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Evaluation of the reinforcing and subjective effects of heroin in combination with dextromethorphan and quinidine

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Abstract

Objective—Studies have suggested that the N-methyl-D-aspartate antagonist dextromethorphan may be useful in the treatment of opioid dependence.

Design—This double-blinded, placebo-controlled inpatient study evaluated the effects of 0, 30, and 60 mg of dextromethorphan and quinidine (DMQ) on the reinforcing and subjective effects of heroin in recently detoxified heroin abusers.

Participants—Nine heroin-dependent participants were admitted and then detoxified from heroin over the course of several days.

Interventions—Participants were subsequently stabilized on 0, 30, or 60 mg of DMQ. Each dose of DMQ was administered for two consecutive weeks, and the effects of heroin (0, 12.5, and 50 mg) were studied under each DMQ maintenance dose condition. DMQ and heroin dose were administered in random order both within and between participants.

Results—Planned comparisons revealed statistically significant increases in progressive ratio breakpoint values and positive subjective ratings as a function of heroin dose. There were no consistent changes in any of the responses as a function of DMQ maintenance dose, other than a modest reduction in craving.

Conclusions—In summary, results from this study suggest that maintenance on dextromethorphan in combination with quinidine has a limited role in the treatment of opioid dependence.

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Keywords

self-administration; NMDA receptor; opiate; heroin

INTRODUCTION

N-Methyl-D-aspartate (NMDA) receptor antagonists have been of interest because they are nonopioid medications that appear to inhibit the development, expression, and maintenance of opioid dependence in rodents.[1–7] Noncompetitive or low-affinity NMDA antagonists such as memantine and clextromethorphan have been of particular interest due to the lack of phencyclidine-like side effects at clinically relevant doses.[8–13] These medications have been studied extensively in combination with morphine in rodents. For example, pretreatment with dextromethorphan before a naloxone challenge dose dependently reduced behaviors associated with opioid withdrawal in morphine-dependent mice[14] and reduced naltrexone-precipitated withdrawal symptoms in morphine-dependent neonatal rats.[15] Memantine reduced the acquisition of self-administration of morphine,[16] and it blocked both the reinstatement of conditioned place preference for morphine and the sensitization to morphine.[17–20] Like memantine, dextromethorphan disrupted conditioned place preference for morphine, reduced morphine self-administration, and prevented the development of morphine-induced tolerance and dependence.[2,21–25] Thus, several preclinical studies point to the effectiveness of both memantine and dextromethorphan in reducing the reinforcing effects of morphine.

In humans, dextromethorphan has been studied primarily in relation to opioid withdrawal. Early trials suggested that approximately 360 mg/d dextromethorphan was effective in managing opioid withdrawal.[26–28] This set of approximately 8-day trials indicated that many signs of withdrawal resolved by the third or fourth day of treatment with dextromethorphan in combination with other medications including diazepam, chlorpromazine, diazepam plus butylscopolamine, and tizanidine. However, these clinical studies were not sufficient to draw firm conclusions about the effects of dextromethorphan because they were confounded by multiple medications, initial and differential attrition, and other problematic methodological choices.

Other studies investigating the effects of dextromethorphan on withdrawal in humans have shown conflicting results. Bisaga et al.[29] used a dose of approximately 375 mg/d in an uncontrolled design on a chemical dependence unit and found a complete attenuation of several signs and symptoms of withdrawal and craving for heroin in patients who completed this approximately 6-day trial. Yet, no effects were found from doses of 60, 120, or 240 mg on naloxone-precipitated opiate withdrawal in a randomized, controlled laboratory study[30] or in a separate controlled laboratory study investigating naloxone-precipitated opiate withdrawal using doses of dextromethorphan up to 120 mg.[31] In a randomized, double-blind clinical trial using dextromethorphan and quinidine (DMQ) to treat withdrawal from morphine, there were no differences between placebo and 60 mg of DMQ on retention or subjective and objective ratings of withdrawal.[32]

The relationship between the NMDA antagonists and the reinforcing effects of opioids has been less widely studied in humans. Memantine produced modest reductions in subjective measures of high and good drug effect, as well as craving, liking, quality, potency, and amount that would be paid for heroin.[33] Memantine also produced a modest effect on self-administration such that self-administration of a moderate dose of heroin was significantly reduced by maintenance on memantine when compared with placebo maintenance. The effects of dextromethorphan on the reinforcing effects of opioids have not been studied.

