Available online at www.sciencedirect.com
SCIENCE DIRECT®
Pharmacology, Biochemistry and Behavior 76 (2003) 401–407
PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR
www.elsevier.com/locate/pharmbiochembeh

Amantadine does not modulate reinforcing, subjective, or cardiovascular effects of cocaine in humans☆

Eric D. Collins*, Suzanne K. Vosburg, Carl L. Hart, Margaret Haney, Richard W. Foltin

Division on Substance Abuse, New York State Psychiatric Institute, New York, NY, USA
Department of Psychiatry, College of Physicians and Surgeons, Columbia University, New York, NY, USA

Received 28 March 2003; received in revised form 4 August 2003; accepted 18 August 2003

Abstract

Data from several clinical studies have suggested that amantadine, which has dopaminergic agonist and glutamatergic antagonist effects, may be useful for the treatment of cocaine dependence. The interaction between amantadine and smoked cocaine was examined in 10 cocaine smokers (7 men, 3 women), who participated in a 26-day inpatient study. Participants were maintained on amantadine (0 and 100 mg bid) for 5 days prior to laboratory testing, using a double-blind crossover design. Under each medication condition, participants smoked a sample dose of cocaine base (0, 12, 25, and 50 mg) once, and were subsequently given five choice opportunities, 14 min apart, to self-administer that dose of cocaine or receive a merchandise voucher ($5.00). Each cocaine dose was tested twice under each medication condition, and the order of medication condition and cocaine dose varied systematically. Cocaine produced stimulant-like reinforcing, subjective, and physiological effects. Amantadine maintenance did not modify the choice to self-administer smoked cocaine. These findings, taken together with the decidedly mixed literature, suggest that amantadine (100 mg bid) will not have a role in the treatment of cocaine dependence.

Keywords: Cocaine; Amantadine; Dopamine; NMDA antagonists; Self-administration; Subjective effects; Cardiovascular effects; Human

1. Introduction

In the search for medications for cocaine dependence, attention has focused on medications with dopaminergic activity and, more recently, on medications with glutamatergic activity, principally antagonist activity at *N*-methyl-D-aspartate (NMDA) receptors. Amantadine, because it has both dopaminergic (Gianutsos et al., 1985) and noncompetitive NMDA antagonist activity (Kornhuber et al., 1994), may be a promising candidate medication for cocaine dependence. Thus far, the preclinical and clinical literature on amantadine for cocaine-use disorders has been mixed.

The preclinical literature on amantadine–cocaine interactions is itself contradictory. Chronic amantadine administration did not affect cocaine self-administration by baboons (Sannerud and Griffiths, 1988), although, in rats, it eliminated cocaine tolerance associated with continuous cocaine infusion but reduced behavioral effects of a single cocaine dose in a paradigm of intermittent cocaine injections (King et al., 1994).

In the clinical literature, findings from a few well-designed studies have suggested a role for amantadine in the management of cocaine dependence. Maintenance on amantadine 200 mg/day for 10 days reduced cocaine-positive urine samples at the end of treatment and at 1-month follow-up (Alterman et al., 1992). Sixteen weeks on amantadine 200 mg/day produced better treatment retention and higher rates of recent, although not sustained, cocaine abstinence at 8 and 16 weeks of treatment, compared with placebo (Shoptaw et al., 2002). Amantadine produced lower cocaine withdrawal scores than bromocriptine (Tennant and Sagherian, 1987) and, at a dosage of 400 mg/day, improved scores on the Brief Psychiatric Rating Scale (BPRS) during the first 15 days of acute cocaine abstinence, an effect that disappeared with amantadine, but not bromocriptine, over the next 15 days (Giannini et al., 1989).

☆ This paper is dedicated to the memory of Marian W. Fischman, who was an inspired mentor to the authors of this manuscript. Her contribution to this work was also significant, although she died before this manuscript could be prepared.

