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Naltrexone Attenuates the Subjective Effects of Amphetamine in Patients with Amphetamine Dependence

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Amphetamine abuse and dependence is a global health concern with a collateral increase in medical and social problems. Although some of the neurobiological mechanisms underlying amphetamine dependence and its devastating effects in humans are known, the development of rational and evidence-based treatment is lagging. There is evidence from preclinical studies suggesting that the endogenous opioid system plays a role in mediating some of the behavioral and neurochemical effects of amphetamine in a variety of controlled settings. In the present study we assessed the effects of naltrexone, an opioid antagonist (50 mg) on the subjective physiological and biochemical response to dexamphetamine (30 mg) in 20 amphetamine-dependent patients. Patients received naltrexone/amphetamine followed by placebo/amphetamine, 1 week apart in a randomized double-blind placebo-controlled design. The primary objective of the study was to evaluate the effect of pretreatment with naltrexone on the subjective response to amphetamine, using a Visual Analog Scale. The secondary objective was to investigate the effects of naltrexone on physiological and biochemical responses to amphetamine, as measured by changes in blood pressure, heart rate, skin conductance, and cortisol. Naltrexone significantly attenuated the subjective effects produced by dexamphetamine in dependent patients ($p<0.001$). Pretreatment with naltrexone also significantly blocked the craving for dexamphetamine ($p<0.001$). There was no difference between the groups on the physiological measures. The results suggest that the subjective effects of amphetamine could be modulated via the endogenous opioid system. The potential of naltrexone as an adjunct pharmaceutical for amphetamine dependence is promising.
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INTRODUCTION

Amphetamine addiction is a disease that affects millions of people worldwide. An estimated 35 million persons are reported to abuse amphetamines, which is more than the total number of cocaine and heroin abusers combined (Vocci and Ling, 2005). A majority of i.v. drug users in Sweden abuse amphetamine (mostly racemic amphetamine) pushing this disorder to the forefront of psychiatric problems, which in addition to the concomitant increases in medical and social consequences makes this a significant public health concern (CAN, 2001). The emergence and spread of amphetamine abuse has closely followed that of the cocaine epidemic in the 1980s, however research on medication development for the former has just begun (Vocci and Ling, 2005). More specifically, a Cochrane review showed that there has been a lack of controlled clinical trials for amphetamine-dependence pharmacotherapy (Srisurapanont *et al*, 2001).

In recent years there has been a growing body of evidence that psychostimulant drugs modulate the endogenous opioid system in the brain regions with high dopaminergic input (Wang and McGinty, 1995; Fagergren *et al*, 2003). This has led to an interest in evaluating the potential role of neural systems, such as the endogenous system and its link to dopamine's (DA) action in the treatment of psychostimulants. For example, animal studies have shown that opioid antagonists, such as naltrexone (NTX) and naloxone block specific effects of amphetamine, eg amphetamine-induced locomotion, self-stimulating behavior, and conditioned place preference (Trujillo *et al*, 1989, 1991; Jones and Holtzman, 1992). NTX has also been reported to reduce the rewarding and behavioral effects of cocaine (Kuzmin *et al*, 1997; Kiyatkin and Brown, 2003). There is some evidence from clinical treatment studies suggesting that the endogenous opioids are involved in the subjective effects of cocaine, leading to a decrease in subjective 'high' craving and consumption (Kosten *et al*, 1992; Oslin *et al*, 1999;

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Schmitz *et al*, 2001). In a recent imaging study, the importance of this dopaminergic–opioid interaction in the human brain with regard to cocaine abuse was further demonstrated with an increase in μ-opioid receptor (mOR) binding in brain regions in individuals diagnosed with cocaine dependence (Gorelick *et al*, 2005). The mOR binding in limbic brain regions was also correlated with the intensity of craving, suggesting a role of the opioid system in cocaine craving. Although these changes were observed in cocaine abusers, a similar effect could be expected also among amphetamine abusers considering the common pharmacological mechanism of the drugs. In our previous work with healthy volunteers, NTX significantly decreased the subjective effects of amphetamine (Jayaram-Lindstrom *et al*, 2004). The results from our Phase I study provided some evidence of the interaction effect of NTX on the positive subjective effects of amphetamine, in healthy individuals.