Dextromethorphan has a unique metabolic profile when compared with other NMDA antagonists. It rapidly converts to dextrorphan on first-pass metabolism by CYP2D6 enzymatic activity.[34] It has been demonstrated that although dextrorphan has a similar affinity for the NMDA receptor as dextromethorphan, dextrorphan is rapidly glucuronidated and eliminated. This process suggests that when taken as a single entity, little systemic dextromethorphan remains available once the drug is metabolized. Researchers have found that the inclusion of quinidine, a CYP2D6 inhibitor, protects the dextromethorphan from metabolism, thereby enhancing its effects.[35] For instance, a study investigating whether response to a naloxone challenge varied as a function of dextromethorphan, DMQ, or dextrorphan administered 2 hours prior to the study drug in opiate-dependent mice found that the administration of dextrorphan (30 mg) reduced chewing; however, the administration of DMQ (30 mg) reduced both chewing and pawshake.[36] This dose of DMQ led to higher levels of dextromethorphan and lower levels of dextrorphan in the brain, which were in turn correlated with the behavioral measures, suggesting that increased levels of dextromethorphan led to the lessening of withdrawal symptoms.[36,37] DMQ was used in the current study to investigate whether this combination would have an effect on subjective responses and self-administration of heroin in humans under controlled laboratory conditions.

MATERIALS AND METHODS

Participants

Nine male (four Black, five White/Hispanic) healthy volunteers with a mean age of 40 (standard deviation [SD] = 4) years completed the study. Participants reported using heroin for approximately 13 (SD = 7) years and spending approximately $50 (SD = $20) per day on heroin. Seven participants smoked tobacco cigarettes (M = 10, SD = 9 cigarettes per day), six reported using alcohol approximately four times per month (SD = 5), four reported using cocaine approximately once per month (SD =1), and one reported using marijuana one to two times per month. All participants were intranasal (IN) heroin users and were dependent on heroin before the onset of the study, as verified by a naloxone challenge test.[38] Participants were not currently seeking treatment for their drug use.

After an initial telephone interview, eligible participants completed detailed questionnaires on drug use, general health, and medical history. Urine drug toxicologies (opioids, cocaine, benzodiazepines, cannabinoids, and amphetamines) were conducted. Physical and psychiatric evaluations were performed by a physician, while research psychologists assessed participants' degree of drug use. Participants were excluded from the study if they were seeking drug treatment, dependent on alcohol or illicit drugs other than heroin, or had a

major axis I psychiatric diagnosis other than opioid dependence. Those who had recent histories of violence or who were on parole/probation were also excluded from the study. Prior to admission, participants completed a training session, during which the study procedures were explained to them in detail. Volunteers were paid $25 per inpatient day and an additional $25 per day bonus if they completed the study. In addition, participants had the opportunity to earn money during the experimental sessions ($20 per sample session, plus up to $20 per self-administration session). Participants signed consent forms describing the aims of the study and the potential risks and benefits of participation. This study was approved by the Institutional Review Board of the New York State Psychiatric Institute (NYSPI).

Apparatus

During experimental sessions, participants were seated in a room equipped with Macintosh computers. All computer activities, vital signs, and behaviors were continuously monitored by the experimenters in an adjacent control room via a continuous on-line computer network, video cameras, and vital signs monitors (cardiovascular function was measured with a Sentry II Vital Signs Monitor; NBS Medical, Costa Mesa, CA; arterial oxygen saturation was measured with a pulse oximeter Model 400; Palco Laboratories, Santa Cruz, CA). Communication between the staff and participants was kept to a minimum during experimental sessions.

Detoxification and medication maintenance procedures

Participants were admitted into the hospital, and they were detoxified. Emergent withdrawal symptoms were treated with clonidine for piloerection, sweating, lacrimation, rhinorrhea, and hot/cold flashes; ketorolac tromethamine for muscle pain; prochlorperazine for nausea; and clonazepam for anxiety and insomnia. Participants were subsequently transitioned onto a maintenance dose of DMQ (0, 30, or 60 mg/d; given once per day at 08:30 hours) and stabilized (see Table 1 for a representative schematic of a dosing schedule). They then completed a series of experimental sessions (described in “Experimental sessions” section), after which they were transitioned onto the second DMQ maintenance dose. After the second series of experimental sessions, participants were transitioned to the third DMQ maintenance dose after which they completed the third set of experimental sessions. This dosing schedule was flexible and could be extended to 8 weeks if there were scheduling conflicts or if other interruptions were necessary. DMQ maintenance doses and heroin doses were randomly ordered among all participants.

General procedures

The purpose of this approximately 8-week inpatient study was to examine whether maintenance on DMQ (0, 30, or 60 mg/d) altered the reinforcing and subjective effects of IN heroin (placebo, 12.5, and 50 mg). Participants were maintained on each dose of DMQ for approximately 14 days, during which six laboratory sessions (one per day) were run. Table 1 depicts that detoxification took place from days 1 to 5 (week 1), after which participants were maintained on 30 mg of DMQ from days 6 to 19 (weeks 1–3). During this first maintenance dose condition, experimental sessions took place on days 11, 12, 15, 16, 18, and 19. Sessions were typically run 4 days per week with a day in between the heroin doses.

