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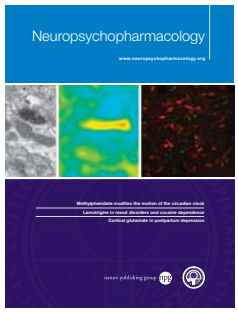

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THE EFFECTS OF NALTREXONE ON SUBJECTIVE RESPONSE TO METHAMPHETAMINE IN A CLINICAL SAMPLE: A DOUBLE-BLIND, PLACEBO-CONTROLLED LABORATORY STUDY

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Abstract

Methamphetamine (MA) use disorder is a serious psychiatric condition for which there are no FDA-approved medications. Naltrexone (NTX) is an opioid receptor antagonist with demonstrated efficacy, albeit moderate, for the treatment of alcoholism and opioid dependence. Preclinical and clinical studies suggest that NTX may be useful for the treatment of MA use disorder. To inform treatment development, we conducted a double-blind, randomized, crossover, placebo-controlled human laboratory study of NTX. Non-treatment seeking individuals meeting DSM-IV criteria for MA abuse or dependence (n = 30) completed two separate 5-day inpatient stays. During each admission, participants completed testing sessions comprised of MA cue-reactivity and intravenous MA administration (30 mg) after receiving oral NTX (50 mg) or placebo for 4 days. This study tested the hypotheses that NTX would (a) attenuate cue-induced MA craving, and (b) reduce subjective responses to MA administration. Results largely supported the study hypotheses such that (a) NTX significantly blunted cue-induced craving for MA and (b) attenuated several of the hedonic subjective effects of MA, including craving, during controlled MA administration and as compared to placebo. NTX decreased overall subjective ratings of "crave drug," "stimulated," and "would like drug access," decreased the the post MA administration timecourse of "anxious" and increased ratings of "bad drug effects," as compared to placebo. These findings support a potential mechanism of action by showing that NTX reduced cue-induced craving and subjective responses to MA. This is consistent with positive treatment studies of NTX for amphetamine dependence as well as ongoing clinical trials for MA.

Key Words: Naltrexone, methamphetamine, subjective response, human laboratory, craving

INTRODUCTION

Recent estimates suggest that over 12 million people in the U.S., ages 12 years and older (4.7% of total responders) have used methamphetamine in their lifetimes, with over 379,000 of those individuals meeting DSM-IV criteria for methamphetamine (MA) dependence (Substance Abuse and Mental Health Services Administration (SAMHSA), 2013). Efficacious pharmacotherapies for methamphetamine (MA) use disorder remain elusive despite extensive research on the neurobiology of the effects of amphetamines (Brensilver *et al*, 2013; Elkashef *et al*, 2008). Naltrexone (NTX) is an opioid receptor antagonist with empirically supported efficacy and FDA-approval for the treatment of alcoholism (Anton *et al*, 2006; O'Malley *et al*, 1992; Volpicelli *et al*, 1992) and opioid dependence (Cornish *et al*, 1997). Preclinical models suggest that NTX may also affect methamphetamine use, as NTX attenuated MA-induced sensitization (Chiu *et al*, 2005), amphetamine drug-seeking reinstatement (Haggkvist *et al*, 2008), and cue-induced MA seeking (Anggadiredja *et al*, 2004) in rodents. In particular, preclinical studies suggested that μ-opioid (Chiu *et al*, 2006) and δ-opioid (Suzuki *et al*, 1997) receptors may underlie MA-induced behavioral sensitization, analogous to compulsive drug seeking behavior in humans (i.e., drug craving; Itzhak and Ali, 2002), through its modulatory actions of the mesolimbic dopamine system (Ford *et al*, 2006). Preclinical studies have observed naltrexone-related decreases in d-amphetamine and alcohol self-administration in adult rhesus monkeys (Jimenez-Gomez *et al*, 2011), and attenuated amphetamine-induced reinstatement with no effect on food taking behavior in the rat (Haggkvist *et al*, 2009).

