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ORIGINAL INVESTIGATION

Adam Bisaga · Sandra D. Comer · Amie S. Ward
Piotr Popik · Herbert D. Kleber
Marian W. Fischman

The NMDA antagonist memantine attenuates the expression of opioid physical dependence in humans

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Abstract *Rationale:* Preclinical observations suggest that NMDA receptor-mediated glutamatergic neurotransmission is involved in the expression and maintenance of opioid dependence. *Objective:* The present study evaluated whether memantine, the clinically available non-competitive NMDA receptor antagonist, decreases naloxone-precipitated withdrawal in morphine-dependent humans. *Methods:* Eight heroin-dependent, non-treatment seeking, inpatient participants were stabilized on a fixed dose of morphine (30 mg PO qid). Subsequently, they received a series of challenges with naloxone (0.4 mg, IM) and the severity of opioid withdrawal was monitored. Either placebo or memantine (60 mg PO) was given 6 h before each naloxone challenge. A modified multiple baseline, across-participants design was used to evaluate the effects of memantine on the severity of naloxone-precipitated opioid withdrawal. *Results:* Naloxone increased ratings and produced physical changes consistent with opioid withdrawal. Memantine attenuated the severity of opioid withdrawal as assessed with the Clinical Institute for Narcotic Withdrawal Scale scale. Withdrawal was significantly reduced when naloxone was administered at 6 and 52 h after memantine, but not when administered 126 h (5 days) after memantine. Medication effects, assessed 5 h after memantine administration and before naloxone administration, included significant increases in ratings of "strong" and "good" drug effect, and "I feel sedated", "mellow", and "high". *Conclusions:* Memantine attenuated the expression of opioid physical dependence in humans, indicating that glutamatergic neurotransmission at the NMDA receptor site contributes to the maintenance of opioid dependence. This finding suggests that memantine may be a useful adjunct in the treatment of opioid dependence.

Keywords Memantine · Opioid · Dependence · Naloxone · Withdrawal · NMDA

A. Bisaga (✉) · S.D. Comer · A.S. Ward · H.D. Kleber
M.W. Fischman
Department of Psychiatry,
Columbia University College of Physicians and Surgeons,
New York, USA
e-mail: bisagaa@pi.cpmc.columbia.edu
Fax: +1-212-5435991

P. Popik
Institute of Pharmacology, Polish Academy of Sciences,
Smetna St, Krakow, Poland

A. Bisaga
New York State Psychiatric Institute, Unit #120,
1051 Riverside Drive, New York, NY 10032, USA

Introduction

Chronic administration of opioids produces physical dependence characterized by the emergence of withdrawal, a wide range of distressing physiological, behavioral, and subjective changes after significant reduction or cessation of opioid administration (Himmelsbach 1941). The presence of physical dependence may pose clinical problems in the management of patients with pain who require prolonged treatment with opioids. The emergence of withdrawal symptoms may also contribute to the failure in achieving and sustaining abstinence in heroin-dependent individuals. Therefore, it is of clinical importance to determine the mechanisms underlying physical dependence and to develop medications that can prevent the development of dependence or to reverse existing dependence. In humans, physical dependence can be assessed by observing the emergence of a withdrawal syndrome following discontinuation of chronic opioid administration or the administration of a competitive opioid antagonist like naloxone (Wikler et al. 1953). Antagonist administration can be used to probe the degree of underlying dependence (Wang et al. 1974), and can serve as a model to test new medications to treat the abstinence syndrome (e.g., Rosen et al. 1996a for the model used in this study).

The pathophysiology of opioid dependence is not well understood, but is thought to involve neuroadaptive changes in multiple neural systems that develop gradually over time with the repeated administration of opioids (Koob and Bloom 1988). Nevertheless, some neural

changes are induced after single exposure to an opioid (Martin and Eades 1964), and a measurable withdrawal syndrome can be precipitated in humans even after administration of a single dose of morphine (Bickel et al. 1988). It appears that one of the systems important in the development, expression and maintenance of physical dependence is neurotransmission at NMDA glutamatergic receptors (see Bisaga and Popik 2000, for review). Coadministration of NMDA antagonists prevents the development of opioid dependence in morphine-treated rats (Trujillo and Akil 1991), and attenuates the expression of motivational and physical manifestations of opioid dependence in rats (Popik and Danysz 1997). Once established, physical dependence persists even though opioid agonists are no longer present; administration of an NMDA receptor antagonist in opioid-free, dependent rats abolishes this persistent dependence (Popik and Skolnick 1996). This line of evidence suggests that the development and persistence of neuroadaptations that underlie opioid dependence may rely on NMDA-receptor-mediated neurotransmission.

Results from previous studies that evaluated the interaction between the NMDA receptor system and physical dependence on opioids in humans have been inconclusive (Isbell and Fraser 1953; Koyuncuoglu and Saydam 1990; Koyuncuoglu 1991; Rosen et al. 1996b; Bisaga et al. 1997), but they differed greatly in the methodologies used. In the present study, the effects of memantine were evaluated. Memantine is a non-competitive NMDA antagonist that has been used in Europe for over 15 years for the treatment of a variety of neurological diseases. It has a favorable side-effect profile, good pharmacokinetic properties, and low abuse potential (Parsons et al. 1999). Memantine has been tested extensively in preclinical models of opioid dependence. It was found not only to suppress the development, expression, and maintenance of opioid dependence in laboratory animals but was also found to reduce morphine self-administration (Popik and Skolnick 1996; Popik and Danysz 1997; Dravolina et al. 1999; Semenova et al. 1999).