After a set of six experimental sessions, participants were transitioned to the next maintenance dose (Table 1 shows that the DMQ maintenance dose changed to 60 mg on day 20). This schedule took place under each DMQ dose.

Experimental sessions

During all sessions, participants completed computerized tasks and subjective-effects questionnaires. Heart rate and blood pressure were measured every 5 minutes, and blood oxygen saturation was monitored continuously with a pulse oximeter and recorded every minute during experimental sessions. Participants received breakfast between 08:00 and 09:00. There was one experimental session per day between 10:00 and 12:30. Only one heroin dose was administered per day to minimize the possibility that dependence would develop. Participants were not allowed to smoke tobacco cigarettes during experimental sessions but a cigarette break just prior to each session was permitted.

Physiologic, subjective, and performance effects were measured both before and after drug administration (see descriptions later). Heroin or placebo was administered only if vital signs were within safe limits (SpO_2 > 93 percent). The Subjective Opioid Withdrawal Scale (SOWS) was administered before drug administration. A photograph was taken of the right pupil 40 minutes before and 4, 10, 40, and 60 minutes after drug administration, along with the subjective-effects battery to capture the early time course of drug effects. A task performance battery was administered before 10 and 60 minutes after drug administration, while the Drug Effects Questionnaire (DEQ) was administered 60 minutes after drug administration. The self-administration task (see description later) was completed only during Choice sessions.

Laboratory procedures

Four questionnaires (Visual Analog Scale [VAS][35,39]; Opioid Symptom Checklist [OARCI][40–41]; SOWS[42]; DEQ[43]) and a task battery consisting of four tasks (Digit Symbol Substitution Task [DSST][44]; Divided Attention Task [DAT][45]; Rapid Information Processing Task [RIT][46]; Repeated Acquisition of Response Sequences Task [RA][47]) were used to assess subjective and performance effects at 4, 10, and 60 minutes after drug administration.

The VAS included a series of 26 items, each of which consisted of a 100-mm line. Participants rated their mood, drug effect, and craving between 0 mm (“Not at all”) at one end and 100 mm (“Extremely”) at the other end, for example, “I feel … Stimulated,” “High,” or “Good Drug Effect.” The DEQ measured drug effect through a series of questions such as “How strong a drug effect are you feeling?” “Do you feel any good effects from the drug?” where each response was measured on a discrete scale ranging from 0 (“No effects”) to 4 (“Very strong/good”). In addition, participants indicated in which drug class they thought that the drug effects were most like, ie, placebo, stimulant, or sedative, and rated drug liking from −4 (dislike very much) to 4 (like very much). The OARCI measured opioid intoxication by requiring participants to rate each of 13 symptoms (“My skin is itchy,” “I feel like I am nodding,”) either true or false to indicate whether or not they were experiencing the symptom, whereas the SOWS measured opioid withdrawal by participants

rating the degree to which they were experiencing 13 withdrawal symptoms (“My bones and muscles ache,” “I feel like yawning,”) from 0 (“Not at all”) to 4 (“Extremely”).

The task battery consisted of the 3-minute DSST, in which there were nine random 3 row by 3 column squares (with one square blackened per row) displayed across the top of the computer screen. A randomly generated number indicated which of the nine patterns should be emulated on a keypad by the participant on a particular trial. Participants were required to emulate as many patterns as possible by entering the patterns associated with randomly generated numbers appearing on the bottom of the screen. The 10-minute DAT consisted of a concurrent pursuittracking task and a vigilance task. The participant tracked a moving stimulus on the video screen using the computer mouse and had to signal when a small black square appeared at any of the four corners of the video screen. During the 10-minute RIT, a series of digits was displayed rapidly on the computer screen (100 digits per minute), and participants were instructed to press a key as quickly as possible after three consecutive even or odd digits. Lastly, during the 3-minute RA, four buttons were illuminated, and then participants were instructed to learn a 10-response sequence of button presses. A position counter incremented by one each time a correct button was pressed and remained unchanged whenever the participant responded on an incorrect button. A points counter increased by one each time, and the 10-response sequence was correctly completed. The sequence remained the same throughout the 3-minute task; however, a new, random sequence was generated every time the task occurred again. Participants were instructed to earn as many points as possible during the task by pressing the buttons in the correct sequence.