A few clinical studies have tested NTX in amphetamine users. Notably, a placebo-controlled clinical trial found that NTX (50 mg) significantly increased amphetamine abstinence compared to placebo, as measured by negative urine samples, over the course of 12 weeks of treatment (Jayaram-Lindstrom *et al*, 2008a). A related placebo-controlled human laboratory study found that NTX (50 mg) blunted craving and subjective responses during a dexamphetamine (30 mg oral) challenge in a sample of amphetamine dependent subjects (Jayaram-Lindstrom *et al*, 2008b) as well as in healthy controls (Jayaram-Lindstrom *et al*, 2004). On balance, these preclinical and clinical studies suggest that

modulation of the endogenous opioid system via naltrexone may be useful for the treatment of MA use disorder.

In recent years, there has been renewed interest in the application of NTX for drug dependence. A clinical trial of a NTX depot implant demonstrated significant benefit over placebo on measures of treatment retention, drug free urines, and global assessments of functioning in a hard-to-treat sample of heroin and amphetamine polydrug dependent individuals (Tiihonen *et al*, 2012). Further, a recent behavioral pharmacology study found that acute oral NTX significantly reduced cocaine craving during cocaine administration in a sample of non-treatment seeking cocaine users (n = 12) (Comer *et al*, 2013). However, in the aforementioned study, NTX did not alter the cardiovascular or subjective effects of smoked cocaine (0, 12.5, 25, and 50 mg), and as oral amphetamine (0, 10, and 20 mg) produced no discernable subjective effects, NTX effects on subjective response to amphetamine could not be assessed in this sample. If NTX were to blunt subjective response to IV MA, that may be indicative of its ability to blunt less reinforcing routes of MA administration. In summary, these recent studies suggest that NTX may reduce drug use (heroin and amphetamines) in a clinical sample and attenuate cocaine craving in the lab. Based on these results along with the preclinical literature, testing NTX for MA use disorder represents a promising avenue towards advancing medications development.

This study uses a human behavioral pharmacology approach to elucidate the biobehavioral mechanisms of NTX for MA dependence by focusing on the effects of NTX on cue-induced craving for MA and on subjective responses to MA in the laboratory. In this double-blind, randomized, crossover, placebo-controlled trial, non-treatment seeking individuals meeting DSM-IV criteria for MA abuse or dependence (n = 30) completed two separate 5-day inpatient stays. During each admission, participants completed testing sessions comprised of MA cue-reactivity and MA administration (30 mg IV) after receiving NTX (50 mg) or placebo for 4 days. This study tested the hypotheses that NTX would (a) attenuate cue-induced MA craving, and (b) attenuate subjective responses to MA administration.

METHOD

Participants

A community-based, non-treatment seeking sample of MA users was recruited via online and print advertisements in the Los Angeles area. The study protocol and all procedures were approved by the Institutional Review Board of the University of California, Los Angeles. Inclusion criteria were: (a) meet current DSM-IV criteria for MA abuse or dependence; (b) be fluent in English; (c) be between 18 and 50 years of age; (d) produce a MA-positive urine prior to study entry; and (e) agree to abstain from MA during the study, as evidenced by a MA-negative urine upon each inpatient admission and every morning during their stay. Exclusion criteria were: (a) be currently in treatment for MA use, have a history of treatment in the 30 days before enrollment, or be currently seeking treatment for MA use; (b) receive a DSM-IV diagnosis of current (last 12 months) drug dependence, other than MA, lifetime schizophrenia, bipolar disorder, or any psychotic disorder, or current major depressive disorder with suicidal ideation; (d) report current use of psychoactive drugs, other than marijuana and MA, verified by a toxicology screen; (e) have significant medical problems, as indicated by physical examination or laboratory tests (i.e. a blood chemistry panel and liver profile); (f) report currently taking any medications that could interact adversely with NTX; (g) testing positive for pregnancy, are currently nursing, or refusing to use reliable method of birth control, (h) report intranasal as the only route of MA administration, and (i) cardiovascular abnormalities in EKG or vital signs (e.g. HR <50 or >90; SBP <105 or >140, DBP <45 or >90), as determined during the physical exam.