We used a model of naloxone-precipitated opioid withdrawal, a validated model for testing medications to treat opiate withdrawal (Rosen et al. 1996a), to study the effects of memantine. An extensive battery of assessment measures were used in order to evaluate behavioral, physiological, subjective, and cognitive changes resulting from the administration of morphine, memantine, and naloxone.

In this study, following preliminary observations, we used a non-concurrent, multiple baseline, across-individuals design. Pilot data indicated that memantine had long-lasting effects and therefore it was not feasible to use a more traditional crossover, counterbalanced design with adequate washout periods, because the length of the study would have been extended greatly. In a multiple baseline design, the changes in outcome variables following treatment intervention are said to be functionally related to the treatment variable since they occur in concert with the treatment procedure that was implemented at random points (Watson and Workman 1981). This design also eliminates the assumption of the reversibility of treatment effects that is applied in traditional crossover designs. This is particularly important to the study of phenomena like physical dependence or learning that are long-lasting and may not be fully reversible.

Materials and methods

Participants

Two female and six male, non-Hispanic Caucasian healthy volunteers with a mean age of 33.5 years (range: 23–42 years) participated in the study. All participants reported using heroin for an average of 9.8 years (range: 2–25 years), and spending an average of $47 per day (range: $20–100) on heroin. Participants were not currently seeking treatment for their drug use. Seven participants smoked tobacco cigarettes (4–20 cigarettes per day), one participant used barbiturates (once a week or less), and three participants used marijuana (once a week or less). Four participants drank alcohol: three participants drank alcohol 2–4 times per week, and one drank alcohol twice per month.

After an initial telephone interview, eligible participants received additional screening at the laboratory, which included completing detailed questionnaires about drug use, general health and medical history, and a medical and psychological evaluation. Urine drug toxicologies (opioids, cocaine, benzodiazepines, cannabinoids, and amphetamines) were also performed. Participants were excluded from the study if they were pregnant, seeking drug treatment, dependent on illicit drugs other than heroin, or had an axis I psychiatric diagnosis other than opioid dependence. Participants who had recent histories of violence or who were on parole/probation were excluded from the study. Participants were required to be physically healthy, and fully able to perform all study procedures. Participants were dependent on opioids, as verified by a naloxone challenge test administered just prior to admission into the hospital (Wang et al. 1974).

Prior to admission, participants completed one training session, during which the study procedures were explained to them in detail. Volunteers who participated in the study protocols were paid $35 per day and an additional $35 per day bonus if they completed the study. Participants signed consent forms describing the aims of the study, and the potential risks and benefits of participation. The discussion of study risks included warnings about the possibility of severe withdrawal with the injection of naloxone and the risk of psychotic symptoms induced by memantine. This study was approved by the Institutional Review Board of the New York State Psychiatric Institute.

General procedures

Throughout the study, participants resided on the General Clinical Research Unit and were given oral morphine (30 mg qid) to maintain physical dependence. Participants were stabilized on oral morphine for 4–7 days until withdrawal signs and symptoms had dissipated. A modified multiple baseline design was used to evaluate the time course of memantine's ability to alter the severity of naloxone-precipitated opioid withdrawal. Experimental sessions were separated by 48 or 78 h, and either placebo or active memantine was administered orally at 0900 hours prior to each session. A dose of 0.4 mg naloxone was administered intramuscularly (IM) during each experimental session at 1500 hours, 6 h after placebo or active memantine. During each experimental session, physiological and subjective effects measures were completed before and repeatedly after the naloxone injection (see experimental session below). Performance measures were completed once during each session, prior to naloxone administration. Physiological and subjective effects measures were also collected each day immediately prior to oral morphine administration.

All participants received a single dose of memantine (60 mg PO) during the study; placebo was administered 2 and 5 days after

Table 1 Design of the study: multiple baseline across-participants

Participants	Naloxone challenge*						
	–4	–3	–2	–1 (42 h pre-M)	1 (6 h post-M)	2 (54 h post-M)	3 (126 h post-M)
A				**P**	M	P	P
B				**P**	M	P	P
C			**P**	**P**	M	P	P
D			**P**	**P**	M	P	P
E		**P**	**P**	**P**	M	P	P
F		**P**	**P**	**P**	M	P	P
G	**P**	**P**	**P**	**P**	M	P	P
H	**P**	**P**	**P**	**P**	M	P	P

P Baseline challenges with placebo memantine pretreatment, *M* challenge with memantine pretreatment, *P* post-treatment challenges with placebo memantine pretreatment

active memantine. The number of placebo baseline assessments varied across participants: two participants received one placebo baseline assessment, two participants received one placebo baseline assessments, two participants received three placebo baseline assessments, and two participants received four placebo baseline assessments (see Table 1). The time interval between each treatment condition was the same for all participants: (1) 48 h between the last placebo pretreatment and the active memantine treatment, (2) 48 h between active memantine and the first post-active memantine treatment and (3) 72 h between the first and second post-active memantine treatment. In each case, a naloxone challenge was administered 6 h later. Each participant that entered the study was randomly assigned to one of the pre-determined baseline lengths as described above. Participants and raters were blind to the study design and treatment condition.

