue, headaches and dizziness.

Ninety-one percent of the memantine group, and 71% of the placebo group reported experiencing at least one adverse effect of at least moderate severity (Table 2). There were no significant differences between treatment groups (p= .086). Adverse effects were not measured in 16% of participants, all of whom dropped shortly following discharge from the hospital. Most of the adverse effects occurred during the first two weeks following naltrexone initiation, suggesting they were likely the result of protracted opiate withdrawal. None of the reported effects were sustained and there were no participants who reported discontinuing study participation because of AEs. There were no differences between treatment groups at the end of treatment in terms of blood pressure (SBP and DBP), heart rate, respiration, oral temperature, and weight.

There was one serious adverse event (SAE) that occurred in this study. The SAE occurred following discharge in a participant treated with memantine 40mg. The participant attended two outpatient visits, and was removed from the study due to psychiatric worsening (irritability, insomnia, and disorganized thinking).

4. Discussion

This randomized, placebo-controlled trial suggests that memantine (40mg/d), is not effective in reducing early attrition and decreasing opioid use in individuals maintained on long-acting naltrexone combined with weekly psychotherapy. In fact, participants who received memantine were more likely to drop out of treatment prematurely than participants receiving placebo. There were no significant differences between groups in the proportion of participants using opiates, CGI ratings, opiate craving, and ratings of depression between the

two groups over the 12 weeks of the trial. However, severity of opioid withdrawal symptoms during the first three weeks of the trial appeared to be lower in the group receiving memantine. The frequency of adverse effects, most of which occurred during the first two weeks following detox, was comparable between both groups. This finding suggests that they were most likely the result of protracted withdrawal, and not effects of the memantine. A similar adverse effects profile was observed in our earlier trial with oral naltrexone, in which, again, no significant differences were detected between treatment conditions (Bisaga et al., 2011).

This is the second clinical trial that did not support the very promising results of preclinical studies and early clinical trials suggesting the beneficial effects of memantine in treatment of opioid dependence. In the present trial we have made design changes to maximize the potential of the trial to test the efficacy of memantine. We introduced memantine early in treatment so that participants were expected to have therapeutic dose and experience benefits of the medication starting early during the introduction of naltrexone and we used an extended form of naltrexone to increase chances that participants remain in treatment to experience benefits of adjunctive memantine. The severity of withdrawal was lower in the group treated with memantine in the early weeks of treatment, which is consistent with preclinical and early clinical studies (Bisaga et al., 2001; Krupitsky et al., 2002; Popik & Skolnick, 1996). However administering memantine had no impact on the retention in treatment. Actually, after the first month of the trial, the severity of withdrawal-like, possibly medication-induced aversive symptoms was greater in the group receiving memantine, which might have contributed to the higher rate of treatment drop-out. Therefore the side-effects profile of memantine may counteract its presumed beneficial effects when used over extended period of time but perhaps it may still be clinically beneficial if it was used only during the first 2–3 weeks of the trial. In addition, a main advantage of treatment with XR-NTX is to provide a therapeutic level of medication that is sustained over a long period of time and obviates the need for a daily compliance with oral medication. With that, there might be a limited usefulness of adjunctive medications that need to be taken daily unless this is limited to a relatively short time period. It is therefore possible that memantine, given during the first few weeks of treatment, could still play a clinically significant role in treatment. Memantine might also be useful when used as an adjunct to a detoxification regimen that does not include naltrexone. Future studies could concentrate on the efficacy and the mechanism of memantine’s effect used alone or as an adjunct to a standard treatment regimen to facilitate opioid detoxification and during the initiation of treatment with naltrexone.

Compared to our earlier trial that used memantine in combination with oral naltrexone (Bisaga et al., 2011), participants treated with XR-NTX were more likely to remain in treatment at week 4 (80% this trial vs. 35% prior trial), and complete all 12 weeks of treatment (56% vs. 24%). This confirms findings from other studies showing the advantage of extended-release versus daily oral preparations of naltrexone (Hulse, Morris, Arnold-Reed, & Tait, 2009; Krupitsky et al., 2012).

