HHS Public Access

Author manuscript

Drug Alcohol Depend. Author manuscript; available in PMC 2016 November 01.

Published in final edited form as:

Drug Alcohol Depend. 2015 November 1; 156: 243–253. doi:10.1016/j.drugalcdep.2015.09.020.

Memantine improves buprenorphine/naloxone treatment for opioid dependent young adults

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Abstract

Background—Opioid use disorders are considered a serious public health problem among young adults. Current treatment is limited to long-term opioid substitution therapy, with high relapse rates after discontinuation. This study evaluated the co-administration of memantine to brief buprenorphine pharmacotherapy as a treatment alternative.

Methods—13-week double-blind placebo-controlled trial evaluating 80 young adult opioid dependent participants treated with buprenorphine/naloxone 16-4 mg/day and randomized to memantine (15mg or 30mg) or placebo. Primary outcomes were a change in the weekly mean proportion of opioid use, and cumulative abstinence rates after rapid buprenorphine discontinuation on week 9.

Results—Treatment retention was not significantly different between groups. The memantine 30mg group was significantly less likely to relapse and to use opioids after buprenorphine discontinuation. Among participants abstinent on week 8, those in the memantine 30mg group (81.9%) were significantly less likely to relapse after buprenorphine was discontinued compared to the placebo group (30%) ($p < 0.025$). Also, the memantine 30mg group had significantly reduced opioid use (mean = 0, SEM ± 0.00) compared to the placebo group (mean = 0.33, SEM ± 0.35; $p < 0.004$) during the last 2 weeks of study participation.

Conclusions—Memantine 30mg significantly improved short-term treatment with buprenorphine/naloxone for opioid dependent young adults by reducing relapse and opioid use after buprenorphine discontinuation. Combined short-term treatment with buprenorphine/naloxone

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Conflicts of Interest

All authors declare that they have no conflicts of interest.

Contributors

Dr. Gonzalez designed the study and protocol. Drs. Gonzalez, DiGirolamo and Romero-Gonzalez conducted the statistical analysis and prepared the results section of the manuscript. Drs. Gonzalez, DiGirolamo, and Kolodziej implemented the study protocol. Dr. Gonzalez was the study Principal Investigator and wrote the first draft of the manuscript. All authors made significant contributions and approved the final manuscript.

may be an effective alternative treatment to long-term methadone or buprenorphine maintenance in young adults.

Keywords

Memantine; Buprenorphine; Opioid dependence; Early relapse; Young adults

Introduction

Opioid use disorders are considered a serious public health problem that is associated with increased morbidity and mortality (Degenhardt et al., 2014; Im et al., 2015; Larney et al., 2015; Yokell et al., 2014). While the recent rate of heroin use in the general population has remained relatively stable, with perhaps even some slight reduction in the use of prescription opioids among 12th graders in 2014 (Johnston et al., 2015), the last-year prevalence of heroin (~0.7%, MTF) and prescription opioid use (8.8%, NSDUH) among young adults is disproportionately elevated (Johnston et al., 2014; SAMHSA 2014). With this increased opioid usage among young adults, optimized treatment is necessary. Currently, medication-assisted treatment with μ-opioid agonist continues to be the most effective treatment for opioid use disorders with the strongest evidence of its beneficial effects during active substitution (Gonzalez et al., 2004). However, after medication discontinuation, there is a high risk of relapse (>50%) despite prolonged treatment duration (Gandhi et al., 2003; Kornor et al., 2006, 2007), and adjunctive psychotherapy (Weiss et al., 2011; Woody et al., 2008). This high post-substitution relapse rates among young opioid dependent patients is problematic, perhaps suggesting the need to recommend medication-assisted treatment indefinitely. However, long-term or lifetime opioid substitution therapy is unlikely to be the optimal solution. Creating additional active interventions, combining treatments or sequencing multiple interventions should be investigated to change or reverse elements of opioid using behavior that improve post-substitution outcomes. This need may be especially important for young adults whose treatment options may entail far more extended or life-long substitution medication, and uncertainty about the long-term effect of substitution medication on the developing brain. Thus, the development of a shorter treatment option different from detoxification or maintenance may be particularly relevant for younger adults who are still in neural development, relatively treatment naïve, likely to have a briefer period of addiction due to their age, and may be reluctant to commit to long-term substitution treatment. Shorter substitution therapy combined with other medications may help reduce opiate usage during treatment and improve post-substitution outcomes. One promising line of research suggests that medications that modulate glutamatinergic inputs (and a short-term opioid substitution) are a potential alternative to long-term substitution treatment alone.

The modulation of glutamate neurotransmission has been identified as having an important role in the development of physical dependence and sensitization to the chronic administration of opioids, and may have clinical implications for the treatment of opioid dependence. Trujillo and Akil (1991,1994) showed that modulation of glutamate input with co-administration of a non-competitive NMDA receptor antagonists in rodents attenuated the development of tolerance to the analgesic effects of morphine, without affecting acute

morphine analgesia. The co-administration of the non-competitive NMDA medication also led to a reduction in the development of dependence to morphine as assessed with naloxone-precipitated withdrawal. Memantine (mem), an uncompetitive open-channel NMDA receptor antagonist which is FDA approved for the treatment of dementia, is a good candidate to modulate glutamate neurotransmission. Memantine has a short binding time and off-rate from the channel that limits pathological activity of the NMDA receptor while sparing normal synaptic activity (Chen and Lipton, 1997, 2005; Chen et al., 1992; Lipton, 2004), and may interact with a partial mu-agonist (e.g., buprenorphine) to modify opioid using behavior and relapse. Several lines of evidence suggest effectiveness of a co-administration of memantine to reduce opioid usage.

First, a series of pre-clinical studies evaluated the effect of memantine on its ability to modify opioid using behavior in animal models. The co-administration of memantine reduced the development of opioid tolerance (Popik et al., 2000) and reduced the expression of opioid dependence (Popik and Skolnick, 1996). Memantine also suppressed the self-administration of morphine (Semenova et al., 1999) and inhibited the expression of morphine-conditioned place preferences (Popik et al., 2005). Finally, co-administered memantine also alleviated the expression of withdrawal after acute doses of morphine (Harris et al., 2008) and inhibited the development of sensitization to the locomotor stimulant effects of morphine (Mendez and Trujillo, 2008). These preclinical studies suggested that co-administration of memantine had the ability to change key elements associated with opioid using behavior.

Clinical studies also supported the use of memantine in the treatment of opioid dependence. Bisaga and colleagues (2001) showed that a single 60 mg dose of memantine reduced the expression of opioid withdrawal symptoms among opioid-dependent patients who had been stabilized on oral morphine (30 mg q.i.d) when acutely withdrawn. Another study (Comer and Sullivan, 2007) evaluated the administration for 2–3 weeks of three doses of memantine (0, 30 & 60mg per day) on the effects of intranasal heroin administration (0, 12.5, & 50mg) in heroin users and showed that memantine reduced the subjective effects of 12.5 mg of heroin. A third study (Krupitsky et al., 2002) evaluated treatment with memantine (titrated to 30mg/day over 3 weeks) in heroin dependent subjects who completed a one week in-patient detoxification, and found that memantine reduced protracted withdrawal and early relapse. While these studies support the use of memantine for the treatment of opioid dependence, two other studies that evaluated the MOR antagonist naltrexone with memantine yielded negative results (Bisaga et al., 2011, 2014).

The objective of this study was to evaluate the extent to which the interaction of buprenorphine and memantine treatment could improve the overall reduction of opioid use and prevent early relapse with the goal to investigate a voluntary shorter-term buprenorphine treatment alternative for young adults. Our first hypothesis was that memantine would significantly reduce opioid use during the 13 weeks of treatment compared to placebo. The second hypothesis was that the combination treatment of memantine with buprenorphine would significantly reduce opioid use during the 7 weeks of the stabilization period beyond the efficacy of buprenorphine alone. The third hypothesis was that the combination treatment of memantine and buprenorphine would reduce early opioid use relapse after rapid

buprenorphine discontinuation at week 9 compared to buprenorphine alone. Finally, since the short course of buprenorphine treatment was voluntary and chosen by the participants over other treatment alternatives, we anticipated good completion rates regardless of their opioid use status after buprenorphine discontinuation.