The goal of the present experiment was to investigate the effect of NTX on the subjective, physiological, and biochemical response to dexamphetamine, in patients with chronic amphetamine dependence, using a randomized double-blind placebo-controlled within-subject design. Our primary hypothesis was that an acute dose of NTX pretreatment would attenuate the subjective effects of an oral dose of dexamphetamine, also in patients with a history of amphetamine dependence. A secondary aim of the study was to evaluate if NTX would alter also the physiological arousal, ie increased pulse, blood pressure, galvanic skin response (GSR), and hypothalamic–pituitary–adrenocorticoid (HPA) axis activity (cortisol and prolactin serum levels) following a dexamphetamine challenge. Blood levels of dexamphetamine were also monitored to further examine the mechanism of NTX, ie whether it attenuates the reinforcing effects of amphetamine by altering its pharmacokinetics or if NTX's effect pertains mainly to modulation of the appetitive effects (as measured by subjective scales).

In summary, the study aimed at investigating the role of the endogenous opioid system in mediating the subjective and physiological effects of amphetamine, using dexamphetamine as a model substance in patients diagnosed with amphetamine dependence.

METHODS

Subjects

Twenty abstinent amphetamine-dependent patients were recruited for the study from the outpatient substance dependence clinic at the Karolinska University Hospital, Stockholm. Patients provided their written consent for participation in the study, which was approved by the regional ethical review board in Stockholm, the Swedish Medical Products Agency and conducted in accordance with Good Clinical Practice (ICHGCP, 1996) and the Declaration of Helsinki.

As this was an outpatient study, for ethical reasons the patients recruited were from a larger pool of currently drug-free amphetamine-dependent patients awaiting psychostimulant treatment for their ADHD diagnosis. The high comorbidity of ADHD and psychostimulants implies that the sample of patients in this study may be considered representative of the general amphetamine-dependent population (Jaffe *et al*, 2005). Further data from our own clinic (unpublished data) has revealed that among all the amphetamine-dependent patients who underwent the full battery of psychiatric assessment during the years 2002–2006, 50% of them fulfilled the DSM-IV criteria for amphetamine dependence and ADHD.

The inclusion criteria for the study were (1) men between the ages 20 and 45, (2) DSM-IV criteria for amphetamine dependence, (3) DSM-IV criteria for ADHD, (4) drug-free from amphetamine for a minimum of 30 days, and (5) residence in Stockholm county. The exclusion criteria were (1) dependence on any substance other than amphetamine and nicotine, (2) any other major psychiatric diagnosis (other than ADHD and amphetamine dependence), and (3) testing positive on urine toxicology on the morning of testing and between the test days.

Procedures

The study was a double-blind placebo-controlled crossover design. Human laboratory studies of amphetamine have typically used doses between 10 and 30 mg orally and this has been associated with stimulant-type subjective effects (Martin *et al*, 1971; Mayfield, 1973). In the present study, dexamphetamine (the dextrorotatory isomer of amphetamine) was used at a dose of 30 mg (Metamina, Recip, six 5 mg tablets). The dose of NTX (ReVia, DuPont) was set at 50 mg, as this dose has proven to be efficacious in the treatment of the alcohol dependence syndrome (O'Malley *et al*, 1992; Volpicelli *et al*, 1992). Patients thus received either a 50 mg dose of NTX or identical placebo, followed by a 30 mg dose of dexamphetamine in a randomized design on 2 study days, 1 week apart. They received instruction to abstain from nicotine and caffeine on the morning of testing. Prior to starting the session, breath alcohol levels were assessed and supervised urine samples were collected to verify abstinence from commonly abused drugs. The urine samples were screened for central stimulating amines, opiates, cocaine metabolite (benzoylecgonine), cannabis, dextropropoxyphen, and benzodiazepines. In the event of relapse the patients would be considered dropouts (as measured by self-reports and urine toxicology) and referred back to the clinic for treatment. The study protocol allowed for dropouts to be replaced, to meet the total sample size of 20.