More then 60% of participants used opiates early in treatment following the first injection of XR-NTX, and more than 40% used after the second injection however many of them

remained in treatment, and the rate of treatment completion was not different in users as compared to those who did not use following initiation of naltrexone. In the present study blood levels of naltrexone were sufficient to provide full blocking effect, which is essential in the first months of treatment when most of blockade testing takes place. The fact that testing blockades early in treatment was not detrimental to the treatment outcome is reassuring and consisted with previous reports (Foster, Brewer, & Steele, 2003; Sullivan et al., 2013). These findings have an important clinical implication supporting the continuing monthly administration of XR-NTX in participants who are using opiates early in treatment, but remain blocked by naltrexone. Many, perhaps most such patients will be able to initiate abstinence later in treatment if naltrexone is continued. Considering this, it appears that a course of two XR-NTX injections represents a minimum duration of treatment with XR-NTX, but most likely a longer duration of treatment will be necessary to guarantee long-term abstinence. Alternatively, for participants who do not have easy access to the XR-NTX, treatment may include transitioning to oral preparations of naltrexone after the first two injections.

The failure to confirm beneficial effects of memantine on treatment retention might be related to the limitations of preclinical animal and early clinical studies in predicting treatment outcome for participants that are treated on outpatient basis with opioid antagonist (Bisaga et al., 2011; Haney, 2009). For example, the preclinical studies may not be able to model the motivation to continue self-administration of an antagonist, which is one of the core features of this type of treatment. A previous human laboratory study showed that memantine attenuated heroin craving but not heroin reinforcing effects which may be more relevant to detect medications effective in preventing relapse (Comer & Sullivan, 2007). This suggests that we need to develop preclinical and early clinical models of antagonist-based treatment of opioid dependence for the purpose of testing putative efficacy of adjunctive medications. The opioid antagonist naltrexone, in long-acting injectable form, is an important addition to the armamentarium of medications for preventing relapse to opioid dependence, a group with high risk for overdose and other poor outcomes, and more research is needed on adjunctive treatments to improve its efficacy.

In summary, the present findings partially supported beneficial effect of memantine on opioid withdrawal and during the initiation of treatment with naltrexone. However, the present findings did not support the efficacy of memantine as a relapse prevention strategy when used in combination with extended-release naltrexone for 12 weeks. Extending the duration of treatment with memantine beyond the first month may actually lead to increase in treatment drop-out. Injection naltrexone itself continues to appear promising as a treatment alternative for opioid dependence.

Acknowledgments

Funding for this study was provided by NIDA grant DA15822 (Dr. Bisaga) and K24 DA022412 (Dr. Nunes). The NIDA had no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; or in the decision to submit the paper for publication.

Drs. Bisaga and Nunes designed the study and wrote the protocol. Dr. Bisaga was study Principal Investigator and wrote the first draft of the manuscript. Mr. Glass conducted statistical analyses and prepared the Results section of the manuscript. Ms. Mishlen was a study coordinator, prepared data for analyses and prepared Methods section of

the manuscript and Tables. Drs. Bisaga, Sullivan, Carpenter, Mariani, Levin, and Nunes implemented the study protocol. All authors contributed to and have approved the final manuscript.

We wish to thank Nabil Khan, Daniel Brooks and the staff of STARS treatment program as well as the pharmacy staff for their contribution to this project.