* Corresponding author. Division on Substance Abuse, College of Physicians and Surgeons, Columbia University, Unit 120, 1051 Riverside Drive, New York, NY 10032, USA. Tel.: +1-212-305-8732; fax: +1-212-305-9842.
E-mail address: edc3@columbia.edu (E.D. Collins).

0091-3057/$ – see front matter © 2003 Elsevier Inc. All rights reserved.
doi:1.1016/j.pbb.2003.08.013

Several clinical studies of cocaine-dependent patients in opioid agonist maintenance treatment have also suggested a role for amantadine in selected individuals. Patients with comorbid antisocial personality disorder (ASP) showed a poor response to amantadine compared with non-ASP patients, who more than doubled their percentage of cocaine-free urine over 12 weeks, while placebo-treated non-ASP patients did not improve (Leal et al., 1994). In similar patients with comorbid depression, both amantadine and desipramine, but not placebo, reduced cocaine use and Beck Depression Index scores (Ziedonis and Kosten, 1991). Finally, among patients maintained on buprenorphine, amantadine and desipramine improved treatment retention and reduced cocaine use compared to fluoxetine (Oliveto et al., 1995).

In contrast, however, there are comparably many well-designed but disappointing clinical studies of amantadine. Four weeks of amantadine 300 mg/day had no effect on cocaine use (Kampman et al., 1996), although a subsequent analysis suggested that amantadine did reduce cocaine use in individuals with more severe cocaine withdrawal scores (Kampman et al., 2000). At a dosage of 400 mg/day, amantadine was no better than placebo on measures of treatment retention, cocaine craving, or urine toxicology (Weddington et al., 1991). Cocaine craving did not improve with a single dose (Gawin et al., 1989) or with chronic administration of flexible dose amantadine (Robbins et al., 1992). Several studies of methadone-maintained cocaine users indicate that amantadine is unlikely to have a role in this population (Handelsman et al., 1995; Kolar et al., 1992; Kosten et al., 1992).

Despite the inconsistent findings on the potential utility of amantadine for cocaine dependence, the medication combines potentially therapeutic dopaminergic and glutamatergic actions with a long history of safe clinical use. The laboratory model of cocaine self-administration by cocaine-dependent individuals offers a more controlled environment than is available in clinical settings in which to elucidate interactions between cocaine and amantadine. Prior laboratory studies of dopamine agonists had suggested some potentially beneficial interactions of dopaminergic agonists with cocaine (Haney et al., 1998, 1999) although the NMDA antagonist, memantine, did not appear promising (Collins et al., 1998). The present study investigated the effects of amantadine on smoked cocaine self-administration and the subjective and cardiovascular effects of cocaine among frequent cocaine smokers.

2. Methods

2.1. Participants

Ten research volunteers, seven male (six Black, one Caucasian) and three female (two Black, one Hispanic), aged 30–45 years (mean = 37.4 years), all active "crack" cocaine smokers, were solicited through word-of-mouth referral and newspaper advertisements in New York. Every individual specifically denied a desire for treatment for cocaine dependence, even when offered free referrals. The research participants reported spending $\$338 \pm 228$ per week on cocaine. All denied using heroin, methadone, or other opiates. Nine participants also smoked an average of 19 tobacco cigarettes daily (range 5–30 cigarettes/day). The participants had completed 12.5 years of education (range 8–16 years).

All participants passed a medical and psychological evaluation prior to the study, and none was receiving psychiatric treatment. Each participant signed a consent form, approved by the Institutional Review Boards of the College of Physicians and Surgeons of Columbia University and the New York State Psychiatric Institute. The consent form described the study, outlined the possible risks, and indicated both that the research participant could choose to smoke cocaine and that an experimental medication or placebo would be given daily. Two additional participants (both Black males) began the protocol but were discharged prior to completion, because each developed nonspecific electrocardiogram T-wave changes (one following cocaine administration and one prior to receiving any cocaine in the study) that precluded further research participation.

2.2. Apparatus

The apparatus and laboratory setup were as previously described (Collins et al., 1998; Foltin et al., 1995; Haney et al., 1999).