A total of 126 individuals (74% male) completed an initial in-person screening session, and 46 individuals completed a secondary medical screening with the study physician. Study attrition from screening to enrollment was due to participant drop out (n = 32), inability to produce a positive MA urine no verify MA use history (n = 18), positive urine test for other exclusionary substances (n = 7) and failing to meet eligibility criteria based on the SCID (either not meeting MA abuse/dependence criteria or meeting criteria for other exclusionary psychological conditions; n = 14). Thirty-two individuals (75% male, mean age = 36.47 [SD = 8.68]) completed at least one experimental session, thirty of whom (73.3% male, mean age = 36.93 [SD = 8.77]) completed both experimental sessions, one while at the target dose of NTX and the other on matched placebo, and were included in the final analyses.

Screening Procedures

Interested individuals called the laboratory and completed a telephone-screening interview. Eligible callers were invited to the laboratory, and after receiving a full explanation of study procedures and providing written, informed consent, participants completed the in-person screening visit. At the beginning of the screening visit, participants were required to have a breath alcohol concentration (BrAC) of 0.00g/dl, produce a positive MA test result on a urine toxicology screen, and have negative test results for all other drugs (excluding marijuana). Participants then completed questionnaires on demographics, drug use history, and psychological functioning. The following interviews were administered by trained masters-level clinicians: (a) the 30-day Timeline Follow-Back (TLFB) to capture daily MA use over the 30 days prior to the visit (Sobell et al., 1988); and (b) the Structured Clinical Interview for DSM-IV (SCID) (First, 2005) to assess criteria for MA dependence and abuse, and to screen for exclusionary psychiatric diagnoses. Regarding major depressive disorder (MDD), a total of 4 participants reported depressed mood in the 2 weeks prior to the assessment (i.e., met screening item of the SCID MDD module) yet the complete assessment of depressive symptoms revealed none of the 4 participants met criteria for a current major depressive episode.

Participants deemed eligible following the in-person screening were invited to return to the laboratory to complete a physical exam with the study physician (K.M.). Participants were required to provide a negative urine toxicology screen for all drugs (including MA, excluding marijuana) at the time of the physical exam, which consisted of clinical laboratory testing (i.e. a blood chemistry panel and liver profile), and an electrocardiogram (EKG).

Medication Administration and Inpatient Procedures

Individuals who passed the physical exam were then admitted to the UCLA Clinical and Translational Research Center (CTRC) inpatient unit on the same day, at which time they were randomized to take the first study medication (NTX or matched placebo). Participants took the study medication under staff supervision for four days and completed the first experimental session on medication day four, which consisted of a cue-reactivity paradigm and an intravenous (IV) MA

administration. The last dose of NTX, or placebo, was administered 2 hours prior to the MA infusion. Participants were discharged from the unit on day five, and following a 7-14 day washout period were re-admitted to the hospital for their second inpatient stay at which time they received the second study medication (NTX or placebo), in counterbalanced, randomized, and double-blind fashion. NTX was titrated, to minimize adverse events, from 25mg on day one to 50mg doses on days two through four. Side effects were monitored throughout each inpatient stay using the Systematic Assessment for Treatment Emergent Effects (SAFTEE) (Levine and Schooler, 1986). Following completion of the study and prior to discharge on day five, participants completed a motivational interview session targeting MA use reduction and promoting treatment seeking. The intervention was delivered by Master's level clinician under the supervision of a licensed psychologist (L.A.R.). Participants received $40 for completing the in-person screening visit and were compensated $40 per inpatient day ($400 total) and $50 for each of the two experimental sessions. Participants who completed all parts of the study received a $100 bonus.

Cue Reactivity Paradigm & Measures

On day four of each admission, participants completed a guided cue exposure protocol (Monti *et al*, 1987) modified for relevance to MA. The cue exposure protocol included the presentation of two audiotaped scripts (MA and control), each approximately 5 minutes in length, delivered in a non-counterbalanced fashion (neutral first) to avoid potential carryover effects. The scripts instructed the participant to recall sensory and emotional memories related to their use of MA (or water). At various times during the exposures, the participant was instructed to handle physical cues (e.g., glass MA pipe or glass of water) to increase the potential for cue-related reactivity. Previous work has shown MA paraphernalia exposure to be similar to video and pictorial cue exposure in terms of eliciting significant cue-induced MA craving (Tolliver et al, 2010). Consistent with standard procedures, participants were systematically exposed to both a neutral cue (a glass of water) and a drug cue (glass MA pipe) in a non-counterbalanced fashion (neutral first) to avoid potential carryover effects. Previous work has shown MA paraphernalia exposure to be similar to video and pictorial cue exposure in terms of eliciting significant cue-induced MA craving (Tolliver *et al*, 2010). After each standardized exposure participants completed