In addition to the subjective-effects measures, a self-administration task was also used where sample and choice sessions occurred on two separate but consecutive days.[33] During the sample session, participants received a “sample” dose of heroin and $20. During the choice sessions, the reinforcing effects of IN heroin (0, 12.5, and 50 mg) were examined using a self-administration procedure: participants were given the opportunity to work for increments of the sampled heroin dose and/or money amount using a modified progressive ratio procedure. Responses consisted of finger presses on a computer mouse. Standardized instructions were read to each participant explaining the self-administration task. Heroin and money were available under independent progressive ratio schedules, and participants were given 10 opportunities to choose between the two options. Ten percent of that day’s heroin dose or money value was available at each choice opportunity. Thus, if the dose of heroin for that day was 50 mg, at each opportunity participants could respond for 5 mg (10 percent of 50 mg) or $2 (10 percent of $20). Completion of the ratio requirement for each choice was accompanied by a visual stimulus on the computer screen. The response requirement for each of the two options increased independently such that the initial ratio requirement for each option was 50 responses. Thereafter, the ratio increased each time the option was selected (100, 200, 400, 800, 1,200, 1,600, 2,000, 2,400, and 2,800). Although it required high rates of responding, participants were capable of completing 11,550 responses in the allotted time.

At the start of each self-administration task, two illustrations appeared on the computer screen: an empty balance scale and an empty bank. As each choice was completed, either the scale filled up with a pile of powder or a dollar sign was added to the bank. Thus,

participants could always see how many money and drug choices had been made. No reinforcers were delivered until after the entire task was completed. At that time, the participant received whatever he or she had chosen: money and/or drug. Heroin and DMQ doses were administered in nonsystematic order both within and among participants.

Physiological measures

With the exception of pupil diameter measurements, physiological measures were recorded automatically (see "Apparatus" section). A blood pressure cuff, attached to the nondominant arm, recorded automatically every 5 minutes. Participants were also connected to a pulse oximeter via a soft sensor on a finger of the nondominant hand, which monitored arterial blood oxygen saturation (percentage of SpO_2). For safety, supplemental oxygen (2 L/min) was provided via a nasal cannula during all experimental sessions. Pupil photographs were taken and measured by the study research assistants. A specially modified Polaroid camera with a close-up lens (2× magnification) mounted on a desk-level tripod was employed for this purpose. Participants were instructed to stare straight ahead in the direction of the camera. All photographs were taken under ambient light conditions. Horizontal and vertical measurements of pupil diameter were made using calipers, and then these two measurements were averaged and divided by 2 to correct for the 2× magnification.

Drugs

Heroin HC1 was provided by the National Institutes on Drug Abuse (Rockville, MD) and prepared by the NYSPI research pharmacy. For nasal insufflation of heroin, lactose powder was used as the placebo and was added to each dose of heroin (12.5 and 50 mg) to achieve a final weight of 100 mg. Each dose was placed in a small plastic cup along with a short soda straw. Participants were instructed to insufflate the entire dose within a 30 second period into either one or two nostrils. For safety, a catheter was placed in an antecubital vein, and physiological saline solution was infused continuously during experimental sessions. Heroin was administered at 11:00 hours during laboratory sessions, and 3 hours after the morning DMQ dose.

Dextromethorphan hydrobromide and quinidine sulfate (DMQ) tablets (30 mg of dextromethorphan hydrobromide and 30 mg of quinidine sulfate per active tablet, and 0 mg per placebo tablet), pack aged in size 0 capsules (each active dose capsule contained 30 mg DMQ), were obtained from Avanir Pharmaceuticals (Greensboro, NC), along with matching placebo capsules. DMQ was administered once per day at 08:30 hours, and two capsules were administered at each dosing time.

Supplemental medications available to all participants for the duration of the study included trazodone for insomnia, Mylanta® (aluminum hydroxide, magnesium hydroxide, simethicone), for stomach upset, acetaminophen and ibuprofen for muscle pain, docusate and magnesium for constipation, and multivitamins with iron. To reduce their impact on our study measures, these medications, when needed, generally were given only during the evening hours. During each stabilization period, the additional following medications were available: clonidine, ketorolac tromethamine, prochlorperazine, and clonazepam.

Morning urine samples were collected daily. One random sample per week was screened for the presence of other illicit substances. No illicit substances were found in the participants' urine samples.

Statistical analyses

Repeated measures analyses of variance (ANOVAs) were performed for progressiveratio breakpoint values (the highest ratio that participants completed) that were collected during the choice session. Analyses were designed to answer two basic questions: 1) Does each active heroin dose function as a reinforcer across DMQ maintenance dose conditions?, and 2) Do the reinforcing effects of heroin differ between 0, 30, and 60 mg/d DMQ? Heroin and money breakpoint values were analyzed as a function of DMQ dose and heroin dose. Planned comparisons were performed to answer the two questions mentioned earlier, namely, 1) Each active heroin dose was compared with placebo, and 2) breakpoint values for each heroin dose were compared among the 0, 30, and 60 mg doses of DMQ.