On the test day patients arrived at the clinic at 0800 hours where they received a standardized breakfast of 150 ml yogurt and 150 ml orange juice. At 0830 hours, a venous catheter was inserted in their left arm to draw blood at regular time intervals during the day. At 0930 hours the patients received an oral dose of either NTX or placebo. At 1130 hours (2 h postingestion of NTX/placebo) the patients received an oral dose of 30 mg dexamphetamine. A standardized battery of tests was administered during the entire test day comprising subjective and physiological measures. Patients were also provided with a standardized lunch. The testing procedures were identical on Days 1 and 2. Adverse effects were monitored systematically during the test days and also on the visits between the test days by the study physician (in the form of an interview and also by self-rating of symptoms from 'mild to severe' and the

duration of symptoms). All patients underwent 2–3 urine toxicology tests between the two test sessions (ie in a span of 1 week). Patients received debriefing at the end of each test day to discuss questions and experiences related to the testing. Upon completion of the study, all patients received a bag of groceries worth 50 Euro.

Subjective Measures

An analog rating scale (Visual Analog Scale, VAS) was administered to describe current drug effects. The VAS comprised four scales: 'feel the drug', 'like the effect', 'feel aroused', and 'want more', providing a composite measure of the subjective effect. The patients rated their experiences 30 min after ingestion of the first dose of NTX/placebo and then 60, 90, 120, 180, 210, 240, 300, and 330 min thereafter.

The shortened version the Profile of Mood Scale (POMS) was used to assess the general mood state of the individuals (McNair *et al*, 1971). The subjects indicated the extent to which the various adjectives matched with their current mood on a four-point scale. The POMS was administered every hour during the test day, over a total of 6 h.

Patients recorded the level of craving they experienced at the present time, every hour until the end of the test day using a Craving for Amphetamine Scale (Tiffany *et al*, 1993), adapted from the Tiffany craving scale. The scale consisted of 10 items and each item is a seven-point VAS with 'strongly disagree' on one pole and 'strongly agree' on the other.

Physiological Measures

To measure physiological effects of amphetamine, heart rate and blood pressure were recorded manually. These recordings were made at 30 min after ingestion of the first dose of NTX/placebo and then at 60, 90, 120, 180, 210, 240, 300, and 330 min. Sweat production was measured using GSR, via electrodes connected to the fingertips of the subjects. Skin conductance (μMHOS) was recorded at a 2 Hz frequency using fingertip electrodes connected to a PC computer via an RS232 beltpack/interface unit.

Biological Samples

Measurements of plasma cortisol were obtained at baseline (prior to consumption placebo/NTX) and then at scheduled intervals (−120, −60, 0, +15, +30, +45, +60, +90, +120, +150, +180, and +210). The samples were collected in heparin tubes and stored on ice immediately. They were then centrifuged at 4°C and serum was transferred to a microtube and stored at −20°C until assayed. Plasma cortisol concentrations were measured by standard radioimmunoassay at the clinical chemistry laboratory, Karolinska University Hospital.

Plasma samples (2 ml) were separated and collected to perform the pharmacokinetic analysis. Dexamphetamine was quantified in plasma using electrospray liquid chromatography–mass spectrometry (Agilent 1100 LC-MS) using amphetamine-D5 as an internal standard. A QC sample containing 25 ng/ml of amphetamine in blank plasma was analyzed together with the study samples.

Pharmacokinetic Evaluation

The pharmacokinetics of dexamphetamine was evaluated by compartment analysis. Initial estimates were obtained from the JANA stripping program (Dunne, 1985). The final estimates of the pharmacokinetic parameters were obtained from the PC-NONLIN program (Statistical Consultants Inc., 1986). The reciprocal of measured plasma concentrations was used as weights in the iterative procedure. The data was fitted to a one-compartment model with a zero or first-order absorption phase (10 and 14 cases, respectively). The optimal pharmacokinetic models were established by visual inspection of the fitted plasma concentration time curves and from the weighted squared residuals using the F-ratio test (Boxenbaum *et al*, 1974).

Data Analysis

The primary hypothesis of the study was that NTX attenuates the subjective effect of amphetamine in patients diagnosed with amphetamine dependence. The primary outcome measure was the difference in subjective measures of amphetamine effects. This was operationally defined as the composite score of the four VAS scales for the various time points, during each test day, comparing NTX *vs* placebo. The primary outcome measure was analyzed using repeated-measures ANOVA.

The scores of the Craving for Amphetamine Scale and POMS were analyzed in a similar manner, where the aggregate scores of the scales were calculated for the various time points, compared between the two treatment groups, using repeated-measures ANOVA.