the MA Urge Questionnaire (MAUQ), which was adapted from previously published and validated studies of craving assessment (Bohn *et al*, 1995; MacKillop, 2006). The MAUQ, an 8-item questionnaire, captures craving by having participants indicate how much they agree or disagree with a series of statements regarding MA. Examples of these statements include, "All I want to do now is use methamphetamine," "It would be difficult to turn down methamphetamine at this minute," and "I want to use methamphetamine so bad I can almost feel it." An average of the items was computed, and internal reliability for this measure was very high at each assessment (Cronbach's $\alpha \geq 0.95$; variance explained by a one-factor solution $\geq 85\%$). Measures of heart rate and blood pressure were recorded before and after cue administration in each condition.

MA Administration Procedures & Measures

Approximately 2 hours after the cue reactivity paradigm, participants completed a MA challenge, consisting of two 15 mg IV MA infusions administered over 2 minutes, separated by 30 minutes for safety monitoring, for a total dose of 30 mg. The IV administration method was selected to provide optimal control over MA dosing and previous research demonstrated a similar pattern of pharmacokinetic and subjective response to MA when comparing IV and smoking routes of administration (Cook *et al*, 1993). Assessment of subjective responses began immediately following the second dose administration. Continuous cardiac telemetry, serial EKG, and vital signs were monitored during and after the infusions. Cardiac functioning was monitored using a GE Dash4000 EKG monitor, and the MA was administered using a Baxter AS50 syringe pump. The study physician (K.M.) was present for each MA infusion along with a registered nurse and study staff. Measures of subjective responses to MA (i.e., the Drug Effects Questionnaire; DEQ), MA craving (i.e., the MA Urge Questionnaire; MAUQ), and cardiovascular function (i.e., heart rate and blood pressure), were collected prior to MA administration (i.e., baseline) and then again at 5, 10, 15, 20, 30, 60, 90, and 120 minutes following the second 15 mg MA administration. The DEQ is an 11-item questionnaire that captures subjective effects (Morean *et al*, 2013) comprised of questions such as, "How much do you feel any drug effects?", "How bad are the drug effects you are feeling right now?" in contrast to "How good are the drug effects you are feeling right now?," "How

much would you like to access the drug right now?," and "How much do you like the effects you are feeling now?" Participants are asked to rate their current feelings on a Likert scale ranging from 0 (none at all) to 10 (a lot). Participants were asked in an open-ended fashion to report on any adverse events (AEs) experienced during the MA infusion. AEs were assessed after the MA infusion session on day four and before discharge on day five.

Medication and Methamphetamine

Naltrexone: NTX was purchased from and compounded by Bayview Pharmacy (Saunderstown, RI) into blister packs containing the 25 and 50 mg doses. These doses were administered orally in one capsule each day. The matched placebo was administered in one capsule each day. Participants took the study medication daily under the observation of CTRC research nursing staff. Medication order was randomized and counterbalanced.

Methamphetamine Hydrochloride (HCl): MA HCl was provided by a NIDA contractor. The UCLA Investigational Drug Pharmacy prepared two 15mg (5ml) infusions in 0.9% sodium chloride solution for each MA administration session. The dose selected and administration procedures were consistent with previous behavioral pharmacology studies (Newton *et al*, 2008; Newton *et al*, 2006), having demonstrated safety and efficacy in producing elevations in subjective effects.

Statistical Analyses

Repeated measures analyses of variance (ANOVA) were used to analyze the effects of NTX on cue-induced craving and subjective response to the MA challenge. For each test we were interested in the main effect of Medication (NTX vs. PLAC), the main effect of Trial (i.e., pre-post cue exposure, or time after acute MA), and the Medication × Trial interaction. For the analyses of subjective effects during the MA administration, we tested medication condition differences on change from baseline across the trial, namely 5, 10, 15, 20, 30, 60, 90, and 120 minutes following MA administration. Notably, there were no significant baseline differences on the subjective response measures of interest across the two medication conditions, *p*s > .09. For variables showing a significant Medication × Trial effect, post-hoc tests were conducted to determine at which time points in trial the medication groups were significantly different.