Method

Participants

Eighty treatment seeking opioid-dependent individuals between the ages of 18 to 25 years old, actively using opioids (heroin or opioid analgesics), were recruited for this study. Recruitment was done by newspaper advertising, referrals from the UMass Addiction and Comorbidity Treatment Service (ACTS), and from community-based substance abuse treatment clinics. This study was approved by the UMass IRB and followed the Declaration of Helsinki for the protection of human research. Interested individuals were initially interviewed by phone to review basic study eligibility and invited for a full screening. Following the consent process, participants were screened for DSM-IV criteria for opioid, or other substance dependence (SCID; First et al., 1995), clinically assessed with physical and psychiatric evaluations, electrocardiogram, laboratory tests, urine drug tests and Addiction Severity Index (ASI; McLellan et al., 1992, 1980). All participants were also educated, counseled and screened for HIV and Hepatitis C, and completed a Brief HIV Risk Questionnaire (Copersino et al., 2010). A study physician reviewed all the screening information and enrolled participants who were aware of the study design and motivated to participate in this brief 9-week treatment with buprenorphine – naloxone. These opioid dependent subjects were actively using opioids or heroin as evidenced by self-report and having a positive urine drug test for opioids or oxycodone at intake, but negative for buprenorphine and benzodiazepines. Other exclusion criteria were (1) current diagnosis of other drug or alcohol dependence (other than cannabis or tobacco); (2) presence of serious medical illness (e.g., major cardiovascular, renal, endocrine, or hepatic disorders); (3) diagnoses of current serious psychiatric disorders or history of psychosis, schizophrenia, bipolar type I disorder, or current suicidal or homicidal thoughts; (4) currently being treated with psychotropic medications; (5) women who were pregnant, nursing or refused to use a reliable form of birth control or refused monthly pregnancy testing; and (6) liver function tests greater than 3 times normal.

Study Design

These 13-week randomized double-blind, placebo-controlled, parallel groups had an induction, stabilization and discontinuation phases. Baseline data was collected during the 1st week of the study. Individuals were inducted onto a fixed dose of buprenorphine-naloxone (16mg-4mg/day) after stopping all opioid use and displaying mild to moderate opioid withdrawal (COWS ≥ 8) while also testing negative for benzodiazepines. Buprenorphine-naloxone treatment was continued at this fixed dose until the end of week 8 and discontinued during week 9 of the study. Concurrent with buprenorphine administration and starting on week 2, participants were randomly allocated to memantine or placebo using an URN randomization (Wei and Lachin, 1988) procedure to balance the treatment groups on their severity of dependence (SDS; Gossop et al., 1997, 1995), gender and years of

opioids use (Table 1). Treatment with memantine remained at their full dose through week 12 and then was discontinued on week 13. All participants received group cognitive-behavioral therapy on a weekly basis delivered by a clinical psychologist trained in CBT and relapse prevention. Subjects attended the clinic on Tuesdays on every week throughout the study, provided supervised urine samples, performed assessments, participated in group therapy, and received weekly supplies of buprenorphine-naloxone and study medications.

Medications

2.3.1—*Memantine* (Namenda; Forest Pharmaceuticals, Inc) was purchased by the research pharmacy and a compounding pharmacy prepared the doses and matching placebo with blue opaque capsules (size 00). In addition, riboflavin (5mg) was added to each capsule (active and placebo) to check for compliance of study medication. These groups started receiving 5mg of memantine (Mem) in the morning of the first day on week 2. The dose was titrated on a twice a day schedule until the target doses of 15 mg/day or 30 mg/day were achieved by week 4. The medication was discontinued over a one-week period on week 13. Patients received a 7-day supply of their medications each week.

The rationale for the dosage selection was based on the recommended dose of memantine for the treatment of dementia that ranges from 10 to 30 mg/day, and most studies started with low doses and progressively increased to 20 mg/day (Areosa et al., 2005; Rossom et al., 2004). Dosage in efficacy studies for Huntington's disease (Beister et al., 2004) and pain (Sang et al., 2002) are in this same dose range. Daily doses between 5mg and 30mg of memantine had serum levels that ranged from 0.025 to 0.529 microM, and CSF levels were highly correlated to these serum levels (Kornhuber and Quack, 1995).

2.3.2—*Buprenorphine-naloxone* tablets (Suboxone; Rieckett Benkkiser Pharmaceuticals) were purchased by the research pharmacy. Participants were instructed to hold the tablets under their tongue until the tablets had dissolved. On day 1 the dose was bup/nal 8mg/2mg, increased to bup/nal 12mg/3mg on day 2, and then increased to bup/nal 16mg/4mg on day 3 where it will remain until the last day of week 8. Participants were observed for one hour on the first day of induction and received a 7-day supply of medication each week. The 7-day discontinuation of bup/nal on week 9 was 12mg, 10mg, 8mg, 6mg, 4mg, 2mg, 2mg and then stopped.

The rationale to discontinue bup/nal at week 9 was two-fold: (i) We were interested in evaluating the extent to which the interaction of the NMDA antagonist memantine with a partial mu-receptor agonist administered for 7 weeks would reduce relapse; and (ii) we selected a 1-week discontinuation schedule based on a discontinuation study showing no significant difference between 7 to 30 day schedules (Ling et al., 2009).

Group Cognitive Behavioral Therapy

The cognitive-behavioral treatment was delivered by an experienced psychologist using the 12 week, 90 minute sessions "Group Drug Counseling Manual" by Daley and colleagues (Daley et al., 2004). This treatment manual was initially developed for the NIDA Collaborative Cocaine Treatment Study (Crits-Christoph et al., 1999), and was subsequently

used and adapted in a variety of clinical research studies (Weiss et al., 2007). The session topics focused on understanding addiction and the recovery process, establishing a support system, managing feelings, coping with high-risk situations, and preventing relapses. Each session followed the procedures to enhance motivation and emphasize commitment to practicing skills acquired in the group sessions (Carroll, 1997). This behavioral counseling intervention across treatment groups was important because it: (1) reduces noise variance in treatment delivery so that the memantine effect can be detected, (2) facilitates treatment retention and memantine/placebo compliance, and (3) delivers enhanced treatment to all participants in the placebo-controlled trial.

Efficacy assessments

The primary outcome variable was the change of the mean proportion of weekly opioid use as determined by self-report and urine drug screen. Self-reported days of opioid use during the previous week for opioid analgesics and/or heroin use was assessed using the time-line followed-back method (TLFB; Ehrman and Robbins, 1994). A urine drug screen result at the end of each week was used to verify the self-reported use of the previous week. Urine samples were screened for opiates, oxycodone, buprenorphine, methadone, and other drugs of abuse. The urine samples were observed under UV light for riboflavin fluorescence that indicated adherence with study medication. Participants scored 100% opioid use if they reported using any opioid each day of the previous week and had positive urine for opiate, oxycodone or methadone at the end of the week. Participants were given a score of 1 for each day of reported opioid use, and a score of 1 for positive opioid urine for that week. Hence, Participants scored 100% if they reported 7 days of use and had positive opioid urine, totaling a score of 8. All other scores less than a 100% were the total score divided by the 8 potential points. Efficacy outcomes also included: (a) survival abstinent curves of participants who were abstinent at week 8 (mean proportion opioid use = 0) after the rapid discontinuation of buprenorphine assessed by any opioid use event (mean proportion opioid use > 0) as measured by the primary outcome variable; and (b) mean proportion of opioid use averaged during the last two weeks of the study.