2.3. Procedure

The research volunteers were admitted to the hospital for 26 days (25 nights). All of the participants took part in a total of sixteen 2.5-h weekday laboratory sessions, two per day on 4 days between study days 7 and 11, and again between study days 21 and 25. Individuals were exposed to each dose of cocaine (0, 12, 25, and 50 mg) twice during each amantadine maintenance condition. The four available cocaine doses were initially tested in four consecutive lab sessions over 2 days, with cocaine doses presented in random order, except that no participant received the highest dose during his very first laboratory session of the study; the four doses were then again tested in four consecutive sessions over 2 of the following 3 days, so that doses given in the morning at the beginning of the week were given in the afternoon at the end of the week. This counterbalanced design reduced the likelihood that time of day factors, including carryover effects from morning to afternoon sessions, would confound the results. Participants were maintained on amantadine (0 or 100 mg bid), for 5.5 days prior to the laboratory testing periods and throughout each testing period. Five of the volunteers received amantadine first (days 1–11), and the remaining five received placebo

first. Research participants, nurses, and the investigators with participant contact were blind to the medication condition throughout the study. During laboratory sessions, research nurses located in the adjacent room continuously observed participants via a one-way mirror, and the participants and staff could communicate via an intercom system. Participants had access to television, radio, and videotape movies while on the Clinical Research Center, but they were allowed no visitors and no passes off the unit.

In each of the 16 laboratory cocaine self-administration sessions, there was a 20-min period of baseline vital sign observations and mood scales (see descriptions below). Following the baseline assessments, research participants were allowed to "sample" the dose of cocaine base (0, 12, 25, and 50 mg) available that session. Cocaine smoking was accomplished by placing the metered dose of cocaine base in an 8-cm glass tube, or "stem," packed with fine metal mesh, blindfolding the participant, and allowing him or her to hold the glass stem while the research nurse held the flame from the lighter until the individual had finished inhaling the smoke. Following the sample dose, participants were given five choice trials, spaced 14 min apart, when they could choose to smoke the same amount of cocaine as in the sample dose or to receive a merchandise voucher worth $5.00. Merchandise vouchers were redeemable at local merchants (Toys 'R Us, Nobody Beats the Wiz Electronics Stores, Barnes & Nobles, Sloan's Supermarkets, or Conway's Department Stores).

Choice trials were signaled by an audible computer-generated tone and the appearance in outline form of two squares (3 × 3 cm) on the computer monitor. Participants selected an option by moving the cursor to the left or right (illuminating the square associated with that position) and pressing a button on the mouse 200 times. Once the response requirement was completed, the message "left (or right) option chosen" appeared at the bottom of the screen. A cocaine dose or merchandise voucher was not given on any trial in which cardiovascular activity was above our criteria for safe drug administration (i.e., maximal heart rate [HR] < 130, diastolic pressure [DP] < 100, systolic pressure [SP] < 165).

2.4. Subjective-effects questionnaire

A visual analog scale subjective-effects questionnaire utilized previously (Collins et al., 1998) was completed at baseline, 4 min following each dose of cocaine or voucher, and 30 min following the last dose of cocaine or voucher.

2.5. Drugs

Cocaine hydrochloride (provided by the National Institute on Drug Abuse) was prepared as described previously (Foltin et al., 1990). Amantadine HCl was obtained by the New York State Psychiatric Institute Pharmacy and packaged in identical blue #00 gelatin capsules (in 0 and 100 mg doses). It was administered at 8 a.m. and 8 p.m. each day on the inpatient research unit without a taper up or down. Amantadine has a half-life of 15 h. The active dosage of amantadine (100 mg bid) was chosen because it was the same dosage employed in the more promising clinical studies (Alterman et al., 1992; Shoptaw et al., 2002).