Repeated measures ANOVA were also performed for pupil diameter, task performance, and subjective ratings that were collected during the sample session. Data were analyzed as a function of DMQ dose, heroin dose, and time. Pulse oximeter data obtained during the sample session were averaged within participants and analyzed as a function of DMQ dose, heroin dose, and time. Planned comparisons were similar to those described earlier, and to avoid potential type I error, effects were only considered statistically significant at $p < 0.01$.

RESULTS

Progressive ratio breakpoint

Figure 1 depicts mean progressive-ratio breakpoint values collected during the choice session for heroin (panel A) and money (panel B) as a function of heroin dose and DMQ maintenance dose. Planned contrasts comparing active heroin doses to placebo revealed that participants administered significantly more of the 12.5 and 50 mg heroin doses than placebo ($p = 0.005$). This was also the case under each maintenance close of DMQ. Correspondingly, progressive ratio breakpoints for money were significantly less as a function of both 12.5 and 50 mg heroin, with no effect of DMQ maintenance doses. Thus, there was no effect of DMQ on heroin self-administration.

Subjective effects (VAS, DEQ, OARCI)

Dose-dependent subjective effects of heroin were captured by the VAS during the sample sessions. For ratings of, "I feel…" "a Good Effect," "High," "Stimulated," "Energetic," and "Mellow," participants reported that the 50 mg dose of heroin elicited the greatest effect, followed by the 12.5 mg dose, with placebo eliciting the least (or no) effect (all $p < 0.01$). The same orderly relationship occurred across the VAS items describing the perceptions of the drug: "Potent," "High Quality," and "Liked the Choice." Under placebo maintenance conditions, participants indicated that they "Would pay" \$1.36 (± \$3.44) for the placebo heroin dose, \$4.39 (± \$6.56) for the 12.5 mg heroin dose, and \$7.81 (± \$6.78) for the 50 mg heroin dose.

There were minimal effects of DMQ on the VAS during the sample sessions. Across the entire 60-minute session, the 12.5 mg dose of heroin was rated as more “Stimulating” under the 30 mg DMQ condition than under placebo or 60 mg maintenance conditions (heroin × DMQ × time, p = 0.008; Figure 2). Additionally, there was a significant DMQ × time interaction with regard to heroin craving (p = 0.0001). The 30 mg maintenance dose of DMQ reduced ratings of “I Want Heroin” in 10 minutes after drug administration, which could be interpreted as a subtle blunting of craving for heroin irrespective of heroin dose shortly after administration (Figure 3) This effect was somewhat in evidence at 60 minutes (p = 0.02).

Ratings on the Drug Effects Questionnaire and the sum score on the OARCI mirrored the VAS. Heroin produced dose-related increases in DEQ ratings of “Good Effect,” “Strength of Drug Effect,” “Drug Liking,” and “Take Again,” as well as the OARCI. DMQ did not significantly interact with ratings of subjective opioid withdrawal. Average scores were relatively low throughout the study, ranging from 0.89 (± 1.05) to 5.11 (± 8.82) of a total possible score of 64.

Performance tasks

Heroin impaired performance on the DAT. The average distance between the cursor and a moving stimulus tracking distance increased from 12,257 pixels after administration of placebo heroin to 22,563 pixels after administration of 50 mg heroin (p = 0.007). Administration of the 30 mg DMQ dose increased latency to identify a target stimulus from placebo levels of 55.4 ± 19.0 ticks to 69.5 ± 28.0 ticks (p = 0.004), whereas the effects of 60 mg DMQ did not differ from placebo. Heroin decreased the maximum speed at which the target traveled from 6.20 ± 1.70 ticks at the placebo dose to 5.15 ± 2.12 ticks at the 50 mg dose (p = 0.0001). There were no effects of heroin or DMQ on incorrectly identified targets. There were no effects of heroin or DMQ maintenance on the remainder of the task battery, including the RA, RIT, and the DSST. Overall, task performance did not vary from placebo performance levels.

Physiological effects

Heroin dose-dependently reduced pupil diameter from 5.4 ± 0.7 mm after placebo administration to 4.9 ± 0.9 mm, and 4.0 ± 1.2 mm after 12.5 and 50 mg heroin administration (p = 0.0001). There was no effect of heroin on arterial oxygen saturation; however, maintenance on 30 and 60 mg of DMQ led to a statistically significant decrease in saturation that did not return to baseline levels in the 30 mg condition (30 mg: BL M = 98.9; 10 min M = 98.5; 20 min M = 98.3, 60 min = 98.4, BL vs 60 min [p = 0.0002]), as opposed to 60 mg, which did return to baseline levels (BL M = 98.7; 10 min M = 98.4; 20 min M = 98.6; 60 min = 98.5). The heart rate decreased over the course of the session (p = 0.0001). There were no effects of heroin or DMQ on arterial pressure, systolic pressure, or diastolic pressure.