In addition, other secondary outcomes included retention in treatment, together with the change from baseline to weeks 8 and 13 on repeated measures of opioid withdrawal symptoms measured by the Clinical Opiate Withdrawal Scale (COWS; Wesson and Ling, 2003) and Opiate Withdrawal Symptom Checklist (OWS; Kosten et al., 1985); opioid craving measured by Heroin Craving Questionnaire-Short Form-14 (HCQ-SF-14; Heinz et al., 2006; Singleton, 1998) and Visual Analog Scale (VAS) for intensity and frequency of craving for heroin and opioid analgesics adapted for opioids from Kampman (1998); and depression symptoms measured by the Center for Epidemiologic Studies Depression Scale (CESD; Radloff, 1977). To assess the effect of memantine on cognition, we also measured impulsiveness as measured by the Barratt Impulsiveness Scale (Patton et al., 1995) and cognitive control measured using the anti-saccade task (Evdokimidis et al., 2002; Hallett, 1978) as a measure of the control over impulsive behavior (Blaukopf and DiGirolamo, 2005) at baseline and week 8.

Tolerability and safety variables

Tolerability and safety were assessed weekly by nursing staff with vital signs, a questionnaire with specific symptoms related to potential side effects of memantine, laboratory test and close assessment of emerging adverse events during the study. In addition, we evaluated the change of symptoms with the Brief Symptom Inventory (BSI; Derogatis, 1993; Derogatis and Melisaratos, 1983).

Statistical Analyses

The primary analyses were conducted on the intent-to-treat sample (n=80) that received at least one dose of study medication. The independent variable was the treatment condition: memantine 30 mg/day plus buprenorphine/naloxone (mem 30mg), memantine 15mg/day plus buprenorphine/naloxone (mem 15mg) and placebo plus buprenorphine/naloxone (PL). The analyses proceeded in several stages. (1) Baseline differences were determined by using Pearson chi-square tests for categorical variables and ANOVA for continuous variables in the randomized groups to use as covariates in subsequent analyses. (2) Treatment retention was determined by using Kaplan-Meier estimates (Kaplan and Meier, 1958) and differences in treatment groups using Mantel-Cox log rank tests (Peto and Peto, 1972). (3) Change of opioid use was evaluated by modeling the mean proportion of opioid use using a mixed-effect linear regression approach to assess the time effect, treatment effect and the interaction of time × treatment effect while adjusting for baseline opioid use with COWS, ASI psychiatric, and legal composite scores as covariates (Hedeker and Gibbons, 1996). The treatment effect on the primary outcome was evaluated in four separated models that included: i) data from week 1 to week 13 for overall treatment effect; ii) data from week 2 to week 13 for the effect after buprenorphine induction; iii) data from week 2 to week 8 during stabilization; and iv) data from week 8 to week 13 for the effect after buprenorphine discontinuation while appropriately adjusting for opioid use and covariates for each of these models. These mixed-effect regression models are designed to account for unbalanced repeated measures with missing data, allowing for intra-subject serial correlation and unequal variance and covariance structures across time. Thus, missing data was handled by inclusion in all these models capable of dealing with missing data without being imputed. (4) The survival curves (remaining abstinent) after rapid discontinuation of buprenorphine was compared using Kaplan-Meier estimates (Kaplan and Meier, 1958) and differences in relapse rates with the last observation carried forward (LOCF) among those in the treatment groups that achieved abstinence at week 8 using Mantel-Cox log rank tests (Peto and Peto, 1972). (5) The effect of treatment across time on secondary outcomes was evaluated by performing mixed-effect regression models on OWS, COWS, HCQ-SF-14, VAS, CES-D. (6) To evaluate between group differences of the primary and secondary outcomes at the end of treatment, ANOVAs were calculated on the average response across the last 2 weeks of treatment. Also, the differential of the measure from baseline to week 8 for Barratt Impulsiveness Scale and cognitive control measure was evaluated with ANOVA. (6) The tolerability and safety was determined by comparing the rates of side effects / adverse events with chi-square tests among treatment groups and performing a mixed-effect regression model on BSI. All analyses were two-tail and statistical significance was set at a p-value < 0.05.

Results

Sample selection

A total of 354 potential subjects were assessed for study eligibility of which 125 young adults with opioid dependence were screened for study participation and 87 subjects were enrolled and randomized to receive the study medication. Thirty-eight of the candidates screened were not eligible or failed to complete the screening procedures. While 87 subjects were initially randomized, 80 subjects were the modified intent-to-treat sample included in the final analyses (Fig. 1). Data from seven subjects were not included because their study medication was stopped after a routine check from the research pharmacy initially identified inconsistencies in the concentration of memantine in those capsules, which were later verified as containing the correct concentration by two external laboratories using capsules from the same lot.

Baseline demographics and clinical characteristics

Participants were on average 22 ± 1.9 years old, predominately single Caucasian males (66%), with high school degree or GEDs (40%), or had some years of college (44%). As shown in Table 1, these participants had a relative short duration of opioid use with 78.8% using non-prescription opioid analgesic by nasal inhalation for an average of 3 years, and 21.2% using heroin intravenously for an average of 1 year. The sample scored high in the severity of dependence scale for opioids (mean = 11.5 ± 2.4), were likely to be depressed (CES-D score; mean = 22.4; SD = 9.9), impulsive (mean = 70.8; SD = 11.3), and were assessed to make 21% errors in the anti-saccade task, that is double the errors made by same age control participants (Munoz et al., 1998). In addition, all treatment groups reported substantial problems on the ASI composite scores on drug use (mean = 0.34; SD = 0.08) and employment (mean = 0.48; SD = 0.27). There were baseline differences among participants that showed a trend of mem 30mg group to have lower ASI legal scores ($F_{(2, 71)} = 2.7$, $p = 0.07$), but to have a significantly higher ASI psychiatric scores ($F_{(2, 76)} = 3.2$, $p < 0.05$).

Treatment retention and compliance

The retention during the stabilization phase was above 85% until week 8, then after discontinuation of buprenorphine on week 9, it dropped to 50% on week 10. The completers of the study were 21 subjects (25%) at week 13. The Kaplan-Meier survival analysis showed that the placebo group remained in the study for an average of 9.7 weeks (95% CI 8.6 – 10.6), the mem 15 mg group remained in the study for an average of 9 weeks (95% CI 7.8 – 10.3) and mem 30mg group remained in the study for an average of 9.3 weeks (95% CI 8.3 – 10.2) with no significant difference in retention between treatment groups (log rank = 0.874; $p = 0.64$). In addition, the verification of medication compliance by fluorescence of riboflavin in weekly urine samples showed over 82.2% compliance with no significant difference between groups. The study completers were significant less impulsive than non-completers as measured by Barratt Impulsiveness with scores of 65.3 (SD = 11) compared to 72.7 (SD = 10) ($p < 0.02$), respectively. All other demographic and key clinical variables between completers and non-completers were not significant.

Treatment effect on opioid use

Overall effect—The weekly mean proportion of opioid use was significantly reduced over time for the memantine 30mg group compared to both the memantine 15mg and the placebo groups ($Z = -2.62$; $p < 0.009$). As shown in Fig. 2, all the groups as expected had a sharp reduction in opioid use after induction onto bup/nal on the first week. The mem 30mg group started with a mean proportion of use of 0.75 (SEM ± 0.04) on week 1 that decreased to a mean proportion of use of 0.00 (SEM ± 0.0) on week 13. Compared to the placebo group that had a mean proportion of use of 0.73 (SEM ± 0.04) on week 1 and reduced their use to 0.39 (SEM ± 0.14). The mem 15 mg group underperformed during the combination treatment (2 to 8 weeks) as seen in the Fig. 2, as this group started with a mean proportion of 0.71 (SEM ± 0.06) on week 1 and ended with a mean proportion of 0.27 (SEM ± 0.10). The mem 15mg group did worse than the other two groups indicated by significant separation on week 5 and 8 ($p < 0.001$ for each of these two weeks). The results of the mixed-effects regression model for repeated measures, while adjusting for baseline opioid use and covariates showed a significant effect of group ($Z = 2.07$, $p < 0.04$) and a significant effect of time ($Z = -2.68$; $p < 0.008$). Both of these effects are, however, qualified by a significant time by group interaction ($Z = -2.62$, $p < 0.009$). All groups improved over time but the mem 30mg group significantly reduced its opioid use over time more than either the placebo or mem 15mg group (Fig. 3A displays the linear regressors of the treatment groups × time from the mixed-effect model). This overall effect is likely driven by the strong reduction in opioid use for the mem 30 group that occurred after buprenorphine discontinuation.