2.6. Data analysis

Data were analyzed using SuperANOVA statistical software for Macintosh. Each scale of the subjective-effects questionnaire was summarized as the maximal score obtained during the session. Maximal rate–pressure product (HR × SP), an index of myocardial oxygen demand (Holmberg et al., 1971; Kitamura et al., 1972), and maximal HR, SP, and DP were analyzed. Because the number of doses taken over the course of a session varied, an analysis similar to that described above was done for the effects of the first dose of cocaine taken during that session. All data were analyzed using a four-factor repeated measures ANOVA with maintenance condition (amantadine vs. placebo) as the first factor, cocaine dose (0, 12, 25, and 50 mg) as the second factor, replication of the session (first vs. second) under each maintenance condition as the third factor, and the order of amantadine dosing (first vs. second) as the fourth factor. Post hoc analyses were done using means comparisons, for differences between amantadine and placebo at each specific dose of cocaine. When cocaine was not given for any reason, participants still completed the subjective-effects measures, and cardiovascular monitoring continued; the data obtained, although cocaine was not administered, were used in all the analyses. Results were considered significant if $P < .05$.

3. Results

3.1. Cardiovascular effects

There were 507 cocaine doses administered in this study, reflecting a total of 532 doses chosen, of which 25 doses were withheld because of blood pressure elevations. The top panel of Fig. 1 shows the effect of cocaine on peak DP as a function of cocaine dose and maintenance condition. Cocaine produced dose-dependent increases in maximal DP [$F(3,24) = 26.75$, $P < .0001$], with the 50 mg dose increasing peak DP by about 19 mm Hg compared with placebo. HR [$F(3,24) = 20.98$, $P < .0001$] and SP [$F(3,24) = 70.99$, $P < .0001$] also increased with increasing cocaine dose, with maximal HR increases of about 24 bpm and maximal SP increases of about 29 mm Hg following the 50-mg cocaine dose compared to placebo. Cardiovascular responses to the first dose of cocaine showed similar dose-dependent increases for HR, DP, and SP [$P < .0001$, data not shown]. Amantadine maintenance did not significantly alter any of the cardiovascular effects of cocaine on any measure.