Experimental sessions

Five hours after active memantine or placebo administration, at the predicted peak concentration of memantine in serum (MERZ, Akatinol Memantine, Product Information), participants completed a drug effects questionnaire (DEQ), visual analog scales (VAS) and computerized performance tasks (see below). Following these assessments, participants were brought into a testing room and both subjective-effects measures (Subjective Opioid Withdrawal Scale: SOWS, Opioid Symptom Checklist: OSC, and VAS) and physiological measures (blood pressure, heart rate, and skin temperature) were assessed 10 min prior to and 10, 20, 30, 45, 60, and 90 min after IM naloxone administration (see below). The Objective Opioid Withdrawal Scale (OOWS), Clinical Institute for Narcotic Withdrawal Scale (CINA), blood pressure, heart rate, and skin temperature were also obtained at these time points. Pupil photographs were taken 10 min prior to and 10, 20, and 45 min after naloxone administration. All naloxone challenge doses, physiological measures, and subjective-effects measures (with the exception of the drug effects questionnaire and performance tasks) were completed in the testing room. Participants were returned to the General Clinical Research Unit after the 90-min assessment, and the SOWS, CINA, opioid symptom checklist, and visual analog scales were completed 120 min after IM naloxone administration.

In addition to the measures completed during experimental sessions, as described above, participants also completed the SOWS, OSC, and VAS scales immediately prior to each oral morphine administration at 0700, 1300, 1900 and 2300 hours. Vital signs and arterial oxygen saturation were also measured at this time. Each morning, participants completed a sleep questionnaire.

Objective and subjective measures

The main rating instrument used to evaluate opioid withdrawal was a modified version of the CINA. This instrument monitors changes in all components of opioid withdrawal (objective, subjective, and physiological), and was specifically developed and validated to assess opioid dependence following naloxone challenge in opioid dependent individuals (Peachey and Lei 1988). An experienced observer administered the CINA during a 5-min period and assessed the following symptoms: nausea/vomiting, gooseflesh, sweating, restlessness, tremor, lacrimation, nasal congestion, yawning, abdominal pain, changes in temperature, and muscle aches. Heart rate and systolic blood pressure were also measured at each assessment time point. For each item, baseline scores were subtracted from the scores obtained after naloxone injection, and then a sum score across the assessment time points was calculated. A total score was the sum of scores for each individual item.

We also used additional instruments assessing the severity of withdrawal in order to explore whether there is a differential effect of memantine on signs and symptoms of opiate withdrawal. The OOWS was used to evaluate 13 physically observable signs of opioid withdrawal. Each item was rated with either 1 (present) or 0 (absent) based on 10 min of observation of the participant by an experienced rater (Handelsman et al. 1987). The 16-item SOWS (Handelsman et al. 1987) was used to assess the severity of symptoms of withdrawal. Participants rated each item on a scale from 0 to 4, with 0 being “Not at all” and 4 being “Extremely”. Both OOWS and SOWS measures were originally developed to assess spontaneous opiate withdrawal and have not been validated with naloxone challenge tests. In our study, SOWS and OOWS were used as secondary measures and results of their analyses are considered preliminary.

Three other questionnaires were used to assess subjective effects throughout the experimental sessions. The first questionnaire was a visual analog scale (VAS) designed to assess subjective states and physiological effects as reported at the time of testing (modified from Foltin and Fischman 1992). The 100 mm lines were labeled with adjectives describing mood states (e.g., “I feel...:” “stimulated,” “anxious,” “depressed,” “mellow,” etc.) and physiological effects (e.g., “I feel dizzy,” “I have muscle pain,” “I have a headache,” etc.). Participants also indicated how much they “wanted” and “needed” each of the following: junk food, chocolate, heroin, cocaine, alcohol, and tobacco. Another item was used to rate withdrawal severity. Participants rated each item on the VAS from “Not at all” (0 mm) to “Extremely” (100 mm). The second questionnaire was a 13-item OSC consisting of true/false questions designed to measure opioid effects (Martin and Fraser 1961). The third questionnaire was a six-item DEQ (Evans et al. 1995) that assessed the effects of the medication given 5 h earlier.

Performance task battery

The task battery consisted of four tasks: a 3-min digit-symbol substitution task (McLeod et al. 1982), a 10-min divided attention task (Miller et al. 1988), a 10-min rapid information processing task (Wesnes and Warburton 1983), and a 3-min repeated acquisition of response sequences task (Kelly et al. 1993).

Physiological measures

An automated blood pressure monitor was used to measure systolic and diastolic pressure, and heart rate (NBS Medical Services, Costa Mesa, Calif., USA). A pulse oximeter was used to monitor arterial blood oxygen saturation (Palco Labs). Thermocouples were used to measure skin temperature (Cole-Parmer). A specially modified Polaroid camera with a close-up lens (×2 magnification) was used to take pupil photographs. All photographs were taken under constant ambient lighting conditions. Horizontal and vertical measurements of pupil diameter were made using a caliper, and these two measurements were averaged and divided by 2 to correct for the ×2 magnification.

Drugs

Participants were stabilized and maintained on oral morphine sulfate (30 mg qid; liquid suspension; Roxane Laboratories, Inc., Columbus, Ohio, USA) during the hospital stay. Morphine was administered daily at 0700, 1300, 1900, and 2300 hours. Supplemental medications available to all participants for the duration of the study included: acetaminophen, ibuprofen, calcium carbonate, magnesium hydroxide, docusate sodium, and multi-vitamins with iron. Clonidine HCl (0.3 mg PO, every 8 h; Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, Conn., USA), ketorolac tromethamine (30 mg PO, every 12 h; Roche Laboratories, Nutley, N.J., USA), and oxazepam (30 mg PO, every 12 h; Wyeth-Ayerst Laboratories, Philadelphia, Pa., USA) were available, as needed, for the first 3 days after admission into the hospital while participants were stabilized on the morphine maintenance dose. Stability was defined as no subjective or objective withdrawal effects. Morning urine samples were collected daily and one random sample per week was screened for the presence of other illicit substances. No illicit substances were found in the participants' urines. Naloxone HCl (Narcan; DuPont Pharma, Wilmington, Del., USA) was administered in IM doses of 0.4 mg. Memantine (Akatinol Memantine; Merz Pharma, Frankfurt am Main, Germany) was administered in a single dose of 60 mg, the maximal dose recommended for the treatment of spasticity.