The secondary outcome measure (heart rate, pulse, GSR) was the difference in physiological measures of amphetamine effects. This was computed by calculating composite scores, for the various time points during the test dates, comparing NTX *vs* placebo condition. The secondary outcome measures were analyzed using repeated-measures ANOVA. All values are expressed as the mean ± SD.

RESULTS

Demographics

A total of 20 patients participated in the study, fulfilling the DSM-IV criteria for amphetamine dependence and ADHD. Two patients dropped out of the study after the first day of testing by reporting an inability to comply with testing procedure (ie staying indoors and filling out questionnaires). As per protocol the two dropouts were replaced by the next patient in line to attain the sample size of 20. The mean age of the subjects was 33.0 years (SD = 8.8). All subjects were male and reported on an average 12.9 years (SD = 6.4) of amphetamine dependence and abused 0.5–1 g of amphetamine per occasion of use. In addition to amphetamine the subjects reported regular use of nicotine (90%) and sporadic use of marijuana (50%) and alcohol (80%). None of the subjects fulfilled DSM-IV criteria for history of past dependence for other substances. All included patients were abstinent from amphetamine and all other illicit substances (minimum of 4 weeks) as verified by bi-weekly urine tests. For 16 participants, the mode of

amphetamine use was intravenous while 4 subjects showed a fluctuating pattern between oral and i.v. use. Seven out of twenty patients had a positive family history of drug dependence.

The patients reported few NTX-induced subjective side effects namely mild fatigue ($n=2$), headache ($n=1$), and nausea ($n=1$), which abated by the end of test day. Two patients dropped out of the study. These were neither due to adverse events nor relapse to drug use but related to noncompliance to the study procedure (staying indoors, filling out forms).

Subjective Effects

Figure 1 displays the primary outcome measure of the study, ie the subjective effects of the dexamphetamine challenge for the two treatment groups over time. First, there was a main effect for time point of measurement ($F=419.6$, $p<0.001$), showing that the amphetamine challenge invoked a subjective drug effect over time. Further there was also a main effect for treatment condition ($F=482.1$, $p<0.001$), showing that the placebo condition produced a higher subjective drug effect compared to the NTX condition, ie NTX significantly reduced the subjective effects invoked by dexamphetamine. The difference between the two treatment conditions emerged at the 150 min time point measurement ($t(19)=-5.17$, $p<0.001$).

As a secondary analysis of subjective high, the specific items of the composite VAS were analyzed (Figure 2). After Bonferroni correction of multiple comparisons, the results of each of the separate VAS items ('feel the drug', 'like the effect', 'feel aroused', and 'want more') were consistent with the overall results of the VAS.

With regard to the POMS scale (subscales of vigor and fatigue) there was no difference between the two treatment conditions.

Figure 3 displays mean craving score for the NTX *vs* placebo condition. The NTX treatment condition produced a significantly lower mean craving score when compared to the placebo condition using the Craving for Amphetamine Scale ($F=44.8$, $p<0.001$).

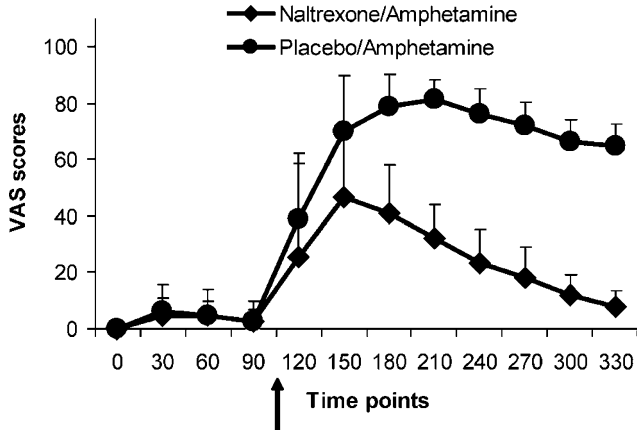

Figure 1 VAS mean scores (±SD) of subjective high over the two treatment conditions and at different time points. Pretreatment with NTX (50 mg) significantly ($F=419.6$, $p<0.01$) attenuated the subjective effects of dexamphetamine (30 mg) when compared to placebo. A single dose of NTX/placebo was administered at time point 0. The arrow indicates the administration of the 30 mg dose of dexamphetamine. Data points show mean scores for all 20 patients over the two conditions.