Effect after buprenorphine induction—As mentioned above, buprenorphine treatment had a dramatic effect in reducing opioid use during the first week such that we also evaluated the treatment effect after this improvement. The results of the mixed-effects regression model from week 2 to 13, while adjusting for opioid use on weeks 1 and 2 and baseline covariates showed a significant time effect ($Z = 5.9$, $p < 0.001$) and significant time by group interaction ($Z = -3.18$, $p < 0.002$). Fig. 3B displays the linear regressors of the groups × time showing that the placebo and mem 15mg groups worsen their opioid use over time after the initial drop in opioid usage after induction, while the mem 30mg group appears to remain stable even after buprenorphine discontinuation on week 9.

Effect during short stabilization—The results of the effect during the combination treatment memantine with buprenorphine on opioid use during the short stabilization phase showed a significant time effect ($Z = 2.05$, $p < 0.04$), and a marginal significant interaction of group by time effect ($Z = -1.71$, $p = 0.08$) while adjusting for opioid use and baseline differences. Fig. 3C displays the linear regressors of the treatment groups × time during this period showing the slight reduction of opioid use of mem 30mg group and worsening of the placebo group with an interaction at week 8.

Effect after buprenorphine discontinuation—The results of the model evaluating opioid use from week 8 to week 13 and after buprenorphine was rapidly discontinued on week 9, showed a significant main effect ($Z = 3.2$, $p < 0.002$), time effect ($Z = 5.2$, $p < 0.0001$) and group by time interaction ($Z = -3.5$, $p < 0.0004$). Fig. 3D shows that the memantine 30mg group reduced opioid use over time, while the placebo and mem15 groups

were more likely to increase their opioid use after discontinuation of buprenorphine. In addition, there was a significant difference between groups on the mean proportion of opioid use during the last two weeks of the study ($F_{(2, 35)} = 4.9$, $p = 0.013$) (Fig. 2). Planned comparisons demonstrated significant difference of the mem 30mg group (mean = 0, SEM ± 0.00) compared to the placebo group (mean = 0.33, SEM ± 0.35; $p < 0.004$) and approaching significance compared to the mem 15mg group (mean 0.22, SEM ± 0.2; $p = 0.06$).

Treatment effect on relapse prevention—The results of the survival analysis among those who achieved abstinence at week 8 with the combination treatment (placebo = 10, mem 15mg = 3 and mem 30mg = 11) were used to evaluate the treatment effect on preventing early relapse after the rapid buprenorphine discontinuation that occurred on week 9. Using this approach (Fig. 4), 81.9% (9/11) of mem 30mg group were significantly more likely to remain abstinent compared to the placebo group (30%, 3/10) (Log Rank = 5.1, $p < 0.025$) and marginally significant compared to the mem 15mg/day group (33%, 1/3) (Log Rank = 3.14, $p = 0.07$).

Treatment effect on secondary outcomes

Craving for opioids—The change of weekly scores of craving for opioids (HCQ-SF-14) were significantly reduced over time for the mem 30mg group compared to the other two groups during the 13 weeks ($Z = -2.97$, $p = 0.002$) and significantly attenuated after buprenorphine was discontinued ($Z = -3.82$, $p = 0.0001$), but there were no significant differences between groups before buprenorphine discontinuation. The attenuation effect of mem 30mg on craving was mainly after buprenorphine discontinuation as this group scored 2.7 (SEM ± 0.25) on week 8 that remained unchanged to an average of 2.7 (SEM ± 0.25) during the last 2 weeks compared to placebo that increased from 2.4 (SEM ± 0.23) to 3.46 (SEM ± 0.32), and mem15mg that was barely reduced from 3.4 (SEM ± 0.23) to 3.2 (SEM ± 0.69). During the last 2 weeks, average craving scores were significantly different between the groups ($F_{(2, 38)} = 5.4$, $p < 0.009$). Planned comparisons showed the mem 30mg group had significantly less craving compared to the placebo ($p < 0.004$) or the mem 15mg ($p < 0.03$) group. In addition, the weekly Visual Analog Scale (VAS) scores of the intensity of craving for opioids also showed a similar medication × time interaction where the mem30mg group had a significantly greater improvement than the mem 15mg and placebo groups for the 13 weeks ($Z = -2.1$, $p < 0.04$), before buprenorphine discontinuation ($Z = -1.8$, $p = 0.05$), and a significant attenuation after buprenorphine discontinuation ($Z = -2.0$, $p < 0.05$). The weekly VAS for frequency of craving for opioids was also significant reduced for mem30mg over time compared to placebo for the 13 weeks ($Z = -2.0$, $p < 0.05$) and significantly attenuated after buprenorphine discontinuation ($Z = -2.04$, $p < 0.05$) compared to placebo, but not significantly different when compared to both placebo and mem15mg groups.

Opioid withdrawal symptoms—The change of weekly scores for opioid withdrawal symptoms (COWS) were significantly attenuated for the mem 30mg group after buprenorphine was discontinued compared to placebo and mem15mg groups ($Z = -1.9$, $P < 0.05$) and when compared to placebo group alone ($Z = -2.12$, $p < 0.04$). The mem 30mg

group scored 1.67 (SEM ± 0.38) on week 8, which increased to the highest peak score of 3.1 (SEM ± 0.4) at week 11 and ended with score of 1.4 (SEM ± 0.6) on week 13. This compared to the placebo group that scored 2.25 (SEM ± 0.5) on week 8, had a peak score of 5.1 (SEM ± 1.2) on week 12 and ended with score of 2.17 (SEM ± 1); and the mem 15mg group that scored 2.5 (SEM ± 0.5) on week 8, had a peak score of 3.5 (SEM ± 0.5) on week 11 and ended with 1.5 (SEM ± 0.6). There were no significant between group differences during the last 2 weeks.

Impulsivity, cognitive control and depressive symptoms—The Barratt Impulsivity measure attentional subscale was marginally significantly reduced from baseline to week 8 for the mem 30mg group (−5.9%) compared to worsening of the mem15 group (5%) and of the placebo group (6.5%) ($F_{(2, 39)} = 2.9$; $p = 0.06$). The cognitive control measure (% pro-saccade errors) was improved by the mem 30mg group on average by 26%, compared to the mem 15mg group (10%) and to the placebo group that had a 9.5% worsening on this measure, but these differences did not reach statistical significance. All groups improved on their depressive symptoms (CES-D) with no significant difference between groups.

Side effects and adverse events—There were no serious adverse events, no pregnancy test was positive, and there were no deaths or need to remove any participant from the study for safety reasons. There were a total of 118 reports of different symptoms, side effects, or adverse events throughout the study across all the treatment groups with no significant difference in the number of occurrences between the placebo (N= 49 reports), mem 15mg group (N = 30 reports) and mem 30mg (N = 39 reports) ($X^2 = 10.5$; df = 44; $p = 0.7$). The problems most reported (> 5%) were pain 21%, upper respiratory infection 9.3%, nausea 7.6%, vivid dreams 6.7%, constipation 5.9%, headaches 5%, and drowsiness 5%. The placebo group had the highest frequency of reporting pain (12.7% versus 4.2% mem groups), and nausea (4.2% versus 1.7% mem groups). The Mem 15mg group had the most frequent reporting of headaches (2.5% versus 1.7% Pl group), and the Mem 30mg group reported the most upper respiratory infection (4.2% versus 3.2% Pl group) and constipation (3.3% versus 0.8% Pl group). The reports of experiencing vivid dream were shared equally by placebo and mem 30mg (2.5%). All three groups reported the same frequency for drowsiness (1.6%). All the treatment groups reduced the symptoms assessed by the Global Symptom Inventory of Brief Symptom Inventory from baseline to week 13, and there were no significance difference between groups.