Statistical analyses

Data analyses were conducted using SYSTAT, SuperANOVA and Statistica software. In the analysis of naloxone-precipitated opioid withdrawal, four specific questions were addressed: (1) Does a naloxone challenge produce significant changes in measures of opioid withdrawal? (2) Does memantine decrease the signs and symptoms of opioid withdrawal? (3) If so, how long does this diminution last? (4) What is the duration and severity of withdrawal in relation to the administration of memantine?

Repeated measures analyses of variance (ANOVA) examined the effect of memantine on naloxone-precipitated withdrawal (as measured by CINA, OOWS and SOWS scores, subjective effects, performance, and physiological measures) with time relative to memantine administration (–42 h, +6 h, +54 h, +126 h) and time relative to naloxone administration (–10 min, +10 min, +20 min, +30 min, +45 min, +60 min) as within-subjects measures. All measures returned to baseline values 60 min after the injection and therefore values obtained at +90 min were omitted from the final analyses. Data for each challenge (–10 to +60 min) were also summarized as the area under the curve (AUC) calculated using the trapezoidal method and analyzed independently using ANOVA. Significant interaction effects were examined using Newman-Keuls multiple comparisons procedure.

General linear regression models were used to examine the influence of number of baseline naloxone challenge days and severity of initial withdrawal on memantine response. The effects of memantine alone on DEQ, task performance, and subjective effects scores were examined by comparing the effects of memantine with the effects of placebo that was given on the last of the baseline days, 42 h before administration of memantine. Results were considered statistically significant at $P<0.05$.

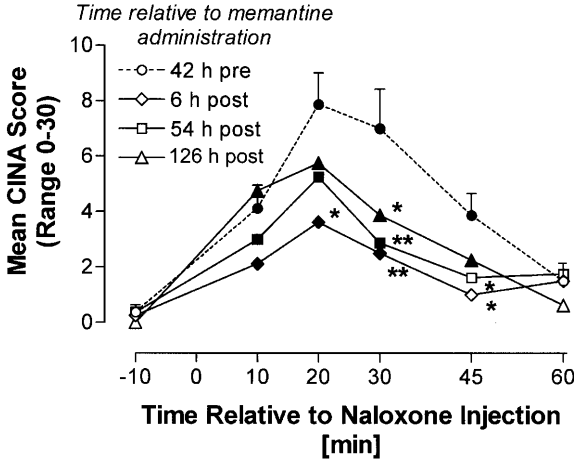

Fig. 1 Mean CINA scores as a function of time relative to naloxone and to memantine administration. *Asterisks* indicate a significant (*$P<0.05$, **$P<0.01$) difference from placebo baseline values (42 h before memantine) using Newman-Keuls test. *Filled symbols* indicate that a given score is significantly ($P<0.05$–0.001) different from time "–10 min" (Newman-Keuls test). For the sake of clarity, only selected SEMs are presented ($n=8$)

Results

Combined measure of withdrawal – CINA

Analysis of the total CINA scores (Fig. 1) indicated a significant main effect of naloxone [$F(5,35)=27.9$, $P<0.0001$] and memantine administration [$F(3,21)=4.65$, $P<0.05$], with a significant interaction between them [$F(15,105)=2.88$, $P<0.001$]. Multiple comparison analysis revealed that the CINA scores recorded 6 and 54 h after memantine administration were significantly lower ($P<0.001$ and $P<0.05$, respectively) than scores recorded 42 h before memantine. Scores recorded 126 h after memantine were not different from pre-memantine baseline or the 6-h post-memantine time point. Similarly, AUC values revealed an overall significant effect of memantine administration [$F(3,28)=4.547$, $P<0.05$]. Post-hoc comparison revealed that CINA AUC values calculated for 6 and 54 h, but not 126 h, after memantine administration were lower ($P<0.01$ and $P<0.05$, respectively) than scores recorded 42 h before memantine (Table 2). Compared to the baseline challenge (obtained 42 h before memantine), the mean CINA scores recorded at 6, 54, and 126 h post-memantine were lower at 20–45 min, 30–45 min, and 30 min post-naloxone, respectively (Fig. 1, asterisks). For the baseline condition (–42 h) and for +126 h post-memantine, CINA scores were higher at 10–45 min post-naloxone, compared to the respective pre-naloxone values. For the 6 and 54 h post-memantine, CINA scores were higher at 10–30 but not 45 or 60 min post-naloxone, compared to the respective pre-naloxone values (Fig. 1, filled symbols). These analyses indicate that the severity and duration of withdrawal measured by CINA scores were significantly reduced 6 and 54 but not 126 h post-memantine.

Table 2 Mean±SEM AUC values for withdrawal scores during naloxone challenge sessions before and after administration of 60 mg of memantine (*n*=8)

Measure	42 h before (baseline)	6 h after	54 h after	126 h after	ANOVA $F(3,21)$	P
CINA	279±21	116±15**	158±16*	192±11[a]	4.54	0.01
OOWS	187±15	78±7**	93±12*	126±5[a]	5.14	0.006
SOWS	747±87	537±88	433±56	470±34[a]	1.01	0.40

Asterisks indicate significant difference from baseline: *P<0.05, **P<0.01, Newman-Keuls test
[a] No difference from 6 h value