Post-hoc analyses assessing medication differences at each post-MA administration time point were conducted using repeated measures ANOVA with medication as a within subject factor. Relevant covariates were considered (e.g., sex, age) but ultimately not found useful, largely because in the crossover design participants serve as their own controls. An alpha threshold of 0.05 was set for all statistical analyses, including post-hoc comparisons.

RESULTS

Sample Characteristics

Thirty participants who completed the entire study were included in the statistical analyses reported herein. Sample characteristics are reported in **Table 1**, including details on MA use quantity and frequency. Twenty-six participants met DSM-IV diagnostic criteria for MA dependence, whereas four met for MA abuse without dependence. When converting to the DSM-V criteria (craving symptom not assessed/included), all participants were found to meet criteria for current (i.e. past month) MA use disorder (19% mild, 25% moderate, and 56% severe). All subjects reported experience smoking MA as intranasal only users were excluded for safety reasons.

Cue-Reactivity

Craving: Analyses revealed a significant Medication × Trial effect on cue-induced craving for MA, [$F(1,29) = 4.32$, $p < .05$], such that NTX attenuated cue-induced craving for MA, measured by the MAUQ, as compared to placebo; see **Figure 1**. Follow-up comparisons suggested that while there was a significant increase in self-reported craving during the MA cue compared to control cue in the placebo condition [$F(1,30) = 14.47$, $p < .001$], there was no significant effect of MA cues on craving during the NTX condition [$F(1,32) = 1.19$, $p = .28$].

Cardiovascular Response: Elevations in heart rate and diastolic blood pressure in repsonse to the MA cues were blunted in the NTX conditon. Specifically, while the Medication × Trial effects were not statistically significant [$F(1,28) = 2.43$, $p = .13$; and $F(1,28) = 2.66$, $p = .11$, respectively], planned comparisons indicated that there were significant increases in heart rate [$F(1,29) = 7.58$, $p < .01$], and diastolic blood pressure [$F(1,29) = 11.49$, $p < .01$], during the MA cue compared to control cue exposure,

in the placebo condition, yet these effects were not significant in the NTX condition [$F(1,32) = 0.43$, $p = .52$ and $F(1,32) = 0.15$, $p = .70$, respectively; **Supplemental Figure 1**]. Systolic blood pressure increased during presentation of the MA cue versus control cue, [$F(1,28) = 29.98$, $p < .001$] in both medication conditions, and the Medication × Trial effect for systolic blood pressure was not significant [$F(1,28) = 1.61$, $p = .22$]. Together, these results suggest that NTX attenuated cue-induced craving for MA and attenuated the MA cue-provoked increases in heart rate and diastolic blood pressure during the NTX condition.

MA Administration

Subjective Effects: Administration of MA resulted in immediate increases in the subjective effects of "feel drug effects" "like drug effects," "good drug effects," "drug high," "would like more drug," "crave drug," "Stimulated" and "would like drug access" immediately following MA administration [i.e. baseline vs. 5 minutes post MA infusion: *p's* < 0.01]. Complete results for the effects of NTX on subjective effects of MA over the course of the MA challenge, each measured by individual items of DEQ, are presented in **Table 2**. Significant main effects of medication were observed in terms of "crave drug," stimulated," and "would like drug access" [*p's* < 0.05] such that NTX was associated with a blunted increases (from baseline) on these constructs as compared to placebo (**Figure 2**). Furthermore, significant Medication × Trial interactions were observed with respect to "feel drug effects," and "drug high," although post-hoc tests revealed no time points where the simple effect of medication was significant (*p*s ≥ .11; **Figure 3**). Significant Medication × Trial interactions were also observed on "anxious" and "bad drug effects," such that placebo was associated with increased anxiety from MA administration, particularly during later timepoints following the MA infusion, and NTX was associated with increased "bad drug effects" during earlier timepoints following the MA infusion (**Figure 3)**.

Cardiovascular Response: As expected, MA administration produced robust increases in heart rate [$F(8,224) = 40.98$, $p < .0001$], systolic blood pressure [$F(8,224) = 28.93$, $p < .0001$], and diastolic blood pressure [$F(8,224) = 6.05$, $p < .0001$]. However, there was no significant effect of medication on

cardiovascular response to MA during the challenge, indexed by either a main effect of Medication or a Medication × Trial interaction for either cardiovascular parameter [*p*'s > .10].