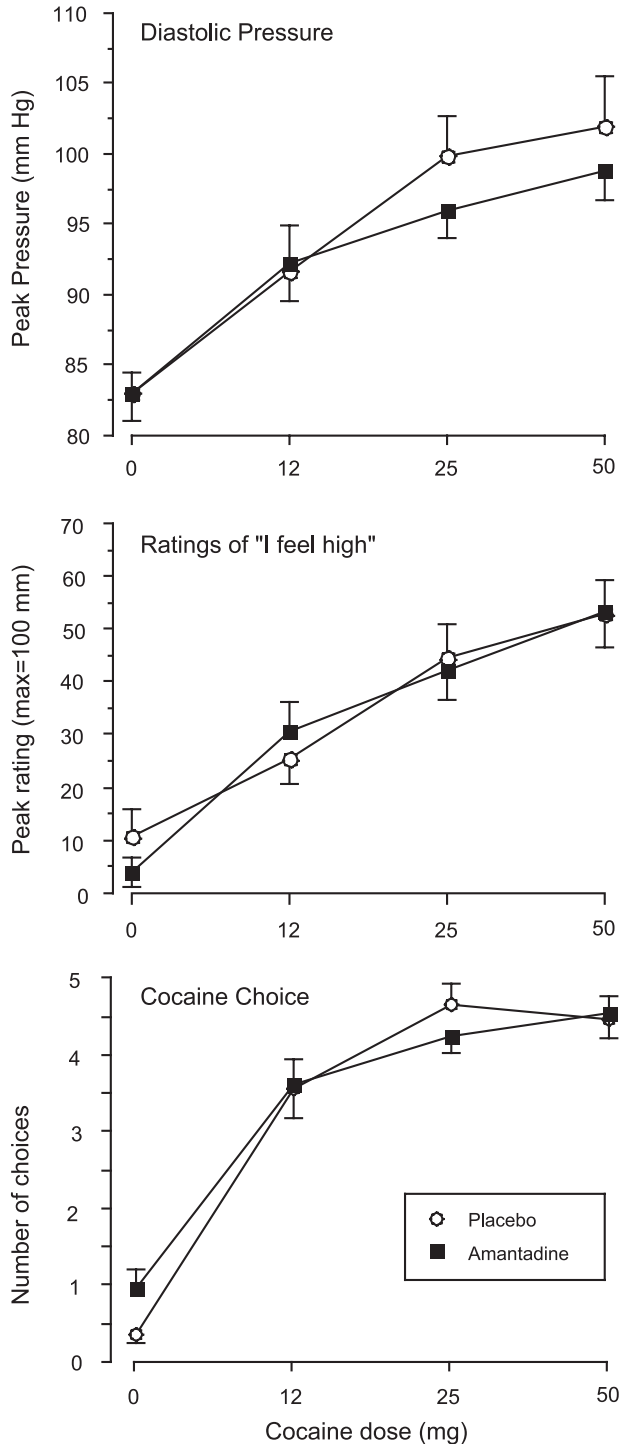

Fig. 1. Mean peak DP, mean peak ratings of "I feel high," and mean number of cocaine choices as a function of cocaine dose and maintenance medication condition. Error bars represent ± 1 S.E.M. Overlapping error bars were omitted for clarity.

3.2. Subjective effects

Cocaine produced dose-dependent increases in peak ratings of "I feel…" "high" [$F(3,24) = 18.51$, $P < .0001$, middle panel of Fig. 1], "stimulated" [$F(3,24) = 13.08$, $P < .0001$], and "a good drug effect" [$F(3,24) = 19.93$, $P < .0001$]; and dose-dependent decreases in "I feel…" "hungry," [$F(3,24) = 5.68$, $P < .004$], "tired" [$F(3,24) = 7.47$, $P < .001$] and "miserable" [$F(3,24) = 5.29$, $P < .006$; data not shown]. On ratings of the cocaine dose just received, cocaine produced dose-dependent increases in ratings of "The choice was of high quality" [$F(3,24) =$

14.56, $P<.0001$], "The choice was potent" [$F(3,24)=16.42$, $P<.0001$], "I liked the choice" [$F(3,24)=18.55$, $P<.0007$], and "For this dose I would pay" [$F(3,24)=11.13$, $P<.0001$]. Responses to the first smoked dose of cocaine showed a similar pattern of dose-dependent increases. Neither peak subjective-effect ratings nor first-dose effect ratings differed as a function of amantadine maintenance condition.

3.3. Cocaine choice

The bottom panel of Fig. 1 shows the mean number of doses of cocaine chosen as a function of cocaine dose and maintenance condition. There was a main effect of cocaine dose on choice behavior [$F(3,24)=58.22$, $P<.0001$], because participants chose all active doses of cocaine significantly more often than placebo. Amantadine maintenance had no effect on the number of times subjects chose cocaine over the alternative reinforcer ($5.00 voucher).

4. Discussion

The present data show that maintenance on amantadine (100 mg bid) had no effect on cocaine self-administration, cardiovascular effects of, and subjective responses to cocaine in cocaine-dependent smokers not seeking treatment. The absence of any cocaine–amantadine interaction is somewhat unusual, as laboratory models have typically demonstrated some effect of putative treatment medications on cocaine effects in humans (Fischman et al., 1990; Foltin and Fischman, 1996; Walsh et al., 1994).

As noted previously, there have been inconsistent results from the clinical and preclinical literature on the interactions of amantadine and cocaine. The indirect dopaminergic agonist actions of amantadine, although relatively weak, could contribute to positive results obtained in some treatment studies. Because other dopaminergic agonists, including pergolide (Haney et al., 1998) and ABT-431 (Haney et al., 1999), under similar laboratory conditions, reduced some subjective effects of cocaine, the lack of any modulation of cocaine effects by amantadine is consistent with the possibility that its dopaminergic effects are too small to be clinically significant.