Physiological Effects

Pretreatment with NTX compared with placebo did not produce any significant differences between the physiological measures of blood pressure, pulse, and GSR.

Cortisol Measures

Figure 4 displays interaction effect between treatment and time for the cortisol levels between the two groups. The mean baseline plasma cortisol concentration (predrug baseline) was 349 mmol/l, with no difference between the two groups. Patients in the NTX/amphetamine condition were significantly higher than the placebo/amphetamine condition ($F=12.2$, $p<0.05$).

Prolactin levels (baseline levels 7.8 mmol/l) did not differ between the two groups.

Pharmacokinetic Measure

Figure 5a and b show the dose-normalized drug exposure, ie AUC/mg/kg, and the elimination half-life, respectively, as a function of age of the patients. There were no differences in the pharmacokinetics of oral dexamphetamine between weeks 1 and 2 (ie between the placebo/dexamphetamine and NTX /dexamphetamine conditions).

CONCLUSION

In this study, we investigated the effects of an opioid antagonist, NTX on the subjective, physiological, and biochemical effects of amphetamine in dependent individuals in a double-blind placebo-controlled design. Pretreatment with NTX significantly blunted the subjective effects of amphetamine. It was hypothesized that in this sample of amphetamine-dependent individuals, a small challenge dose of amphetamine after a period of abstinence would increase their endogenous opioid and related DA activity and produce a desire for more. Furthermore, NTX by virtue of blocking the opioid receptors would in turn dampen the acute subjective effects and craving for amphetamine. The findings of the present study were consistent with this hypothesis that the abstinent patients, when pretreated with NTX, showed a blunted subjective and craving response to an amphetamine challenge. The VAS items describing the drug effects ('feel the drug', like the effect', 'feel aroused', and 'want more') have been shown across studies to reliably predict the reinforcing effects of stimulant drugs. NTX blunted the effect of dexamphetamine on each of the VAS items, making the results on the individual VAS items consistent with the overall subjective results. The current data provide the proof of concept that NTX not only dampens the subjective effect of amphetamine, in the event of drug use, but also decreases the likelihood of additional drug consumption (as evidenced by the reduction in 'want more' and craving).

The potential neurobiological mechanism of NTX's effects on amphetamine can be inferred from preclinical findings. NTX is a nonselective opioid antagonist and binds to opioid