Adverse Events

NTX and methamphetamine were generally well tolerated and there were no serious adverse events during the study nor dropouts related to medication tolerability. A series of Fisher's exact tests, a non-parametric test appropriate for small cell sizes (Fisher, 1922), were conducted comparing the medicaiton versus placebo on each of the 24 items from the SAFTEE administered on day four of each admission (prior to MA administraiton). The only adverse event that differed significantly between medication conditons was increased desire for sex, which was reported with higher frequency on the placebo versus NTX conditions [5/30 on placebo versus 2/30 on NTX; Fisher's Exact $p = .02$]. In addition, we examined medication effects on nausea, which is NTX's most common side effect (O'Malley *et al*, 2000) and found that 3/30 participants reported nausea on NTX as compared to 1/30 on placebo; this difference was not statistically significant [Fisher's Exact $p = .10$] and suggests that adverse events are unlikely to account for the medication effects reported above.

Sex Differences

Owing to the within-subjects design, all reported effects were robust to controlling for sex. Despite the small number of female participants (n = 8), exploratory analyses of sex effects were conducted and some differences were observed. Specifically females reported lower "like drug effects" overall [$F(1, 28) = 4.51$, $p < 0.05$], and reported a larger difference between NTX and placebo in terms of drug "feel drug effects" [Medication × Sex: $F(1, 28) = 4.87$, $p < 0.05$]. Three-way Medication × Trial × Sex interactions were observed in terms of "would like more drug," "depressed," and "would like drug access" [$F(7,196) = 2.32$, 2.44, and 3.25 respectively, *p's* < 0.05]. These effects were such that females demonstrated a larger NTX effect than males in terms of "would like more drug" and "would like drug access," particularly at later time points following the MA administration (e.g. > 60 minutes post infusion; see **supplemental Figure 2**).

DISCUSSION

In this human behavioral pharmacology study, an interesting pattern of results emerged whereby NTX blunted cue-induced craving for MA and attenuated some of the subjective effects of MA during a controlled MA administration and as compared to placebo. Specifically, participants reported lower subjective ratings of "stimulated," "crave drug," and "would like drug access," on the NTX condition, as compared to placebo. Interestinlgy, participants reported lower ratings of "anxiousness" in the NTX condition, as compared to placebo, and these differences were more prominent at later time points following MA administration. Medication also moderated ratings of "bad drug effects" following MA administration, such that ratings of "bad drug effects" were higher on NTX than placebo at earlier time points following MA infusion. NTX did not significantly alter peak MA effects; however, while peak drug responses are important factors in stimulant abuse (Hart *et al*, 2008), the modulation of broader acute subjective effects, such as those observed in this study, represent equally important targets for pharmacological intervention. As would be predicted, there were elevations in heart rate and blood pressure in response to the MA cues and to the MA administration. Notably NTX attenuated the cue-induced elevation of heart rate and diastolic blood pressure.

On balance, these results are consistent with previous work on amphetamines (Jayaram-Lindstrom *et al*, 2008b; Jayaram-Lindstrom *et al*, 2004) and cocaine (Comer *et al*, 2013), suggesting that NTX may have anti-craving properties and may alter subjective respones to stimulants. This is the first study of NTX and methamphetamine and combines several strengths such as a sample comprised of individuals with clinically significant MA problems, a controlled behavioral pharmacology design in the context of inpatient hospital admissions, a crossover design allowing subjects to serve as their own controls, excellent overall retention, and rigorous laboratory paradigms with putative clinical significance such as cue-exposure and MA administration. Study limitations include the single dose of naltrexone, the lack of a placebo MA administraiton, and the non-treatment seeking nature of the sample. Injectable naltrexone was also considered but rejected in favor of the oral formulation given the non-treatment seeking nature of the sample and the need for a timely washout period allowing for the crossover design.

In addition, the present findings are unlikely to be due to NTX-induced side effects for two reasons: First, no significant differences between NTX and placebo were observed on any subjective effects at baseline when side-effects were assessed. Second, the analyses are baseline-corrected, thus reducing the likelihood that these findings are reflective of, for example, NTX-related nausea.