An alternative explanation for some positive clinical studies with amantadine invokes its NMDA antagonist effects, as there is an extensive preclinical literature suggesting a role for NMDA antagonists in modulating cocaine effects (Damianopoulos and Carey, 1995; Matsumoto et al., 1997; Pulvirenti et al., 1997; Witkin, 1993). However, the literature here is also conflicting, with many studies indicating that NMDA antagonists, in moderate dosages, increase the effects of cocaine or other stimulants (Balster and Chait, 1978; Pierce et al., 1997; Ranaldi et al., 1996, 1997). An earlier laboratory study with cocaine smokers indicated that memantine, a noncompetitive NMDA antagonist and major metabolite of amantadine, increased several positive subjective effects of cocaine (Collins et al., 1998). That amantadine produced no effect at all, despite its NMDA antagonist action, could be a function of it producing less NMDA antagonism than the memantine dosage utilized previously, or possibly that dopaminergic effects offset the NMDA antagonist effects. A recent preclinical study showed that memantine and amantadine differentially affect striatal dopaminergic transmission (Peeters et al., 2003).

In the clinical literature exploring amantadine for cocaine dependence, lower doses of amantadine (typically 200 mg/day) seemed to be associated with beneficial effects (Alterman et al., 1992; Shoptaw et al., 2002). The absence of an effect of this dosage in the laboratory may be a function of many phenomena, including differences between treatment seekers enrolled in clinical trials and the non-treatment seekers enrolled here, but it is certainly consistent with the contradictory findings in the clinical literature on amantadine.

The advantages of using the laboratory model to test amantadine effects on cocaine taking lie principally in the greater experimental control available in the laboratory over many factors, including study medication compliance, nonuse of other drugs and medications, and the precise measures of cocaine taking. The laboratory model also offers face validity, in terms of directly measuring cocaine self-administration, rather than relying on the indirect measures of cocaine taking that must be used in treatment settings. A potential weakness in the approach involves the selection of non-treatment-seeking individuals, who may be less motivated to decrease their cocaine use than treatment-seeking individuals. Another potential limitation of the current study includes the use of only a single dose of amantadine (100 mg bid), as relevant clinical effects might occur with larger doses. Further, therapeutic responses could require longer maintenance on amantadine before they become apparent, although amantadine produces a rapid response when used to treat Parkinson's disease (Butzer et al., 1975), and these research participants were at steady-state plasma levels when studied in the laboratory. Finally, generalizing from the laboratory to clinical settings may be difficult. A laboratory model that provides more flexibility in the timing of drug, as compared to the fixed interval used here, may be more sensitive to effects of a medication on cocaine choice. However, the laboratory model utilized has been consistent with clinical outcomes. For example, cocaine craving measured in the laboratory increased with pergolide (Haney et al., 1998), and pergolide worsened clinical outcomes compared with placebo (Malcolm et al., 2001).

The results described here suggest that brief amantadine maintenance at a dosage of 100 mg bid does not reduce cocaine self-administration in a population of non-treatment-seeking frequent cocaine smokers in a laboratory setting. This corroborates the overall interpretation of the mixed findings in the clinical and preclinical literature,

suggesting that any role for amantadine in the treatment of cocaine dependence is likely to be limited.

Acknowledgements

This research was supported by grants DA-06234 and DA-00317 from the National Institute on Drug Abuse. Research participants resided on the Irving Center for Clinical Research of the Columbia-Presbyterian Medical Center supported by Grant No. MOI-RR-00645 from the National Institutes of Health. The assistance of Dr. Amie S. Ward, Dr. Daniel Bloomfield, Lorraine Kemp, Laura Burr, Alyce Stephens, Claudia Tindall, Brenda Fay, Laura E. O'Brien, and Pamela Parris is gratefully acknowledged.

References

Alterman AI, Droba M, Antelo RE, Cornish JW, Sweeney KK, Parikh GA, et al. Amantadine may facilitate detoxification of cocaine addicts. Drug Alcohol Depend 1992;31:19–29.

Balster RL, Chait LD. The effects of phencyclidine on amphetamine stereotypy in rats. Eur J Pharmacol 1978;48:445–50.