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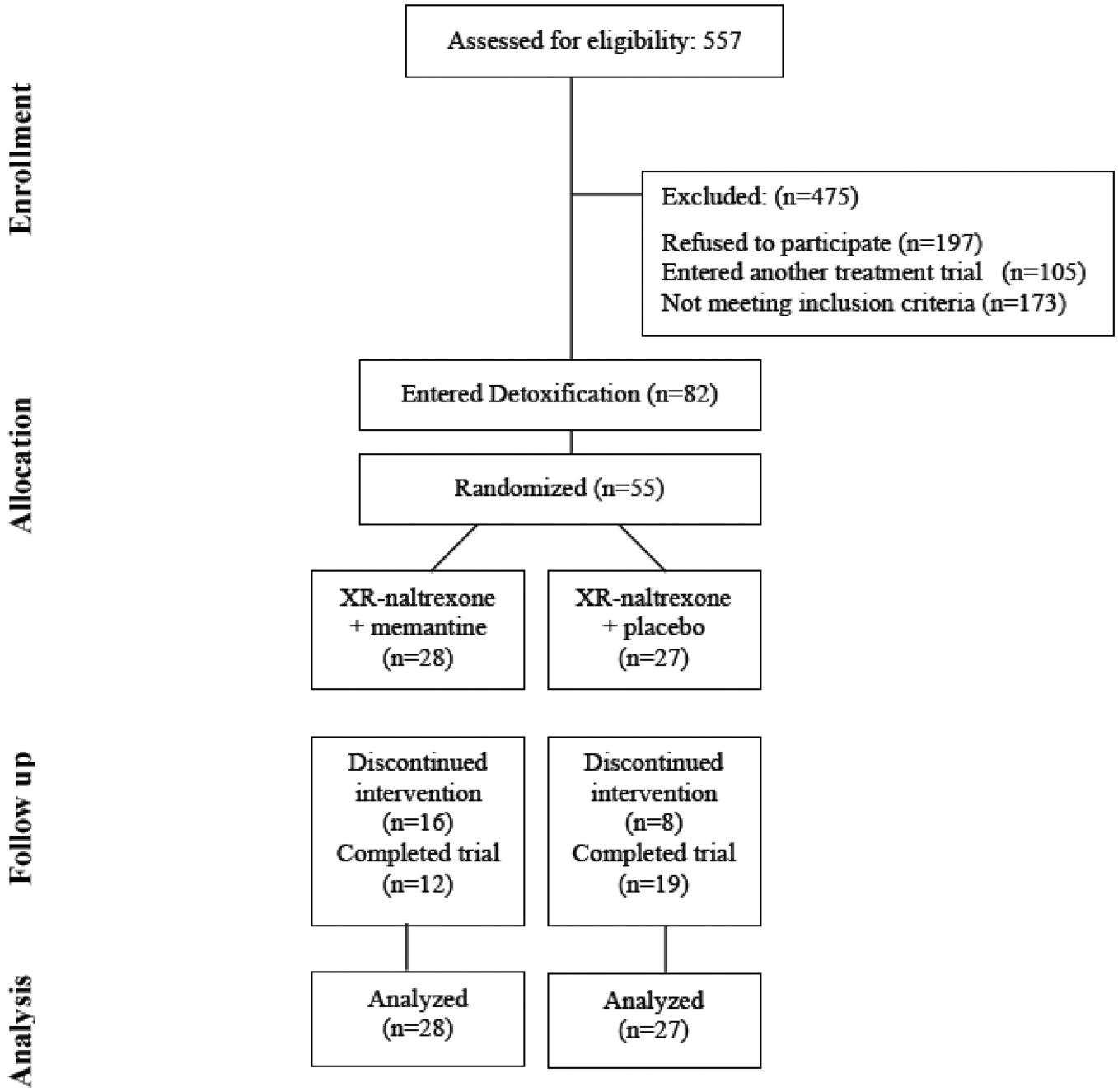