Taken together, this study provides support for the notion that NTX may be useful for the treatment of MA dependence, thus extending upon positive trials for stimulant dependence (Jayaram-Lindstrom *et al*, 2008a) and polydrug dependence (Tiihonen *et al*, 2012). While no clinical trials to date have tested NTX for the treatment of MA dependence, with the exception of a small combination study (Grant *et al*, 2010), the present work suggests that such trials may be warranted. In fact, a clinical trial of long-acting, injectable naltrexone for MA was recently completed (NCT00984360; results are not yeet available) and another is currently under way (NCT01449565).

The potential efficacy of NTX, an opioid antagonist with greatest affinity for the μ-opioid receptor and to a lesser but meaningful extent κ-and δ-opioid receptors (Lee *et al*, 1988; Weerts *et al*, 2008), for the treatment of drug use disorders beyond alcoholism and opioid dependence may lie on a common mechanism of drug effects involving the activation of the endogenous opioid system (Herz, 1997; Kreek, 1996). Acute oral amphetamine administration has been shown to induce endogenous opioid release in many brain regions frequently implicated in addiction, including the basal ganglia, frontal cortex areas, thalamus, and striatum (Colasanti *et al*, 2012; Mick *et al*, 2014). Further, elevated frontal/temporal cortical mu-opioid receptor binding has been observed in cocaine dependence; the degree of which was shown to positively correlate with self-reported cocaine craving (Gorelick *et al*, 2005), and relate to relapse following treatment (Ghitza *et al*, 2010; Gorelick *et al*, 2008). NTX has been shown to block drug-induced β-endorphin, and subsequent dopamine, release in the nucleus accumbens and provide a blockade of drug-induced β-endorphin inhibition of GABAergic inhibitory interneurons in the ventral tegmental area, in the case of alcohol (Johnson, 2008; Zalewska-Kaszubska *et al*, 2006). The decrease in amphetamine-induced dopamine levels in the nucleus accumbens following blockade of the μ-opioid receptor by naltrindole (a selective δ-opioid receptor antagonist) and β-funaltrexamine (an

irreversible μ-opioid receptor antagonist) provides support for a similar NTX mechanism in the case of stimulants (Schad *et al*, 1996). The present study supports the role of the opioidergic system in the incentive salience of MA cues as well as the modulation of the subjective effects of MA during IV administration. Thus, there may be a role for NTX in the treatment of MA use disorders, particularly in light of novel long acting delivery systems that can enhance medication compliance. This may be particularly relevant for drug using populations and is consistent with the hypothesis that low medication adherence may account, at least in part, for the modest effect size of naltrexone in clinical trials (Swift *et al*, 2011). The combination of NTX with other pharmacotherapies may be valuable, as we have recently found in our work combining varenicline and NTX for smokers who drink heavily (Ray *et al*, 2014a, b). Lastly, while exploratory in nature, analyses of sex effects suggested added benefit of NTX for female participants on a few measures of subjective responses. The present sample was comprised primarily of males (75%), hence future analyses in gender balanced samples are warranted.

In conclusion, this behavioral pharmacology study is the first to test the effects of NTX on cue-induced craving and subjective responses to MA among individuals with MA abuse and dependence. These findings suggest that NTX is superior to placebo in attenuating cue-induced craving for MA as well as several dimensions of MA-induced subjective effects (e.g., "stimulated" and "crave drug") measured during controlled MA administration. To the extent to which laboratory measures of cue-induced craving and subjective responses to MA may be predictive of clinical response to this pharmacotherapy among treatment-seekers, these results suggest that clinical trials of NTX for MA dependence may be warranted. While there is enthusiasm for behavioral pharmacology approaches to screen for medications for addiction (Litten *et al*, 2012; Mason and Higley, 2013; Ray *et al*, 2010), a required step consists of demonstrating that laboratory-based measures of cue-induced craving and subjective effects do in fact predict treatment response. Notably, recent studies have demonstrated that cue-induced craving predicted relapse among alcohol (Seo *et al*, 2013) and heroin (Fatseas *et al*, 2011) dependent patients, respectively. While the present study does not effectively link biobehavioral responses in the laboratory to clinical outcomes, it suggests that NTX reduces cue-induced craving for MA as well as craving and stimulation

ratings during MA administration. Given the significance of craving as a determinant of drug intake and possibly as a predictor of relapse, the effects of NTX observed in this study hold promise for clinical studies of this medication for MA dependence.