Butzer JF, Silver DE, Sahs AL. Amantadine in Parkinson's disease. A double-blind, placebo-controlled, crossover study with long-term follow-up. Neurology 1975;25:603–6.

Collins ED, Ward AS, McDowell DM, Foltin RW, Fischman MW. The effects of memantine on the subjective, reinforcing and cardiovascular effects of cocaine in humans. Behav Pharmacol 1998;9:587–98.

Damianopoulos EN, Carey RJ. Evidence for *N*-methyl-D-aspartate receptor mediation of cocaine induced corticosterone release and cocaine conditioned stimulant effects. Behav Brain Res 1995;68:219–28.

Fischman MW, Foltin RW, Nestadt G, Pearlson GD. Effects of desipramine maintenance on cocaine self-administration by humans. J Pharmacol Exp Ther 1990;253:760–70.

Foltin RW, Fischman MW. Effects of methadone or buprenorphine maintenance on the subjective and reinforcing effects of intravenous cocaine in humans. J Pharmacol Exp Ther 1996;278:1153–64.

Foltin RW, Fischman MW, Nestadt G, Stromberger H, Cornell EE, Pearlson GD. Demonstration of naturalistic methods for cocaine smoking by human volunteers. Drug Alcohol Depend 1990;26:145–54.

Foltin RW, Fischman MW, Levin FR. Cardiovascular effects of cocaine in humans: laboratory studies. Drug Alcohol Depend 1995;37:193–210.

Gawin FH, Morgan C, Kosten TR, Kleber HD. Double-blind evaluation of the effect of acute amantadine on cocaine craving. Psychopharmacology 1989;97:402–3.

Giannini AJ, Folts DJ, Feather JN, Sullivan BS. Bromocriptine and amantadine in cocaine detoxification. Psychiatry Res 1989;29:11–6.

Gianutsos G, Chute S, Dunn JP. Pharmacological changes in dopaminergic systems induced by long-term administration of amantadine. Eur J Pharmacol 1985;110:357–61.

Handelsman L, Limpitlaw L, Williams D, Schmeidler J, Paris P, Stimmel B. Amantadine does not reduce cocaine use or craving in cocaine-dependent methadone maintenance patients. Drug Alcohol Depend 1995;39:173–80.

Haney M, Foltin RW, Fischman MW. Effects of pergolide on intravenous cocaine self-administration in men and women. Psychopharmacology (Berl.) 1998;137:15–24.

Haney M, Collins ED, Ward AS, Foltin RW, Fischman MW. Effect of a selective dopamine D1 agonist (ABT-431) on smoked cocaine self-administration in humans. Psychopharmacology (Berl.) 1999;143:102–10.

Holmberg S, Serzysko W, Varnauskas E. Coronary circulation during heavy exercise in control subjects and patients with coronary heart disease. Acta Med Scand 1971;190:465–80.

Kampman K, Volpicelli JR, Alterman A, Cornish J, Weinrieb R, Epperson L, et al. Amantadine in the early treatment of cocaine dependence: a double-blind, placebo-controlled trial. Drug Alcohol Depend 1996;41:25–33.

Kampman KM, Volpicelli JR, Alterman AI, Cornish J, O'Brien CP. Amantadine in the treatment of cocaine-dependent patients with severe withdrawal symptoms. Am J Psychiatry 2000;157:2052–4.

King GR, Joyner C, Ellinwood Jr EH. Continuous or intermittent cocaine administration: effects of amantadine treatment during withdrawal. Pharmacol Biochem Behav 1994;47:451–7.

Kitamura K, Jorgensen CR, Gobel FL, Taylor HL, Wang Y. Hemodynamic correlates of myocardial oxygen consumption during upright exercise. J Appl Physiol 1972;32:516–22.

Kolar AF, Brown BS, Weddington WW, Haertzen CC, Michaelson BS, Jaffe JH. Treatment of cocaine dependence in methadone maintenance clients: a pilot study comparing the efficacy of desipramine and amantadine. Int J Addict 1992;27:849–68.