Figure 1.
Consort diagram summarizing participant flow

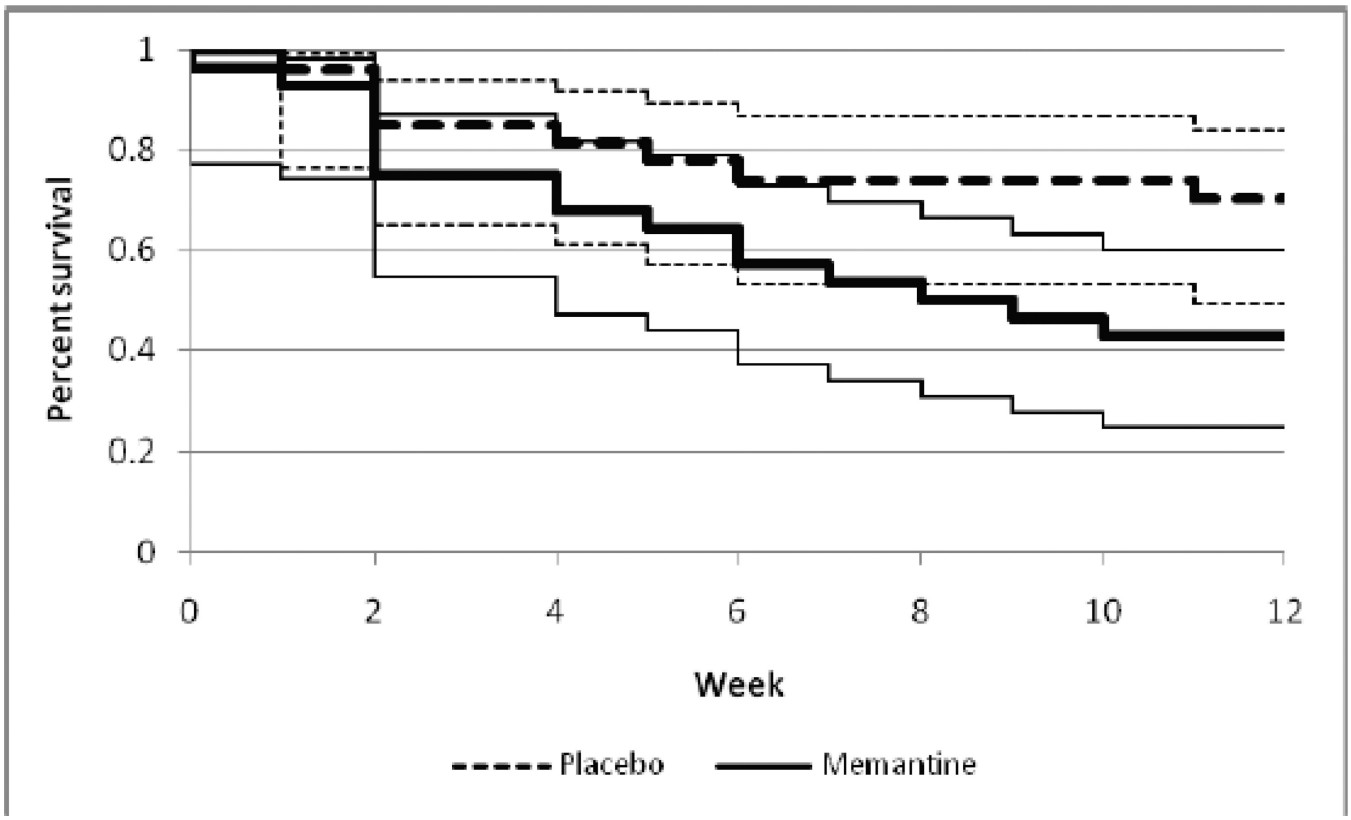

Figure 2.

Kaplan-Meier curve of patient retention throughout the 12-week medication trial by treatment condition with 95% confidence limits.