Other measures of withdrawal

Analysis of the OOWS scores indicated a significant main effect of naloxone [$F(5,35)=23.2$, $P<0.0001$] and memantine [$F(3,21)=7.3$, $P<0.01$], with a significant interaction between them [$F(15,105)=3.3$, $P<0.001$]. Multiple comparison analysis revealed that the OOWS scores observed 6, 54, and 126 h after memantine administration were significantly lower than that observed 42 h before memantine ($P<0.001$, $P<0.01$, and $P<0.05$, respectively). Scores recorded 126 h after memantine were not different from the 6 h post-memantine time point (Fig. 2). Similarly, analysis of AUC values revealed an overall significant effect of memantine administration [$F(3,28)=5.14$, $P<0.01$]. Post-hoc comparisons revealed that OOWS AUC values calculated for 6 and 54 h after memantine administration were lower ($P<0.01$ and <0.05, respectively) relative to baseline (Table 2). Compared to baseline challenge, the mean OOWS scores recorded at 6, 54 and 126 h post-memantine were lower for 30 min post-naloxone (Fig. 2, asterisks). For the baseline condition (–42 h), OOWS scores were higher at 10–45 min post-naloxone, compared to the pre-naloxone value. For 6, 54 and 126 h post-memantine, OOWS scores were higher at 10–30 but not at 45 or 60 min post-naloxone, compared to the respective pre-naloxone values (Fig. 2, filled symbols). These analyses indicate that the severity of withdrawal measured by OOWS scores was attenuated at tests performed 6, 54 and 126 h post-memantine, and that this was observed 30 min after naloxone challenge.

Analysis of the SOWS scores indicated a significant main effect of naloxone [$F(5,35)=10.1$, $P<0.0001$] but not of memantine [$F(3,21)=2.7$, $P=0.07$], with a non-significant interaction between them [$F(15,105)=1.26$, $P=0.24$]. There was a baseline difference in SOWS scores at the –10 min time point. This was due primarily to one participant who reported intensity of symptoms 7-fold greater than the mean of the remaining participants at this time point. When these data were reanalyzed as change from baseline scores, the effect of memantine remained non-significant [$F(3,21)=2.4$, $P=0.11$]. Similarly, analysis of AUC values did not reveal a significant effect of memantine administration [$F(3,28)=1.01$, $P>0.05$]. As seen in Fig. 3, on each of the three test days that followed the administration of memantine there was a trend towards reduction of subjective ratings of withdrawal severity. The overall effect of memantine approached statistical significance.

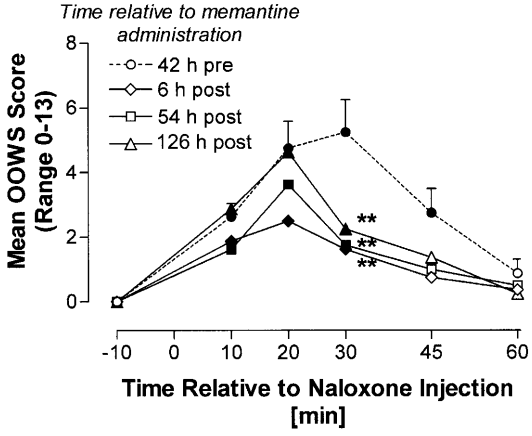

Fig. 2 Mean OOWS scores as a function of time relative to naloxone and to memantine administration. *Asterisks* indicate a significant (**P<0.01) difference from placebo baseline values (42 h before memantine) using Newman-Keuls test. *Filled symbols* indicate that a given score is significantly (P<0.05–0.001) different from time "–10 min" (Newman-Keuls test). For the sake of clarity, only selected SEMs are presented (n=8)

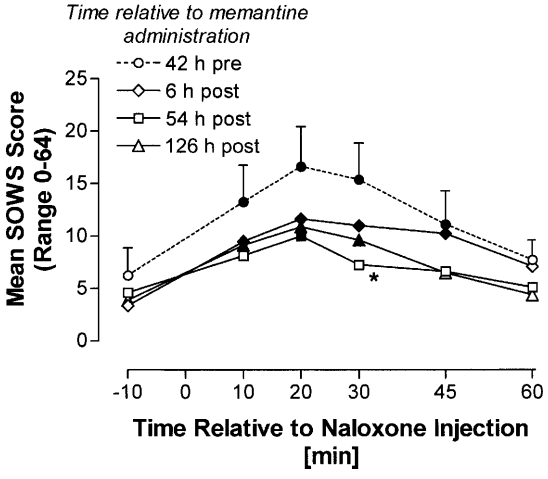

Fig. 3 Mean SOWS scores as a function of time relative to naloxone and to memantine administration. *Asterisk* indicate a significant (*P<0.05) difference from placebo baseline values (42 h before memantine) using Newman-Keuls test. *Filled symbols* indicate that a given score is significantly (P<0.05–0.001) different from time "–10 min" (Newman-Keuls test). For the sake of clarity, only selected SEMs are presented (n=8)

Naloxone's effects on other subjective effects measures, including selected VAS scales ("stimulated," "mellow," "good drug effect"), were not significantly different from the pre-naloxone scores, and there was no effect of memantine. There was a significant (F=5.63, P<0.05) effect of naloxone on the VAS item "bad drug effect," which was not altered by memantine administration. There was a significant effect of memantine alone as seen on the VAS item "sedated" (F=5.31, P<0.05) and "high" (F=8.26, P<0.01), with memantine producing acute increases on both scales. There was no significant effect of naloxone or memantine on the craving VAS scales for "junk food," "heroin," "tobacco," and "alcohol." However, naloxone increased craving for heroin and tobacco at a level approaching statistical significance (P=0.08–0.09).