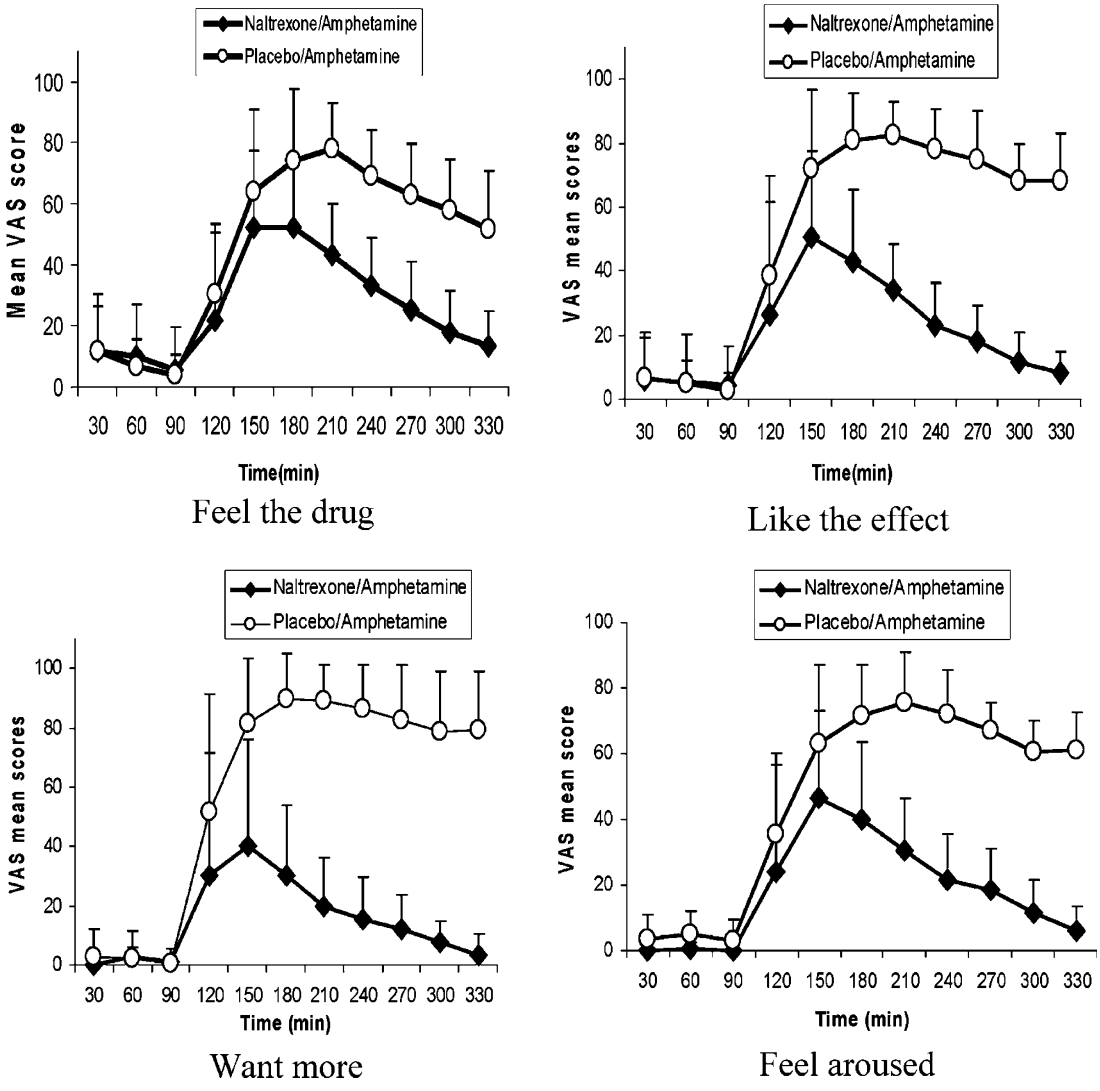

Figure 2 Mean scores of the individual items of the Visual Analog Scale (VAS) scale, over the two treatment conditions (NTX /amphetamine ◆; placebo/amphetamine ○). Data points show mean score for 20 patients.

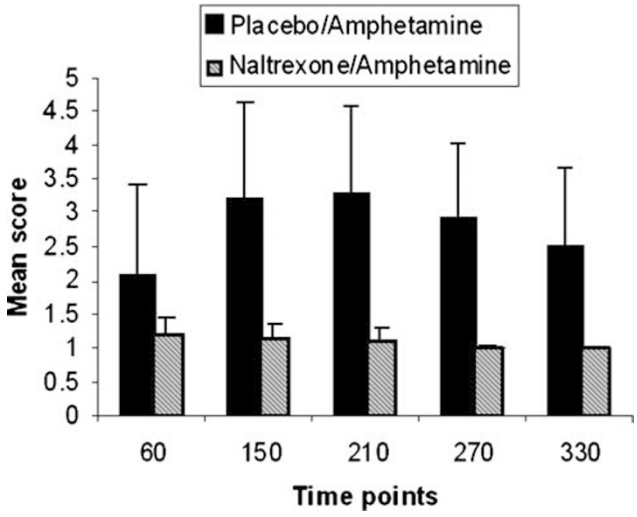

Figure 3 Mean craving scores ($n = 20$) measured by the Tiffany craving scale. Pretreatment with NTX significantly reduced the craving levels when compared to placebo ($F = 44.8$, $p < 0.001$).

receptors (high affinity to μ and δ receptors) which are localized on inhibitory interneurons that regulate DA neurons. Blockade of these receptors subsequently leads to a reduction of DA release (Hitzemann *et al*, 1982; Hurd and Ungerstedt, 1989). NTX may reduce amphetamine reward by blocking the opiate receptors that influence the mesolimbic DA neurons and thereby interfere with amphetamine-stimulated release of DA. It can thus be speculated that the reduction in subjective effects of amphetamine observed in the present study might be linked to NTX's attenuation of amphetamine-induced DA release.