DISCUSSION

Maintenance on DMQ did not alter the reinforcing effects of heroin. Participants self-administered more heroin than placebo, and this was not changed by administration of DMQ. Overall, DMQ minimally affected ratings of subjective effects. However, maintenance on 30 mg seemed to have a pronounced effect on the stimulating effects of 12.5 mg heroin. This dose also led to a modest reduction in heroin craving.

There was a suggestion that DMQ could worsen the respiratory depressant effects of heroin, as suggested by the small but statistically significant immediate decrease in arterial oxygen saturation associated with the 30 mg dose; however, these changes in arterial oxygen saturation were not clinically significant. DMQ maintenance did not substantially affect task performance. Taken together, even when considering the small sample size, these laboratory data suggest that DMQ has limited effects on heroin self-administration or the subjective, physiological, and cognitive effects associated with heroin.

These results should also be taken in the context of data from another noncompetitive NMDA antagonist, memantine. Memantine produced modest effects on the subjective responses elicited by heroin.[33] For instance, 60 mg memantine reduced the amount of money participants would be willing to pay for 12.5 mg of heroin, an effect that lasted up to 40 minutes postdose. In the current study, there were no effects of 30 mg and 60 mg DMQ on ratings of willingness to pay for heroin. Ratings of “I want heroin” were also reduced by 30 and 60 mg of memantine across all dose conditions, whereas in this study, this effect was perceived as only a mild blunting of craving across the session. There was a modest effect of memantine on the reinforcing effects of heroin such that 30 mg reduced self-administration of the 12.5 mg heroin dose; however, there was no such effect in this study.

Nevertheless, a reduction in craving may have clinical utility. Regular drug use has been associated with changes in mental state that may include increased craving for drug.[48] Opioid agonists or partial agonists, such as buprenorphine, have only produced effects on craving at the highest end of the dose spectrum in the labratory,[49,50] while the evidence surrounding the opioid antagonist naltrexone is variable. Self-administration studies have shown both increased and decreased craving as a function of “wanting heroin” in heroin abusers,[51,52] whereas naltrexone had no effect on drugcue-induced craving in patients being maintained on naltrexone for the treatment of opioid dependence.[53] Thus, it is possible that the addition of an NMDA antagonist, such as DMQ or memantine, to an agonist or antagonist treatment regimen may confer additional therapeutic advantage. Such an effect might have been more robustly observed in treatment-seeking individuals; however, this demographic was not included in the present trial.

Overall, these findings are at odds with the preclinical literature, most of which has focused on rodents. Although it is not possible to draw definitive conclusions from the rodent models, it is possible that the difference in findings was due to the higher doses that could be tested in rodents. This supposition is supported by the available human clinical studies, in which doses as large as 375 mg/d produced a positive effect on withdrawal symptoms[29]; yet, doses up to 240 mg/d did not.[30,31]

In addition to the dose range, the other difference in this study when compared with others in the literature is the use of DMQ instead of pure dextromethorphan. Quinidine was used to inhibit cytochrome CYP2D6, and thus prevent the metabolism of dextromethorphan to dextrorphan.[34,54] Given the recent data collected in rodents showing significant behavioral effects of dextromethorphan,[36,55] we hypothesized that increased levels of dextromethorphan likewise would be related to behavioral effects in humans. The combination of DMQ used here (the highest daily dose being 60 mg dextromethorphan plus 60 mg quinidine) should have resulted in a 25-fold increase in peak serum dextromethorphan concentrations,[34] which matched or exceeded estimated serum levels achieved with higher doses of dextromethorphan alone tested in prior studies.

Because of concerns about cardiovascular toxicity, it was not possible to test higher doses of this particular DMQ formulation. A newer formulation with a 3:1 (dextromethorphan:quinidine) ratio is being developed to address possible QT interval prolongation (Zenvia™ Cardiac Safety Overview, May, 2009; ref. 56), and future studies may use this drug in combination with heroin. However, even when taking these considerations into account, the findings here are not particularly encouraging with regard to DMQ. In light of the current data, and when considered together with other human studies examining other noncompetitive NMDA antagonists, the scope of the findings from this class of medications is not robust (especially when compared with current available medications such as buprenorphine, methadone, or naltrexone). On balance, these data suggest that DMQ does not have a promising role as a single entity, but may have a role as an adjunct medication in the treatment of opioid dependence.