Discussion

Memantine 30mg/day significantly improved short-term treatment with buprenorphine/naloxone compared to either a lower dose of memantine or placebo in treatment seeking young adults with heroin and/or prescription opioid dependence after buprenorphine discontinuation. Young adults treated with memantine 30mg relapsed less frequently and reduced more opioid use during the last 4 weeks. Moreover, young adults in the 30 mg group who completed treatment were abstinent by the end of the study. This study was designed to evaluate the extent to which memantine together with buprenorphine/naloxone in a treatment program could be developed into a shorter treatment alternative for young adults with opioid dependence, and these initial results on relapse and opioid use after

buprenorphine discontinuation are encouraging. Memantine was well tolerated with no evidence of serious adverse events or other significant side effects.

These positive results related to the attenuation of opioid relapse are consistent with an earlier trial showing that memantine reduced both protracted withdrawal and early relapse in recently detoxified heroin dependent patients (Krupitsky et al., 2002). In addition, these results are supported by the preclinical studies that evaluated the effect of memantine in animal models of opioid addiction (Harris et al., 2008; Mendez and Trujillo 2008; Popik et al., 2000; Popik and Skolnick, 1996; Popik et al., 2005; Semenova et al., 1999). However, the results of the current study are not supported by two previous studies that evaluated two doses of memantine (30mg & 60mg) with oral naltrexone (Bisaga et al., 2011) and 40mg of memantine with intramuscular injection naltrexone (Bisaga et al., 2014) for opioid dependence that found no effect of memantine. There are some differences between the current memantine-buprenorphine study and the two memantine-naltrexone studies that can elucidate the different results. In the current data, the study population had a lower mean age (22 years versus ~40 years), a shorter duration of opioid dependence (3 years versus ~14 years), and the other two studies had different designs and primary outcomes.

The combination treatment of memantine and buprenorphine lasted for 7 weeks and during the short stabilization we found a marginally significant reduction of opioid use among the combined memantine 30mg with buprenorphine group compared to buprenorphine alone group (Fig. 3C). We hypothesized that the co-administration of the NMDA receptor antagonist memantine with the partial MOR agonist buprenorphine would further reduce opioid use beyond the efficacy of buprenorphine alone, but the results of this study are not conclusive. The short exposure of the combination treatment may in part explain this marginally significant result, and further studies may want to extend this period as the trend suggests an improvement in opioid use over time. During this short stabilization, the mem 15mg group underperformed the placebo and mem 30 group on opioid use with no clear explanation for this difference.

The major evidence of the effect of mem 30mg on opioid use was after the planned buprenorphine discontinuation on week 9, where mem 30 mg group reduced opioid use and achieved abstinence compared to both placebo and mem 15mg that worsened their opioid use. Additionally, memantine 30mg prevented relapse to opioid use among those who achieved abstinence on week 8. These results demonstrate that mem 30mg reduces early opioid use relapse after rapid buprenorphine discontinuation at week 9, and are consistent with the Krupitsky study (2002) that showed a reduction of relapse to heroin use with a three week memantine treatment after inpatient detoxification.

The other significant findings show that mem 30mg attenuates craving for opioids and reduces opioid withdrawal symptoms after rapid buprenorphine discontinuation. The attenuation of opioid withdrawal symptoms are also consistent with findings showing that memantine attenuated the expression of opioid withdrawal among inpatients who did not have access to opioids (Bisaga et al., 2001). While the results showed a significant attenuation of craving and opioids withdrawal symptoms after buprenorphine discontinuation, the difference between groups during the last two weeks was significant for

craving only and not opioid withdrawal. This non-significant difference on opioid withdrawal may be explained by the relapse to opioid use that suppressed opioid withdrawal symptoms among the mem 15mg and placebo groups.

The interaction of the glutamate and opioid systems in modifying opioid using behavior, preventing relapse, attenuating both craving for opioids and opioid withdrawal symptoms is very complex and not fully understood. However, a possible mechanism that may help explain the effect of the combination of memantine and buprenorphine is the existence of physical association and functional bidirectional interaction of MORs and NMDA receptors co-located on neurons throughout the brain implicated in modifying opioid using behavior, and the possible integrated regulatory loop operating between these receptors (Rodriguez-Munoz et al., 2012). Opioid ligands such as heroin (diacetylmorphine) are potent opioid agonists that activate the MOR but are deficient in their ability to induce the internalization and recycling of MOR (Keith et al., 1998; Whistler et al., 1999). Alterations of the MOR trafficking associated with the potentiation of NMDA receptor pathways regulate subsequent MOR signaling (Sanchez-Blazquez et al., 2013). Thus, a mechanism involved in recovery of the MOR function is transitioning from an opioid ligand with poor internalization to another ligand (buprenorphine/nor-buprenorphine) that can induce better MOR internalization (McPherson et al., 2010; Zaki et al., 2000), while simultaneously blocking the glutamate input with a NMDA receptor antagonist memantine to facilitate MOR signaling and recovery of these processes within a shorter period in preparation for the discontinuation of buprenorphine. This proposed model of recovery of the MOR function of buprenorphine with memantine during the stabilization period could also help explain, in part, why other studies that used medications without intrinsic activity on the MOR may have yielded negative results (Bisaga et al., 2011, 2014).

In addition, the attenuation of opioid withdrawal symptoms after buprenorphine discontinuation may be explained by the action of memantine on NMDA receptor signaling during excessive glutamate input. Increased synaptic release of glutamate within the interpeduncular nucleus (IPN) mediates activation of GABAergic neurons via NMDA receptor signaling during nicotine withdrawal, and using an NMDA receptor antagonist reduced the expression of somatic nicotine withdrawal symptoms (Zhao-Shea et al., 2013). Stimulation of the same GABAergic neurons in the IPN in non-dependent nicotine-naïve animals elicited the same somatic withdrawal symptoms suggesting that this may be a common withdrawal expression mechanism for other substances of abuse. Furthermore, there is evidence of an increase of glutamate release in the nucleus accumbens (NAc) during opioid withdrawal and administration of NMDA receptors and AMPA receptors antagonist reduces opioid withdrawal symptoms including craving (Chartoff and Connery, 2014; Shen and Kalivas, 2013). Thus, memantine may have reduced the expression of withdrawal symptoms by attenuating the activation of GABAergic neurons in the IPN and/or by reducing the NMDA receptors activity during the increase of glutamate release in the NAc. Memantine may also have enhanced treatment and helped participants manage their symptoms by a cognitive enhancement effect. This enhancement may be mediated by the ability of memantine to increase prefrontal dopamine (Meltzer et al., 1997; Spanagel et al., 1994), and improve cognitive control (Wroolie et al., 2009) as suggested by the marginally

significant reduction of impulsivity and the numerical increase in cognitive control in the Mem 30 group in our data.

The modest side effect profile and low emergence of adverse events support the safety of adding memantine 30mg/day to medication-assisted treatment with buprenorphine/naloxone for opioid dependence. This combination treatment was well tolerated with no indication of any cumulative effect of the exposure or any impact of worsening symptoms as measured by the brief symptom inventory. However, the rapid 1-week buprenorphine discontinuation component was either not well-tolerated or feared, which generated a high attrition rate among participants despite evidence of memantine 30mg attenuating opioid withdrawal and craving.