There was a significant effect of naloxone administration on heart rate [F(5,35)=6.1, P<0.0001]. Beginning at baseline, collected 10 min before naloxone, heart rate gradually decreased over time. No significant effect of memantine was noted. There was no significant effect of naloxone or memantine on systolic blood pressure. Diastolic blood pressure increased following naloxone administration, with the peak effect occurring at 10 and 20 min. No significant effect of memantine on diastolic blood pressure was found. Naloxone produced significant decreases in skin temperature [F(5,35)=2.6, P<0.05] and increases in pupil size [F(5,35)=8.9, P<0.01], but no effect of memantine was observed on either of these measures.

Effects of baseline length

Regression analyses indicated that neither number of baseline naloxone challenge days nor the withdrawal severity during the first baseline naloxone challenge day was predictive of memantine's effects on precipitated withdrawal.

Effects of morphine and memantine

Participants were maintained on morphine for at least 5 days before they received the first placebo memantine medication. Under such conditions, morphine produced no changes on subjective-effects measures. None of the VAS measures collected at 1 p.m. (before administration of morphine) were significantly different from the same measures collected at 2 p.m. (1 h after morphine and 5 h after placebo memantine).

The subjective effects of active and placebo memantine were measured 5 h after the medication was given, and 1 h after the standing dose of morphine (Table 3). The effects of placebo did not differ on any of the measures between test days. Memantine produced significant increases in DEQ ratings of "strong drug effect" [F(3,21)=8.7, P<0.001] and "good drug effect" [F(3,21)=14.6, P<0.001], relative to the last placebo day. Memantine significantly increased ratings of "drug liking" (P<0.01) and "willingness to take the drug again" (P<0.01). Half of the participants identified memantine as a stimulant while the other half identified it as a sedative or tranquilizer. Memantine produced significant increases in VAS ratings of "sedated" (P<0.05), "mellow" (P<0.01), "high" (P<0.01), and "good drug effect" (P<0.02). Memantine also produced decreases in ratings of "anxious" and "depressed" that approached significance (P=0.06). The effects of memantine on these VAS measures were evident only acutely 5 h after memantine was given but not at any subsequent assessments. There were no changes on the VAS measuring physical and

Table 3 Mean±SD values for subjective effect measures collected 5 h following administration of three doses of placebo or 60 mg memantine (n=8). P values were adjusted for violations of sphericity using the Huynh-Feldt method

Subjective effects measures	Placebo	Memantine	Placebo	Placebo	ANOVA F(3,21)	P
	Time relative to memantine administration					
	–43 h	+5 h	+53 h	+125 h		
VAS						
Sedated	5.0 (±9.5)	13.5 (±14.3)	1.12 (±1.8)	2.0 (±2.0)	4.7	0.037
High	3.75 (±7.3)	26.1 (±20.0)	0.75 (±1.2)	0.87 (±1.0)	13.1	0.004
Good effect	10.6 (±23.0)	29.9 (±28.0)	1.0 (±1.2)	0.9 (±1.4)	5.9	0.012
Bad effect	6.0 (±5.3)	11.5 (±17.6)	0.87 (±1.2)	1.37 (±1.5)	2.3	0.17
Mellow	24.0 (±28.4)	32.6 (±26.4)	17.0 (±19.9)	15.5 (±16.6)	5.3	0.007
High	9.7 (±17.0)	31.5 (±28.0)	1.6 (±1.5)	2.1 (±1.6)	8.3	0.015
Depressed	14.4 (±13.1)	4.7 (±6.0)	9.4 (±7.6)	6.7 (±6.8)	2.3	0.16
Anxious	34.5 (±29.4)	13.9 (±16.4)	30.4 (±32.5)	18.1 (±17.0)	2.2	0.16
Craving for heroin	56.4 (±31.8)	39.9 (±32.7)	61.1 (±35.7)	67.1 (±29.7)	2.7	0.09
DEQ						
Good drug effect	0.37 (±0.5)	1.62 (±.0.9)	0 (±0)	0.12 (±0.3)	14.6	0.001
Drug liking	–0.37 (±1.3)	1.75 (±1.7)	–0.12 (±0.3)	0 (±0)	6.0	0.021
Take drug again	0.75 (±0.9)	2.12 (±1.5)	0 (±0)	0.12 (±0.3)	12.5	0.001
Strong effect	1.0 (±1.1)	2.37 (±1.2)	0.37 (±0.7)	0.25 (±0.5)	8.7	0.001

other subjective effects. No effects of memantine were noted on any of the performance measures. There were no differences between placebo and memantine on the SOWS, VAS, OSC, blood pressure, heart rate, and blood oxygen saturation collected before each oral morphine administration.

Discussion

Results of this study suggest a role of NMDA-mediated glutamatergic neurotransmission in the expression of opioid dependence in humans. Pretreatment with a single dose of memantine attenuated the expression of opioid withdrawal precipitated by naloxone in opioid-dependent individuals maintained on morphine. The severity of precipitated withdrawal was significantly lower, as compared to the pre-memantine values, when assessed 6 and 54 h after memantine administration. This significant treatment effect disappeared 126 h after memantine, as the severity of withdrawal precipitated at that time point was no different from the pre-memantine values. These results suggest that memantine produced transient inhibitory effects on the expression of opiate withdrawal and/or inhibited the process of maintenance of opiate dependence. The effect of memantine was most evident when objective or combined measures of opioid withdrawal were used. A trend towards similar effects were observed for subjective measures, but this effect was not statistically significant. Memantine itself produced changes on a variety of subjective measures in participants maintained on morphine.