Pretreatment with NTX produced a significant reduction in craving in comparison to placebo within 1 h and the craving levels continued to be lower after the dexamphetamine challenge. The results pertaining to the reduction in craving for amphetamine are in concordance with the reduction in the VAS 'want more', adding strength to the concept of using NTX as an anticraving medication. Similar results have also been noted in studies with alcohol dependence (Anton *et al*, 1999; Chick *et al*, 2000). NTX is

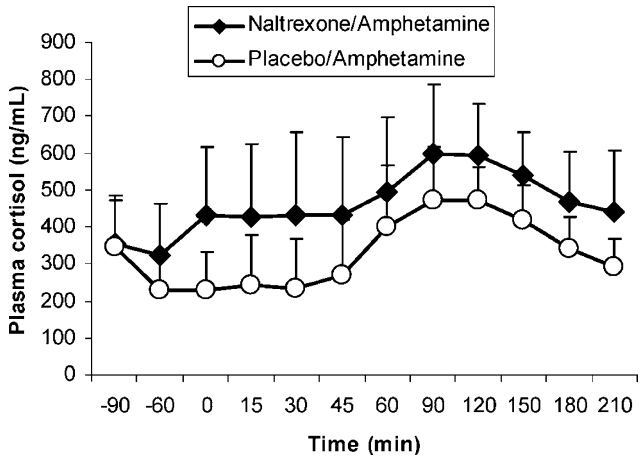

Figure 4 The plasma cortisol ($n = 12$) for the two treatment conditions NTX /amphetamine (◆) and placebo/amphetamine (○). A significant difference was observed between the two treatment conditions ($F = 12.2$, $p < 0.05$). A single dose of NTX/placebo was administered at time point −60 followed by a 30 mg dose of dexamphetamine at time point 0.

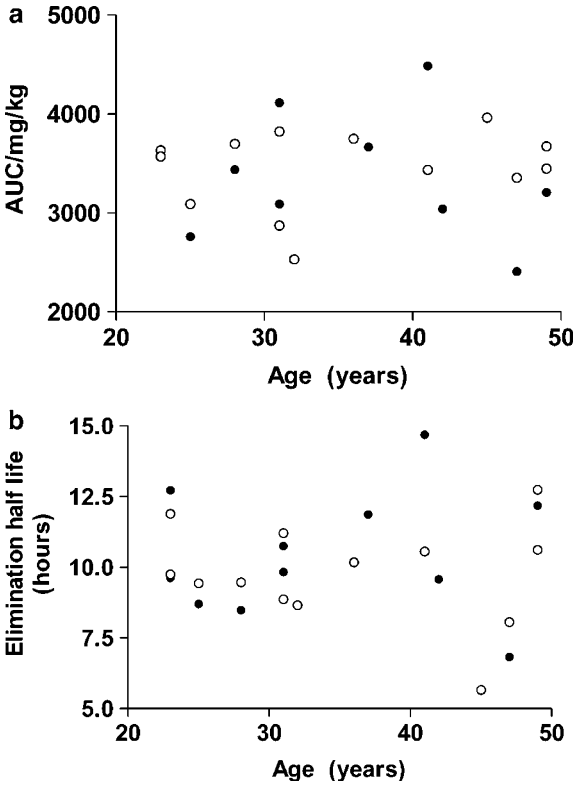

Figure 5 (a) The relationship between systemic dexamphetamine exposure and age of the patients. AUC/mg/kg (dose-normalized area under the plasma concentration time curve) of oral dexamphetamine in weeks 1 (○) and 2 (●), for the two conditions; placebo/dexamphetamine and NTX /dexamphetamine. There was no statistical difference in AUC/mg/kg between weeks 1 and 2, $p = 0.649$ (Mann–Whitney *U*-test). (b) The relationship between terminal half-life of oral dexamphetamine and age of the patients. There was no statistical difference in elimination half-life of dexamphetamine between weeks 1 (○) and 2 (●), $p = 0.531$ (Mann–Whitney *U*-test).

currently used worldwide as an anticraving medication for alcoholism (O'Brien, 2005) and the results of the present study could be indicative of its efficacy also in the amphetamine-dependent population.