The strengths of this study include addressing novel treatment alternatives for young adult patients who are particularly complex due to a variety of biological, cognitive and social maturation factors. The study design emulated clinical practice by including only once a week attendance to the clinic that may facilitate extending the results to clinical settings. The study design also evaluated two doses of memantine against placebo with a fixed dose of buprenorphine. The limitations of the study include the use of a rapid buprenorphine discontinuation schedule that was associated with high attrition rates and a decrease in treatment retention. Also, the study design included 1 weekly urine sample assessment. Future studies evaluating shorter treatment alternatives for young adults should include a slower (4 weeks or longer) buprenorphine taper (Sigmon et al., 2013), thrice weekly visits for urine samples assessments, and a monetary incentive program to improve treatment retention and study completion. In addition, the duration of the exposure of 7 weeks to the combination of memantine and buprenorphine may have been too short, and a longer exposure may have yielded better results during the stabilization period.

The potential clinical implications of these results are: (1) this combination treatment may offer a shorter pharmacological treatment alternative for young adults who have less severity and duration of addiction to opioids; and (2) memantine may be add to patients already in treatment with buprenorphine by facilitating a discontinuation with a reduction in the risk of relapse for those who decided they wanted to discontinue buprenorphine treatment.

In summary, memantine 30mg significantly improved short-term treatment with buprenorphine/naloxone for opioid dependent young adults by reducing relapse and opioid use after buprenorphine discontinuation. However, the rapid buprenorphine discontinuation component was not well tolerated and promoted a high attrition rate that suggests that this component should not be included in future research or clinical treatment programs. These results are the first indication of a potential synergistic interaction between these medications in an outpatient setting that warrant an evaluation in a larger and modified study design before it can be considered an effective short-term treatment alternative for opioid dependent among young adults.

Acknowledgments

We would like to thank Chelsea Hinchey BA, Ethan Cochran BA, Irene Hill RN, Jacob Kagan MD, Amy Harrington MD, and Zafar Naqvi MD for their invaluable help and contributions for the successful completion of

this study. We also would like to thank Ann T. Hunt, DSc and Andrew Tapper, PhD for their helpful comments to an earlier version of the manuscript.

Role of Funding Source

Funding for this study was provided by NIDA grant R01DA027138 (G. Gonzalez) and 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.

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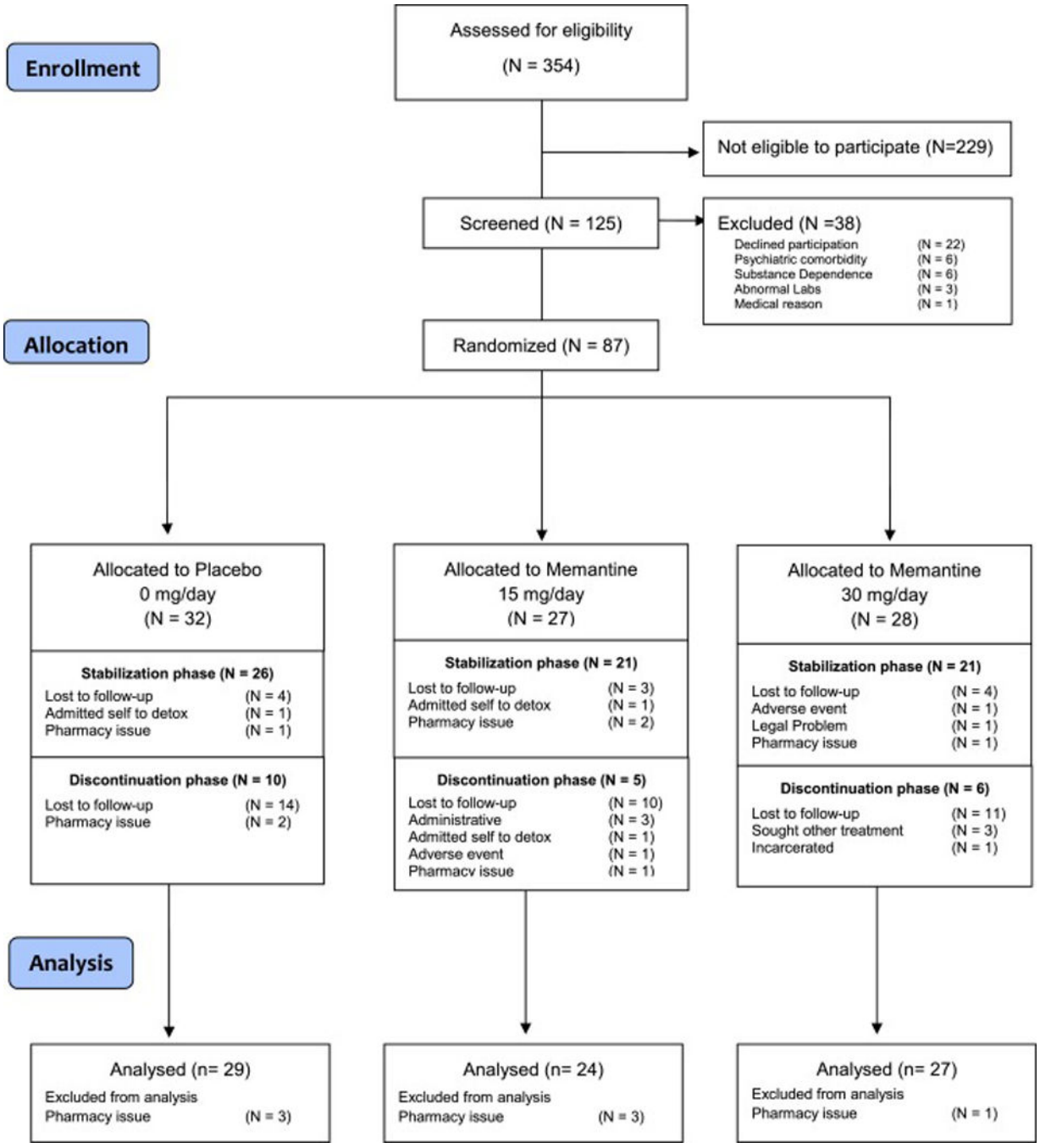

Fig. 1.
Consort diagram summarizing participant flow.