These observations are consistent with the results of several other clinical studies that tested dextromethorphan (DXM), another clinically available NMDA antagonist (Netzer et al. 1993). DXM appeared to be effective in the treatment of opioid abstinence (Koyuncuoglu and Saydam 1990; Koyuncuoglu 1991, 1995; Bisaga et al. 1997), as it reduced signs and symptoms of opioid withdrawal in patients seeking treatment for opioid dependence. However, the results of two laboratory studies (Isbell and Fraser 1953; Rosen et al. 1996b) were negative. Isbell and Frazer (1953) tested the effects of DXM in participants maintained on 120–300 mg morphine daily. They found no significant effect of DXM on the emergence of or the course of the abstinence syndrome. However, many details of the study were not reported in this 1953 paper. In another more recent study, Rosen et al. (1996b), used a counterbalanced design to examine the effects of DXM on naloxone-precipitated opiate withdrawal in participants stabilized on 25 mg/day of methadone, which produces a degree of morphine-like activity in humans equivalent to that produced by 50 mg morphine (Jasinski et al. 1977). In this study, there was considerable inter-individual, and session-to-session variability in response to DXM but no net attenuation of opioid withdrawal was found. It should be noted that most of the participants in the Rosen et al. study had very mild withdrawal. In the few participants with more severe symptoms, DXM appeared to attenuate the severity of withdrawal. Our data are also consistent with the results of numerous preclinical studies indicating that inhibition of the NMDA receptor channel by antagonists acting at a variety of its binding sites attenuate the expression of opioid dependence (see Bisaga and Popik 2000, for review). Previous laboratory studies have shown that memantine attenuated the physical, and motivational aspects of opioid withdrawal precipitated by naloxone in opioid-dependent animals (Popik and Skolnick 1996; Popik and Danysz 1997).

There are a number of possible hypotheses to explain memantine's mechanism of action in alleviating precipitated withdrawal, including direct or indirect interference, alteration of neuroadaptive changes, and potentiation of morphine's effects. First, memantine could interfere directly with receptors already known to be involved in the expression of the abstinence syndrome. For example, opioids, alpha$_2$ adrenergic agonists (clonidine), and benzodiazepines, are known to inhibit or reduce the severity of withdrawal (Bhargava 1994). However, at the dose used in the present study (see Kornhuber and Quack 1995), memantine is selective for NMDA receptors and does not bind to opioid, noradrenergic or GABAergic receptors (Parsons et al. 1999). Therefore, a direct influence of memantine on opioid, alpha$_2$ adrenergic, and GABA receptors seems unlikely. Memantine may have affected the neurotransmitter pathways involved in the expression and maintenance of opioid withdrawal indirectly. For example, memantine may affect mesolimbic dopaminergic projections, which are implicated in the motivational and subjective aspects of opioid withdrawal (Berridge and Robinson 1998) and are under control of glutamatergic projections (Pulvirenti and Koob 1990). Because morphine withdrawal is associated with a decrease in dopaminergic function (Acquas et al. 1991; Rossetti et al. 1992), and this dopaminergic dysfunction may be reversed by NMDA receptor antagonist administration (Rossetti et al. 1992), it is likely that inhibitory effects of memantine on the symptomatology of opioid abstinence found in the present study might be explained by a similar mechanism. Even though most of these mechanisms appear to be mediated centrally, it is also possible that peripheral mechanisms are involved (Rasmussen et al. 1991). Further experiments are needed to elucidate the site and mechanism of memantine's effect.

The present results indicate that a single dose of memantine may have an effect on opioid dependence that lasts for at least 2–3 days. Such a prolonged pharmacological effect was not expected because the maximal blood levels of memantine are observed 4±2 h after oral administration. Based on the estimates of peak memantine concentrations in the brain, we can assume that the dose used in this study would produce 20% occupancy at C_{max}, and this would most likely be sufficient for a meaningful pharmacodynamic effect (see Wenk et al. 1995; Danysz et al. 1997). Although the half life for the terminal phase is 100 h, the half-life for the first phase is

only 4–9 h (Parsons et al. 1999; MERZ, Akatinol Memantine, Product Information). The majority of acute effects, as documented in this and other unpublished studies conducted in our laboratory, peak at 4–6 h and disappear by 12 h. This probably correlates with pharmacodynamically relevant brain concentrations. Most likely, 48 h after a single dose of 60 mg, we cannot expect any pharmacodynamically relevant concentrations of memantine to be left in the brain. Therefore, the effects observed at 54 h post-memantine are likely to be related to the "resetting" properties of an acute dose rather than a persistent suppression of opioid withdrawal due to a continuous presence of memantine in the brain. Nonetheless, the time course of memantine's receptor occupancy of is unknown; it is possible that persisting memantine occupancy of NMDA receptors may have occurred in this study and therefore the alternative hypothesis cannot be excluded.

To our knowledge, this is the first demonstration of an extended effect of a single dose of an NMDA receptor antagonist on opioid dependence. To some extent, it resembles anecdotal reports of the long-lasting effects of ibogaine, another NMDA antagonist (Popik et al. 1995), given in a single dose for the treatment of opioid withdrawal (Alper et al. 1999). A similar persistence of effects on a depressive syndrome was reported in a study using ketamine, another NMDA antagonist (Berman et al. 2000). One explanation of this effect could be that a single dose of memantine may temporarily modify neuronal plasticity, mediating the maintenance of opioid dependence (Siegel 1976). However, this hypothesis has to be viewed in light of findings indicating that NMDA antagonists, although implied in neuronal plasticity of learning and memory processes, do not affect stored memories and well established plastic changes (Danysz et al. 1995).