Although NTX pretreatment had significant effects on amphetamine-induced subjective states it did not influence the physiological effects of amphetamine. Similar results were observed in a recent clinical study showing that an acute dose of NTX lacked effect on cocaine-induced physiological responses (Sofuoglu *et al*, 2003). In the present study an explanation for the lack of effect could be that a small challenge dose is insufficient to produce robust physiological arousal in individuals with a long history of amphetamine dependence, who may have developed physiological tolerance. Further, for 16 out 20 patients the preferred route of administration of dexamphetamine was i.v. This could also have contributed to the absence of any pronounced physiological arousal by the 30 mg oral dose of dexamphetamine.

In the present outpatient study we systematically examined the interaction of NTX and dexamphetamine for 6 h. It is known that a 50 mg oral dose of NTX reaches peak plasma concentration within 1 h and has a mean serum elimination half-life of 6–9 h (Meyer *et al*, 1984). Due to the outpatient study design the patients could not be evaluated over 24 h, however a PET study using C^{11} carfentanil showed a significant blocking of μ receptors for more than 72 h after a single 50 mg dose (Lee *et al*, 1988). This could indicate that in a chronic dosage study, a single daily dose of NTX would enable the maintenance of a high mOR occupancy and blunt the reinforcing or pleasurable effects of amphetamine in dependent individuals.

The endogenous opioid system is also known to have a role in the modulation of the HPA axis (Cushman and Kreek, 1974). Both chronic and acute opioid antagonists have been found to increase peripheral blood levels of adrenocorticotropine (ACTH) and cortisol in healthy volunteers (Naber *et al*, 1981). Blockade of opioid receptors by NTX increases circulating levels of ACTH and cortisol via tonic inhibition of the HPA axis activity. In the present study, analyses of the endocrine measures revealed that the levels of cortisol were significantly higher 1 h posttreatment with NTX than following placebo. The combination of NTX and amphetamine produced a greater elevation of cortisol when compared to placebo and amphetamine. This is in line with an earlier study assessing the effect of the opioid antagonist, naloxone, on the response of the HPA axis to the stimulant drug methylphenidate (Joyce and Donald, 1987). Thus far, the NTX's pharmacological effects have been discussed in terms of its ability to blunt the subjective effects of the drug. From the current results, it could be hypothesized that pretreatment with a single dose of NTX attenuated craving through its ability to transiently increase cortisol levels and in turn reduce the rewarding effects of amphetamine. These findings are preliminary and it remains to be determined whether the acute elevations may also persist during intermediate or long-term treatment with NTX.

The pharmacokinetic data indicate that NTX does not affect the uptake and elimination of dexamphetamine, irrespective of body weight of the patients. By ruling out such an interaction, the results suggest that the mechanism

of NTX (ie blunting of some of the subjective effects of dexamphetamine) is related to its pharmacodynamic properties.

The present study was conducted in a small homogenous population of male amphetamine-dependent individuals. The reason for this design was to examine the specific interaction effects between NTX and dexamphetamine and not of other illicit drugs and also to avoid the impact of confounding factors such as the female hormonal cycle. This, however, is also a limitation of the study. As a next step it would be necessary to extend these findings to a heterogeneous population (ie male and female individuals). Clinical trials examining the effect of chronic NTX treatment in cocaine dependence have been mixed (Schmitz *et al*, 2001, 2004). The latter study by Schmitz *et al* (2004) was conducted in a sample of cocaine- and alcohol-dependent individuals and populations with concurrent dependence may benefit from a higher (100 mg) dose of NTX (Kiyatkin and Brown, 2003). Although the present study investigated the effects of an acute dose of NTX it addresses the important and relevant questions of safety, tolerability, and efficacy for an indication that has no approved medication at present. The current study thus provides support for the feasibility of NTX as a treatment also for psychostimulant dependence.

In summary, the main findings of the study indicate that the blunting of the subjective effects of amphetamine and the reduction in drug craving could be related to the specific antagonism of amphetamine-induced modulation of opioid function. These results provide further evidence of the link between the endogenous opioid and DA systems, also in the pathophysiology of amphetamine dependence. Overall the potential of NTX as a pharmaceutical treatment for amphetamine dependence is promising and merits further investigation.

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DISCLOSURE/CONFLICT OF INTEREST

All authors declare no conflict of interest.

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