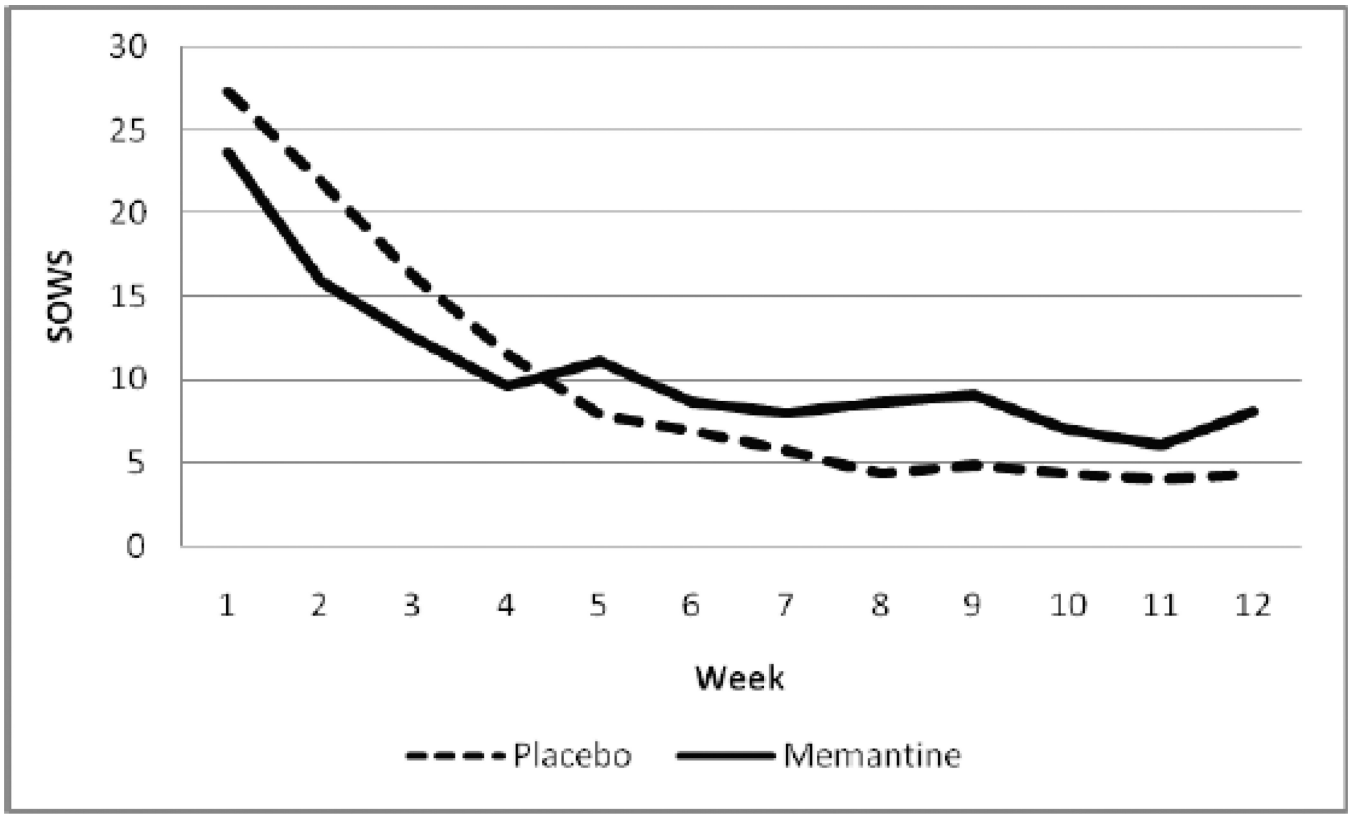

Figure 3.
Observed SOWS scores throughout the 12-week medication trial by treatment condition

Table 1

Demographic characteristics of the participants randomized to placebo or memantine (N=55)

	Placebo	Memantine	
Characteristic	**(n=27)**	**(n=28)**	**p-value**
	mean (SD) or n (%)		
Age (years)	39.0 (11.5)	39.7 (12.0)	0.82
Male	20 (74.1)	24(85.7)	0.28
Race/Ethnicity			0.03
White	15 (55.6)	10 (35.7)	
Black	6 (22.2)	3 (10.7)	
Hispanic	5 (18.5)	15 (53.6)	
Other	1 (3.7)	0 (0)	
Education			0.09
Less than or equal to high school	9 (33.3)	16 (64.0)	
Some college	12 (44.4)	6 (24.0)	
College or more	6 (22.2)	3 (12.0)	
Employment status			0.76
Full-time	6 (24.0)	4 (15.4)	
Part-time	3 (12.0)	3 (11.5)	
Unemployed/others	16 (64.0)	19 (73.1)	
Currently married	6 (22.2)	8 (32.0)	0.43
Pattern of opiate use at baseline			
Duration of use (years)	12.0 (10.7)	13.3 (11.8)	0.68
Amount of daily use (bags)	8.6 (5.0)	10.6 (7.7)	0.27
Intravenous route	8 (36.4)	11(47.8)	0.44
Prescription opiate users	5 (18.5)	5 (17.9)	0.95
Baseline drug and alcohol use			
Cocaine			
Any use in last 30 days	13(48.1)	5(17.8)	0.01
Alcohol			
Any use in last 30 days	17(62.9)	8(28.5)	0.01
Marijuana			
Any use in last 30 days	8(29.6)	13(46.4)	0.20

* Frequencies may not sum to N=55 due to missing values. Three patients did not report their education, marital status and four patients did not report employment status. Percentages may not add up to 100 due to rounding.

Table 2

Summary of Adverse Events reported as moderate or severe, in greater than 5% of randomized participants (n=46)*

	Number (%) of participants	
	Placebo (N=24)	**Memantine (N=22)**
Number of Participants who were removed from trial because of SAEs*	0	1
Number of Participants with at least 1 TEAE*	17	20
Number of Participants requiring dose reduction	2	5
Number of Participants requiring discontinuation of medication	1	1
*TEAEs**		
Insomnia	13(54.1)	17(77.2)
Mood Changes	9(37.5)	7(31.8)
Increase/decreased appetite	5(20.8)	6(25.0)
Fatigue/drowsiness	8(33.3)	7(31.8)
Nausea/Vomiting	4(16.6)	1(4.5)
Diarrhea	7(29.1)	3(13.6)
Headache	4(16.6)	2(9.09)
Body Aches	6(25.0)	4(18.1)
GI Distress	7(29.1)	4(18.1)
Sweating/chills	5(20.8)	2(9.09)
Faintness/dizziness	3(12.5)	2(9.09)

*Reports of AEs were missing from 9 participants

**AE, adverse event, SAE, serious adverse event; TEAE, treatment-emergent adverse event. No significant differences were detected between treatment conditions.

Table 3

Mean concentration of naltrexone and 6-beta-naltrexol in the serum of participants *

	Naltrexon (ng/mL) Mean (SD)	6B Naltrexol (ng/mL) Mean SD
Week 1	6.05 (4.40)	11.99 (8.77)
Week 2	3.55 (2.41)	8.45 (7.73)
Week 3	3.46 (2.59)	6.20 (2.93)
Week 4	2.43 (1.53)	5.39 (4.55)
Week 8	2.27 (1.87)	5.38 (4.89)
Week 12	3.33 (2.22)	5.83 (3.86)

* Extended-release naltrexone (380 mg i.m.) was administered at the beginning of weeks 1, 4, and 8. Blood for medication level was collected at the end of given week