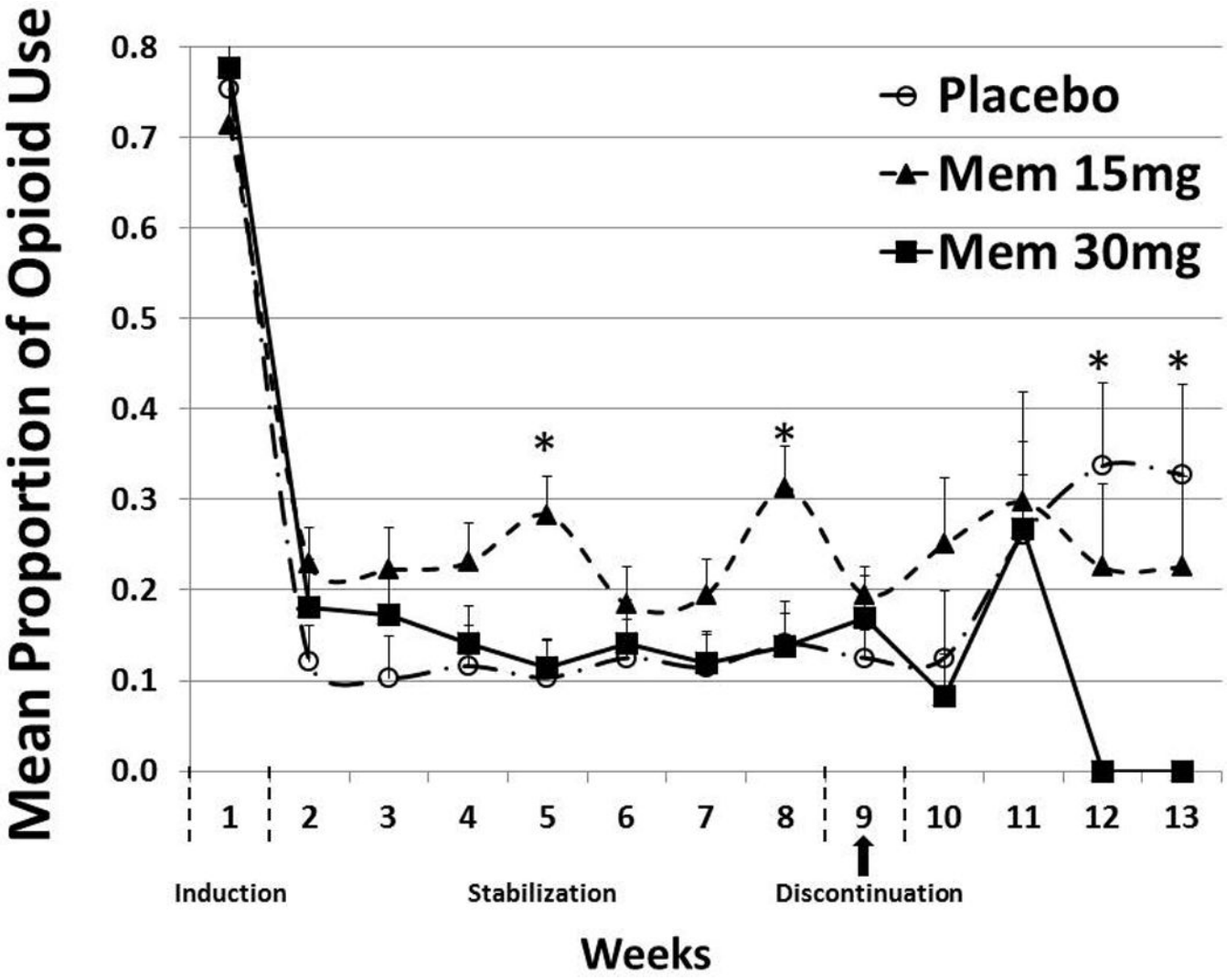

Fig. 2.

Change of weekly opioid use by treatment groups. Weekly mean proportion of opioid use by treatment groups during 13 weeks. Each data point is mean ± SEM and * signifies a significant difference between the groups during that week ($p < 0.05$). Participants were inducted, stabilized and then discontinued on buprenorphine as marked on bottom of figure. The arrow indicates the week buprenorphine was discontinued.

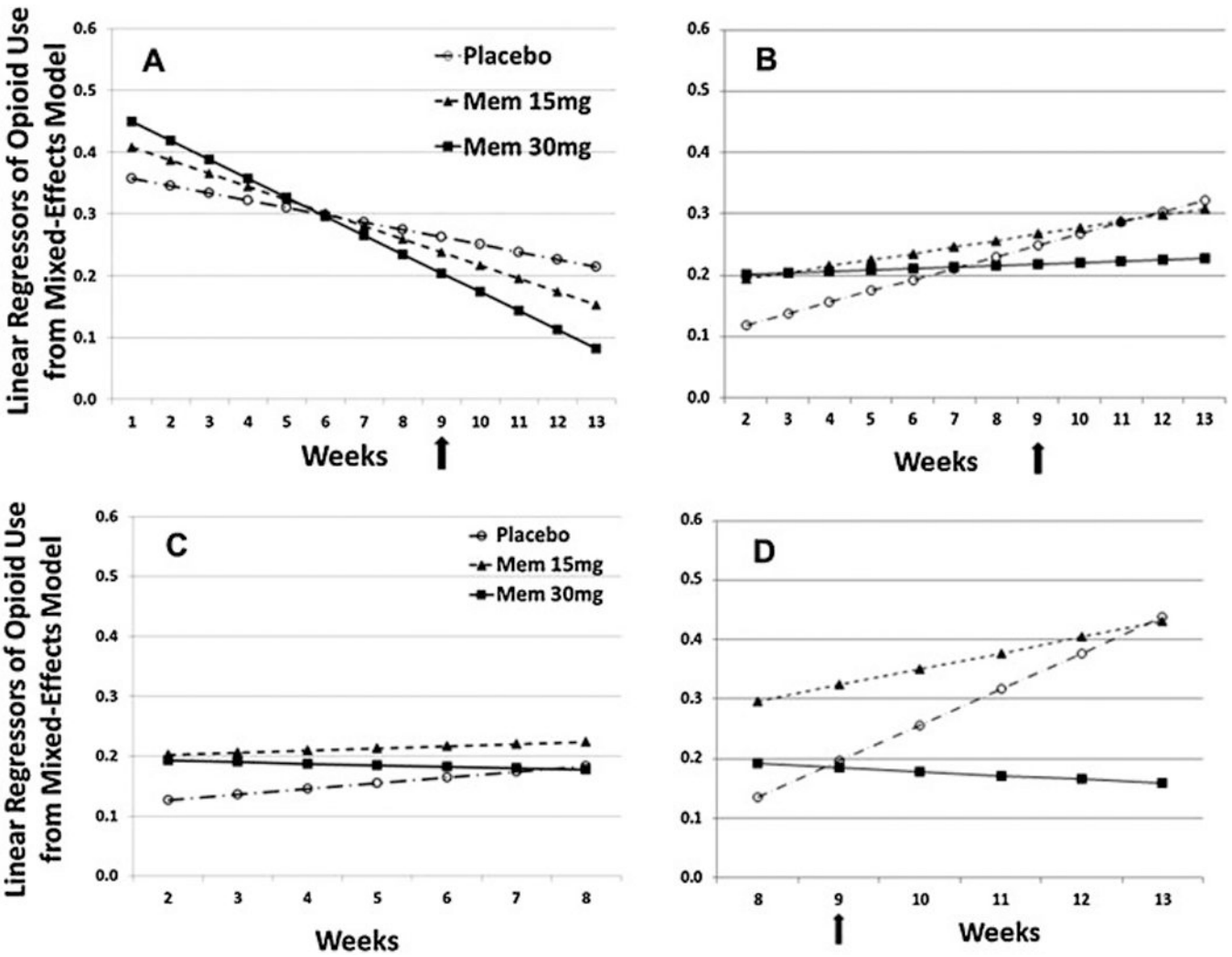

Fig. 3.

Fitted probability of opioid use per week by treatment group. A. Overall effect (weeks 1 to 13). B. After buprenorphine induction (weeks 2 to 13). C. Before buprenorphine discontinuation (weeks 2 to 8) and D. After buprenorphine discontinuation (week 8 to 13). Calculated from mixed-effect regression analyses models that controlled for baseline mean proportion of weekly opioid use with COWS, ASI psychiatric, and legal composite scores as covariates.