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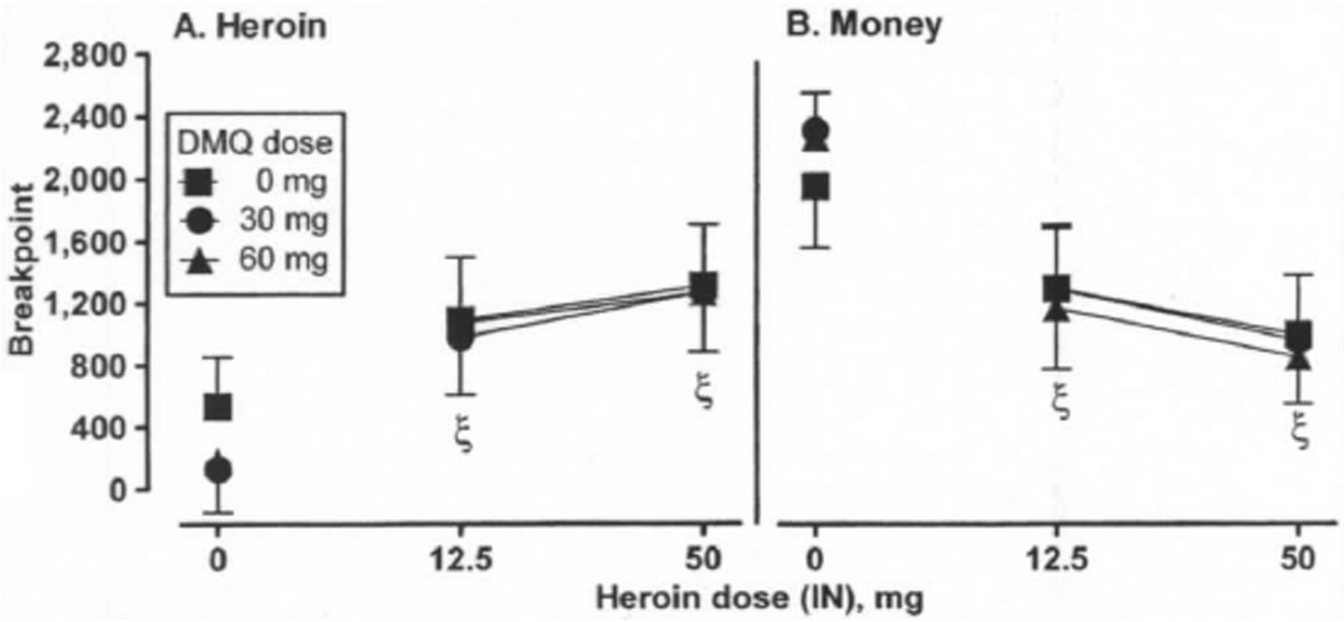

Figure 1.

Progressive ratio breakpoint values for drug (A) and money (B) during choice sessions as a function of heroin and DMQ doses. Data points represent the average values across participants, while error bars represent the standard error of the mean. Breakpoint values range between 0 and 2,800. "ξ" refers to the difference between the heroin dose and placebo (all $p \leq 0.01$). Images (A) and (B) suggest that there was no effect of DMQ on heroin self-administration.

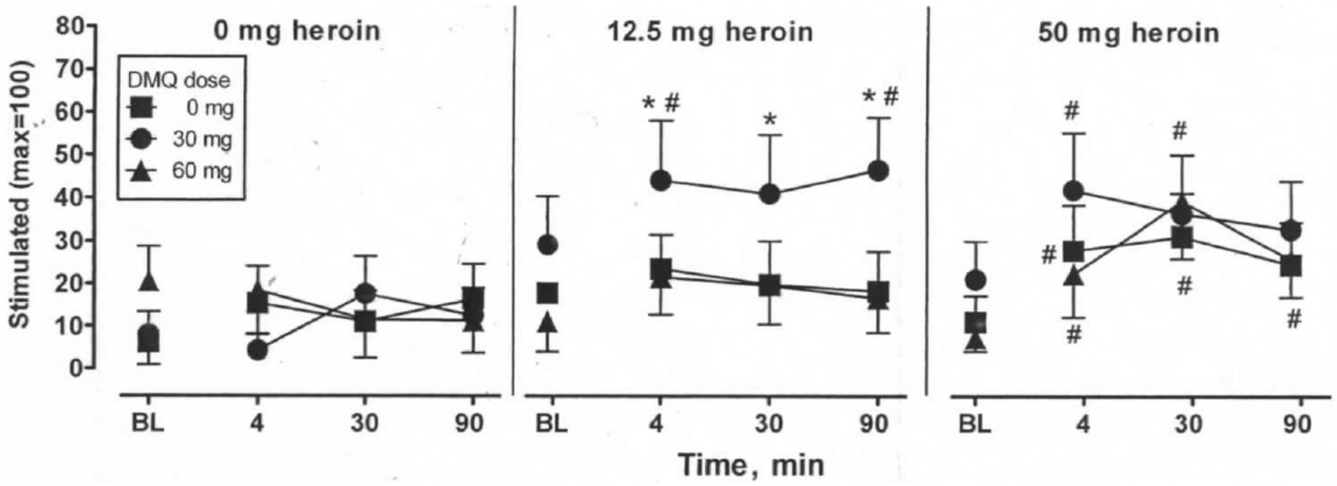

Figure 2.