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Table 1

Sample Demographics

Variable	Frequency or Mean (SD)	Range
Age	36.93 (8.78)	23-50
Sex - Male/Female	22/8	-
Ethnicity		
- Latino	7	-
- Caucasian	11	
- African American	4	
- Asian	2	
- Mixed	6	
Primary Route of MA Administration		
- Smoking	28	-
- Snorting	1	
- Injection	1	
Age of First MA Use	24 (9.83)	13-47
Years of MA Use	12.48 (8.46)	<1-32
DSM-IV MA Abuse/Dependence Symptom Count	6.00 (2.26)	2-11
Number of MA Use Days (past 30 days)	21.26 (8.15)	9-30
Education (years)	12.19 (3.41)	4-21
Current Drug Use		
- Alcohol	21	-
- Marijuana	9	
- Cocaine/Crack	0	
- Ecstasy	0	
- Heroin	0	
Cigarettes Per Day (past week)		
- 0	11	-
- 1 ≤ 10	9	
- > 10	10	
Number of Alcohol Drinking Days (past 30 days)	5.56 (8.63)	0-30
Alcohol Drinks per Drinking Day (past 30 days)	4.07 (3.67)	<1-14

Table 2

Results of ANOVAs testing the effects of Medication, Trial (i.e., time following MA administration), and Medication × Trial effects on subjective responses to MA

	Medication		**Trial**		**Medication × Trial**	
Variable	F	p	F	p	F	p
Crave drug	**5.63**	**0.025**	**4.12**	**< .001**	0.41	0.90
Stimulated	**5.23**	**0.030**	**19.44**	**< .0001**	1.1	0.36
Would like drug access	**5.48**	**0.026**	**7.78**	**< .0001**	0.92	0.49
Feel drug effects	0.33	0.57	**39.48**	**< .0001**	**2.79**	**0.009**
Bad drug effects	2.69	0.11	0.72	0.65	**2.68**	**0.011**
Drug high	0.28	0.60	**34.11**	**< .0001**	**2.45**	**0.020**
Anxious	2.97	0.10	1.22	0.29	**3.32**	**0.002**
Like drug effects	0.98	0.33	**11.88**	**< .0001**	0.46	0.86
Good drug effects	0.11	0.74	**28.08**	**< .0001**	0.75	0.63
Would like more drug	0.82	0.37	**8.74**	**< .0001**	0.87	0.53
Depressed	1.4	0.25	**3.05**	**0.005**	0.2	0.99

Note: Significant effect of medication (i.e., main effect or Medication × Trial effect) are presented in bold type. Medication degrees of freedom = 1, 29. Trial and Medication × Trial degrees of freedom = 7, 203.

Figure Captions

Figure 1. Craving scores (MAUQ), presented with standard errors, following control and MA cue exposure during both placebo and NTX conditions. Analyses revealed a significant Medication × Trial effect such that NTX attenuated cue-induced craving for MA as compared to placebo. Asterisks represent planned comparisons; *** $p < 0.001$.

Figure 2. Subjective response scores (DEQ), presented with standard errors, at baseline and change from baseline at 5, 10, 15, 20, 30, 60, 90, and 120 minutes following MA administration, during both placebo and NTX conditions. Analyses revealed a significant main effect of Medication such that NTX attenuated ratings of "stimulated," "crave drug," and "would like drug access," as compared to placebo.

Figure 3. Subjective response scores (DEQ), presented with standard errors, at baseline and change from baseline at 5, 10, 15, 20, 30, 60, 90, and 120 minutes following MA administration, during both placebo and NTX conditions. Analyses revealed significant Medication × Trial effects on "feel drug effects" and "drug high" as compared to placebo (though no post-hoc tests were significant). Further, NTX was associated with lower "anxious" ratings from MA administration at later later time points and greater "bad drug effects" during early time points. Asterisks refer to statistically significant post-hoc tests which were conducted at each time point in trial; * $p < 0.05$, ** $p < 0.01$.

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