Kornhuber J, Weller M, Schoppmeyer K, Riederer P. Amantadine and memantine are NMDA receptor antagonists with neuroprotective properties. J Neural Transm Suppl 1994;43:91–104.

Kosten TR, Morgan CM, Falcione J, Schottenfeld RS. Pharmacotherapy for cocaine-abusing methadone-maintained patients using amantadine or desipramine. Arch Gen Psychiatry 1992;49:894–8.

Leal J, Ziedonis D, Kosten T. Antisocial personality disorder as a prognostic factor for pharmacotherapy of cocaine dependence. Drug Alcohol Depend 1994;35:31–5.

Malcolm R, Herron J, Sutherland SE, Brady KT. Adverse outcomes in a controlled trial of pergolide for cocaine dependence. J Addict Dis 2001;20:81–92.

Matsumoto RR, Brackett RL, Kanthasamy AG. Novel NMDA/glycine site antagonists attenuate cocaine-induced behavioral toxicity. Eur J Pharmacol 1997;338:233–42.

Oliveto A, Kosten TR, Schottenfeld R, Falcioni J, Ziedonis D. Desipramine, amantadine, or fluoxetine in buprenorphine-maintained cocaine users. J Subst Abuse Treat 1995;12:423–8.

Peeters M, Maloteaux JM, Hermans E. Distinct effects of amantadine and memantine on dopaminergic transmission in the rat striatum. Neurosci Lett 2003;343:205–9.

Pierce RC, Meil WM, Kalivas PW. The NMDA antagonist, dizocilpine, enhances cocaine reinforcement without influencing mesoaccumbens dopamine transmission. Psychopharmacology (Berl.) 1997;133:188–95.

Pulvirenti L, Balducci C, Koob GF. Dextromethorphan reduces intravenous cocaine self-administration in the rat. Eur J Pharmacol 1997;321:279–83.

Ranaldi R, French E, Roberts DC. Systemic pretreatment with MK-801 (dizocilpine) increases breaking points for self-administration of cocaine on a progressive-ratio schedule in rats. Psychopharmacology (Berl.) 1996;128:83–8.

Ranaldi R, Bauco P, Wise RA. Synergistic effects of cocaine and dizocilpine (MK-801) on brain stimulation reward. Brain Res 1997;760:231–7.

Robbins SJ, Ehrman RN, Childress AR, O'Brien CP. Using cue reactivity to screen medication for cocaine abuse: a test of amantadine hydrochloride. Addict Behav 1992;17:491–9.

Sannerud CA, Griffiths RR. Amantadine: evaluation of reinforcing properties and effect on cocaine self-injection in baboons. Drug Alcohol Depend 1988;21:195–202.

Shoptaw S, Kintaudi PC, Charuvastra C, Ling W. A screening trial of amantadine as a medication for cocaine dependence. Drug Alcohol Depend 2002;66:217–24.

Tennant Jr FS, Sagherian AA. Double-blind comparison of amantadine and bromocriptine for ambulatory withdrawal from cocaine dependence. Arch Intern Med 1987;147:109–12.

Walsh SL, Preston KL, Sullivan JT, Fromme R, Bigelow GE. Fluoxetine alters the effects of intravenous cocaine in humans. J Clin Psychopharmacol 1994;14:396–407.

Weddington Jr WW, Brown BS, Haertzen CA, Hess JM, Mahaffey JR, Kolar AF, et al. Comparison of amantadine and desipramine combined with psychotherapy for treatment of cocaine dependence. Am J Drug Alcohol Abuse 1991;17:137–52.

Witkin JM. Blockade of the locomotor stimulant effects of cocaine and methamphetamine by glutamate antagonists. Life Sci 1993;53: PL405–10.

Ziedonis DM, Kosten TR. Pharmacotherapy improves treatment outcome in depressed cocaine addicts. J Psychoactive Drugs 1991;23:417–25.