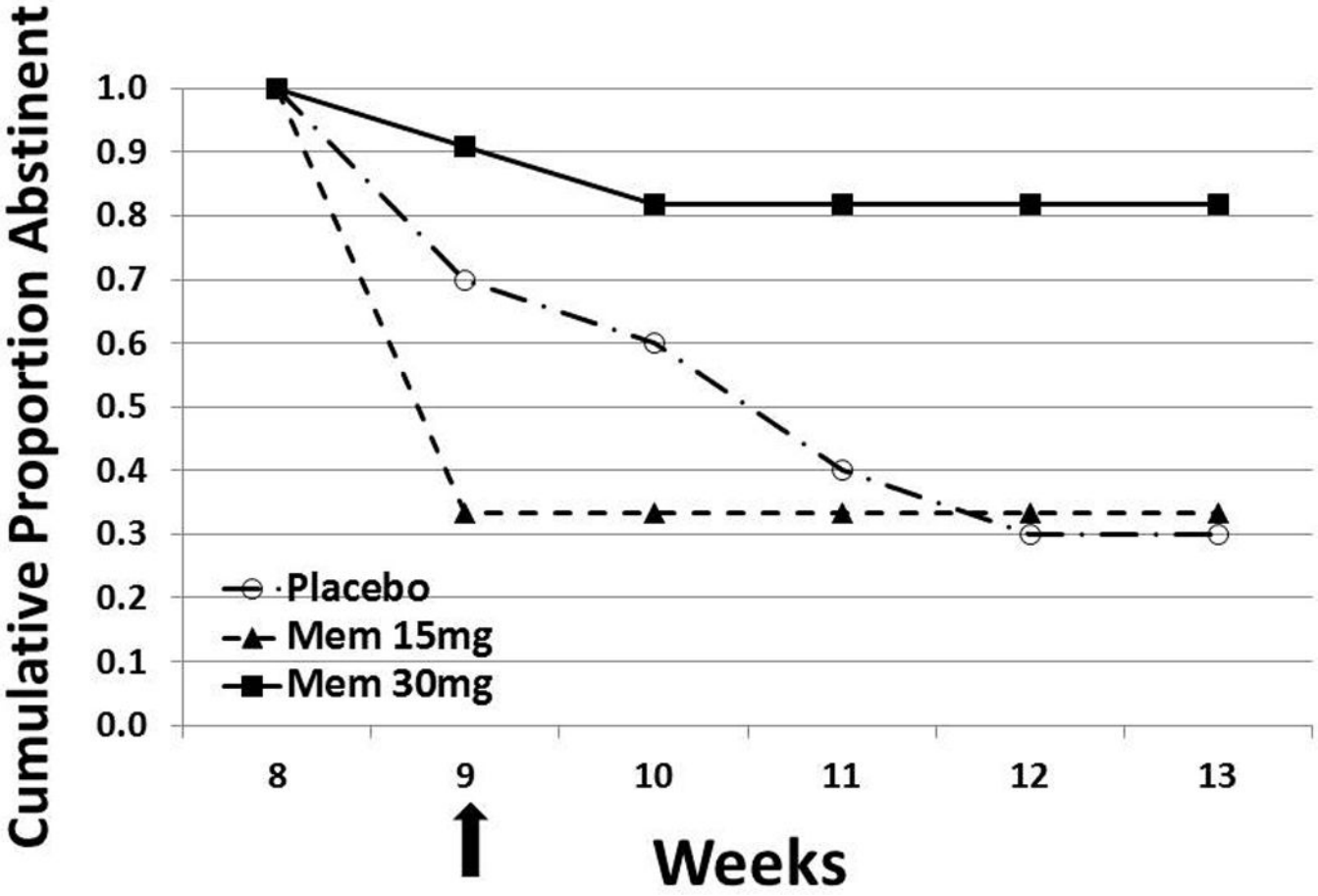

Fig. 4.

Cumulative proportion remaining abstinent after buprenorphine discontinuation. The data point represents the cumulative proportion from week 8 that remained abstinent, after achieving abstinence on week 8. The arrow represents the week buprenorphine was discontinued.

Table 1

Demographic and baseline characteristics.

	Total (N=80)		**Mem 0 mg (N=29)**		**Mem 15 mg (N=24)**		**Mem 30 mg (N=27)**			
Variables	Mean	SD	Mean	SD	Mean	SD	Mean	SD	F	p value
Age (years)	22.6	*1.9*	22.4	*2.1*	22.4	*2*	23	*1.9*	0.8	0.4
	N	%	N	%	N	%	N	%	X^2	*p value*
Gender									0.9	0.6
Male	53	*66.2*	20	*69*	14	*58*	19	*70.4*		
Female	27	*33.8*	9	*31*	10	*42*	8	*29.6*		
Marital Status									3.6	0.1
Never married	78	*97.5*	27	*93*	24	*100*	27	*100*		
Divorced	2	*2.5*	2	*6.9*	0	*0*	0	*0*		
Ethnicity									0.6	0.7
Caucasian	73	*91.2*	27	*93*	21	*88*	25	*92.6*		
Hispanic	7	*8.8*	2	*6.9*	3	*13*	2	*7.4*		
Education									4	0.6
High school degree and GED	32	*40*	10	*35*	12	*50*	10	*37*		
Some college	35	*43.8*	14	*48*	9	*38*	12	*44.4*		
College	5	*6.2*	3	*10*	0	*0*	2	*7.4*		
Others	8	*10*	2	*6.9*	3	*13*	3	*11.1*		
Employment									6.9	0.3
Full time	26	*32.5*	10	*35*	8	*33*	8	*29.6*		
Part time	15	*18.8*	5	*17*	2	*8.3*	8	*29.6*		
Unemployed	26	*32.5*	7	*24*	10	*42*	9	*33.3*		
Student	13	*16.2*	7	*24*	4	*17*	2	*7.4*		
Cannabis use	51	*63.8*	18	*62*	15	*63*	18	*66.7*	0.1	0.9
Opioid use severity										
Opioid analgesic use	63	*78.8*	24	*83*	17	*71*	22	*81.5*	1.2	0.5
Heroin use	17	*21.2*	5	*17*	7	*29*	5	*18.5*	1.2	0.5
Intranasal use of opioids	54	*67.5*	24	*83*	13	*54*	17	*63*	7.8	0.2
Intravenous drug use	19	*23.8*	3	*10*	9	*38*	7	*25.9*	7.8	0.2
Baseline Oxy positive urines	62	*77.5*	26	*90*	15	*63*	21	*77.8*	5.5	0.06
Baseline opiate positive urines	40	*50*	14	*48*	14	*58*	12	*44.4*	1.03	0.5
	Mean	*SD*	Mean	*SD*	Mean	*SD*	Mean	*SD*	Mean	*SD*
Opioid analgesic use (7 days TLFB)	4.4	*2.7*	4.6	*2.6*	3.9	*3.1*	4.7	*2.6*	0.6	0.5
Opioid analgesic use (last 30 days)	20.4	*11*	21.3	*9.4*	17.3	*13*	22.11	*10.7*	1.3	0.2
Opioid analgesic use (years)	3.2	*1.9*	3.7	*2.2*	2.9	*1.3*	2.8	*2.1*	1.8	0.1
Heroin use (7 days TLFB)	1.4	*2.7*	1.2	*2.5*	2	*3.1*	1.3	*2.5*	0.6	0.5
Heroin use (last 30 days)	5.78	*11*	4.5	*9.9*	8.1	*13*	4.9	*10*	0.7	0.4
Heroin use (years)	1.08	*2.1*	1.1	*2.3*	1	*1.6*	1.1	*2.5*	0.02	0.9
Current clinical status										
Severity of Dependence Scale	11.5	*2.4*	11.72	*2.5*	11.7	*2.5*	11.2	*2.1*	0.3	0.7

	Total (N=80)		Mem 0 mg (N=29)		Mem 15 mg (N=24)		Mem 30 mg (N=27)			
COWS	9.2	*3.1*	9.1	*2.7*	8.3	*2.8*	10.4	*3.7*	1.8	0.17
Heroin and opioid craving (HGQ-SF-14)	4.3	*1*	4.3	*1*	4.5	*1*	4.2	*1.1*	0.3	0.7
CES-D scores	22.4	*9.9*	22.8	*11*	20	*9.7*	23.6	*9*	0.6	0.5
Barratt Impulsiveness (Total Score)	70.8	*11.3*	69.7	*13*	70.4	*10*	72.4	*10.9*	0.4	0.6
Inhibitory Control (mean % error)	0.21	*0.17*	0.2	*0.2*	0.2	*0.1*	0.24	*0.2*	0.4	0.6
ASI Composite Scores										
Drug	0.34	*0.08*	0.33	*0.1*	0.33	*0.1*	0.35	*0.06*	0.6	0.5
Alcohol	0.04	*0.07*	0.03	*0*	0.05	*0.1*	0.06	*0.07*	1.4	0.2
Legal	0.13	*0.18*	0.13	*0.2*	0.19	*0.2*	0.07	*0.12*	2.7	0.07
Family	0.14	*0.16*	0.14	*0.2*	0.13	*0.1*	0.15	*0.17*	0.1	0.9
Employment	0.48	*0.27*	0.44	*0.3*	0.52	*0.3*	0.49	*0.3*	0.6	0.5
Medical	0.05	*0.17*	0.09	*0.2*	0.02	*0.1*	0.03	*0.17*	1.3	0.2
Psychiatric	0.19	*0.17*	0.14	*0.1*	0.18	*0.2*	0.25	*0.17*	3.2	0.04