VAS rating of "Stimulated" during choice sessions as a function of heroin and DMQ doses. Data points represent the average values across participants, while error bars represent the standard error of the mean. Values ranged between 0 and 100 mm. The symbol "*" indicates a difference from placebo at that time point, while "#" indicates a difference from baseline (all $p \leq 0.01$). An enhanced stimulating effect of the 12.5 mg heroin dose in combination with 30 mg DMQ is depicted.

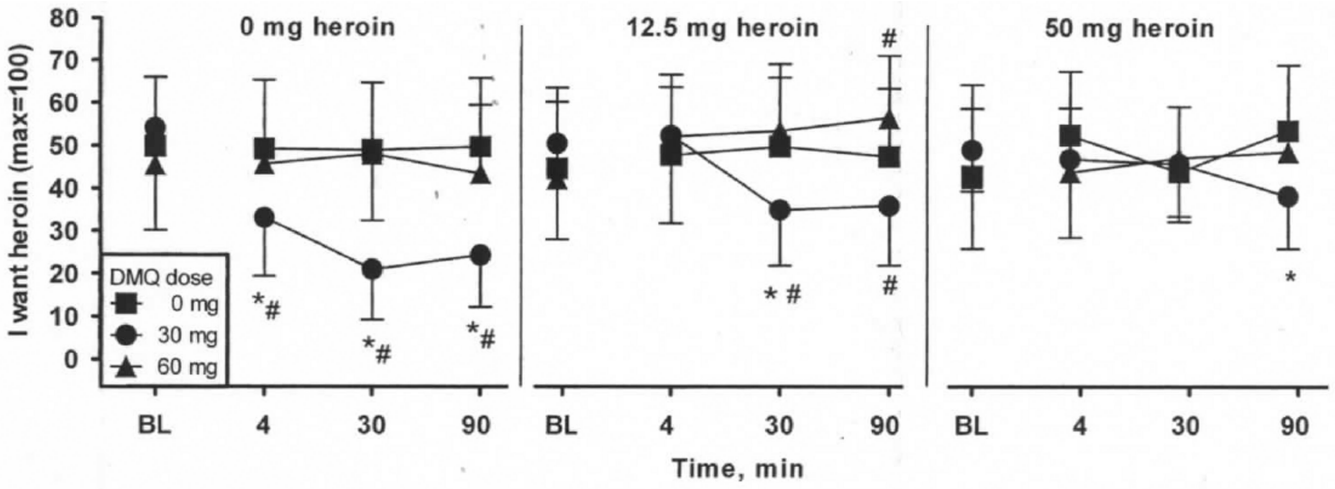

Figure 3.

VAS rating of "I want heroin" during choice sessions as a function of heroin dose, DMQ dose, and time of the session. Data points represent the average values across participants, while error bars represent the standard error of the mean. The symbol "*" indicates a difference from placebo at that time point, while "#" indicates a difference from baseline (all $p < 0.01$). A subde blunting of craving for heroin is depicted.

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Table 1

Representative dosing schematic

Week of study	**Week 1**							**Week 2**							**Week 3**						
Study day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Day of week	M	T	W	Th	F	Sa	Su	M	T	W	Th	F	Sa	Su	M	T	W	Th	F	Sa	Su
DMQ dose*	Detoxification					30	30	30	30	30	30	30	30	30	30	30	30	30	30	60	60
Heroin dose*											0	0			12.5	12.5		50	50		
Laboratory session†											S	C			S	C		S	C		
	Week 4							**Week 5**							**Week 6**						
Study day	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42
Day of week	M	T	W	Th	F	S	Su	M	T	W	Th	F	Sa	Su	M	T	W	Th	F	Sa	Su
DMQ dose*	60	60	60	60	60	60	60	60	60	60	60	60	0	0	0	0	0	0	0	0	0
Heroin dose*				50	50			0	0		12.5	12.5						12.5	12.5		
Laboratory session†				S	C			S	C		S	C									
	Week 7																				
Study day	43	44	45	46	47	48															
Day of week	M	T	W	Th	F	Sa															
DMQ dose*	0	0	0	0	0	D/C‡															
Heroin dose*	Pbo	Pbo		50	50																
Laboratory session†	S	C		S	C																

Abbreviations: M, Monday; T, Tuesday; W, Wednesday; Th, Thursday; F, Friday; Sa, Saturday; Su, Sunday.

*DMQ dose, heroin dose: milligrams (mg)

†Laboratery session: S, sample session; C, choice session.

‡D/C: Discharge.