Several measures were used to assess the effects of memantine on naloxone-precipitated withdrawal. In our analyses, we attempted to evaluate the extent to which memantine alleviates signs versus symptoms of opioid withdrawal. The primary outcome measure, CINA, was developed and validated in the assessment of precipitated withdrawal. It includes four items assessing symptoms, seven items assessing signs, and two physiological measurements. Administration of memantine significantly attenuated withdrawal, as measured by the CINA. Two additional scales were used to separately assess signs (OOWS) and symptoms (SOWS) of withdrawal. There was a substantial overlap between CINA and OOWS, and, to a lesser extent, CINA and SOWS. As expected, results on all of these scales followed a similar pattern. However, memantine's effect on the SOWS did not achieve statistical significance.

Some of the reasons why there seems to be a less prominent effect of memantine on symptoms include lower reliability of subjective measures and the limited power of the current design. Limited reliability of subjective reports have been noted previously, and some consider objective measures to be the most reliable in assessing the severity of withdrawal. In the study by Wang et al. (1974), opioid-dependent patients reported withdrawal symptoms after blinded injections of naloxone and saline, whereas objective signs were absent in patients receiving saline. Subjective measures of opiate withdrawal are usually characterized by greater individual variability. This has been noted previously (e.g., Rosen et al. 1995), and confirmed in the current study. In a relatively low-powered study as is the case here, the greater variability could have contributed to the lack of a significant effect.

It is also probable that memantine may have limited effects on the subjective symptoms of withdrawal, in a manner similar to clonidine. This is important from the clinical perspective because subjective discomfort is most troubling to patients undergoing detoxification. This issue will require a more comprehensive assessment in future studies.

Subjective effects that were measured, 5 h after the study medication was given, are most likely due to the administration of an acute, high dose of memantine. These effects are characteristic of other non-competitive NMDA antagonists like dextromethorphan or ketamine (Krystal et al. 1994; Zawertailo et al. 1998). It is also possible that memantine, given to participants maintained on fixed doses of morphine, potentiated the subjective effects of morphine. In the current analysis, we could only compare the effects of memantine/morphine to the placebo/morphine combination. It is therefore possible that the effects of memantine in non-opioid dependent participants would have been different. These mildly positive effects of memantine might be advantageous from a treatment perspective in that they may foster compliance with the medication. In substance abuse treatment, compliance rates with agonist medications that possess positive subjective effects, like methadone or buprenorphine, are much higher than compliance rates with medications devoid of positive subjective effects, like naltrexone or disulfiram. Opiate agonists, however, have abuse liability. In contrast, there is no evidence of memantine abuse in the last 15 years of its widespread use in Europe, at the doses used in the present study (Parsons et al. 1999).

A multiple baseline design was used as a feasible design that allows monitoring of the time-course of memantine's effects on opioid dependence. This design can fully control for sequence effects, assuming that a tested response (in this case the severity of withdrawal) has reached acceptable stability criteria before the intervention is introduced. This study did not test the reliability of serial naloxone challenges, but relied on previously published reliability data (Rosen et al. 1995). In Rosen's study, the response to naloxone was relatively stable over three consecutive challenges, with the trend for the severity of withdrawal, in particular subjective reports, to be greatest after the first challenge. In our study, all participants received an initial naloxone challenge on the day of admission; the test challenges began 5–8 days later and included one to four baseline challenges. It is,

however, possible that for some participants, in particular those with few baseline challenges, a stable baseline response might have not been reached before memantine was given, which might have contributed to a possible sequence effect. Alternatively, there continued to be a decline in the severity of withdrawal with subsequent naloxone challenges, possibly due to the "resetting" of the opiate receptors, as it was postulated based on the study with monkeys (Krystal et al. 1989) and the detoxification study with patients (Loimer et al. 1990). This hypothesis, however, has not been fully substantiated, as the human laboratory studies showed no change in withdrawal severity with subsequent naloxone challenges (Wright et al. 1991; Rosen et al. 1995) and one rodent study showed increase in the severity of withdrawal following the treatment with naloxone (Spanagel et al. 1998). Another possibility is that the combined administration of memantine and naloxone could have a long-lasting effect on the neuroadaptive changes that underlie physical dependence, and are most evident using subjective measures. Any of these factors might have contributed to the fact that the "reversal" of memantine's effect was not present on some of the measures. However, the fact the "reversal" was seen on CINA, even in such a low powered study, suggests that the multiple-baseline design was adequate to reveal memantine's effects.

In replicating this study, or any similar studies that evaluate the effects of medications on physical dependence, it may be preferable to use a parallel group design with a larger number of research volunteers. An additional limitation of the current study is the use of a single dose of memantine.

In the current study, a single dose of memantine attenuated the expression of naloxone-precipitated opioid withdrawal in individuals maintained on morphine. This effect was present when dependence was evaluated 6 and 54 h after memantine, but disappeared when dependence was evaluated 126 h after memantine and objective measures were used. These data are consistent with the hypothesis that NMDA receptor mediated neurotransmission plays a role in the expression of opioid physical dependence in humans. These findings may have implications for the treatment of opioid addiction and physical dependence associated with chronic opioid treatment. Memantine may be useful in clinical practice because of its extended effect on physical dependence and lack of inter-individual variability in the metabolism of this medication as compared to another NMDA antagonist, dextromethorphan. Memantine may be clinically useful in detoxification from opioids when used alone, with adjunct non-opioid medication(s), or in combination with decreasing doses of an opioid agonist (e.g., methadone). In particular, detoxification from methadone following its long-term use poses a clinical challenge and addition of memantine may facilitate the transition to abstinence. Because this study suggests utility of memantine in detoxification from opioids, further clinical trials should be conducted to confirm its clinical utility (Bisaga et al. 2000). Such studies should include assessment of the dose, duration of treatment, safety, and memantine's effects on symptoms, signs, and craving associated with opioid withdrawal.

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