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Physiological and subjective effects of acute intranasal methamphetamine during extended-release alprazolam maintenance

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Abstract

Background—Medications development for methamphetamine dependence is ongoing, but no widely accepted, effective pharmacotherapy has been identified. Previous studies have demonstrated neurobiological perturbations to central GABA_A activity following chronic stimulant use, and that positive modulation of GABA_A receptors attenuates the neurochemical and behavioral response to stimulant drugs such as methamphetamine. Therefore, GABA_A modulators could be useful as pharmacotherapies for stimulant-use disorders.

Methods—This study tested the hypothesis that intranasal methamphetamine would be safe and well tolerated during maintenance on extended-release alprazolam (XR), and that the effects of methamphetamine would be attenuated. Eight non-treatment-seeking, stimulant-dependent individuals completed an inpatient experiment in which ascending doses of intranasal methamphetamine (0, 5, 10, 20 and 30 mg) were administered after four days of alprazolam XR maintenance (0 and 1 mg/day).

Results—Intranasal methamphetamine produced prototypical effects (e.g., increased positive subjective ratings and elevated cardiovascular signs). The combination of intranasal methamphetamine and alprazolam XR was safe and well tolerated. Alprazolam XR produced

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small, but orderly, reductions in some of the subjective effects of methamphetamine, and performance impairment.

Conclusions—The present results demonstrate that methamphetamine use during alprazolam XR treatment would not pose a significant safety risk. Given the potential of GABA_A positive modulators to manage certain aspects of stimulant abuse and dependence (i.e., drug-induced seizures, anxiety and stress), but the relatively small impact on the acute abuse-related effects of methamphetamine observed here, additional research with GABA_A positive modulators is warranted, but should consider their use as an adjunct component of combination behavioral and/or drug treatment.

Keywords

methamphetamine; human; pharmacotherapy; alprazolam; benzodiazepine; subjective effects

1. Introduction

Methamphetamine abuse and dependence are significant public-health concerns. Methamphetamine is the most widely used illicit drug worldwide, with the exception of cannabis (United Nations Office on Drugs and Crime, 2009). Alarming, treatment admissions for methamphetamine use more than doubled from 1998 to 2007 in the United States (Substance Abuse and Mental Health Services Administration, 2009). Estimates from the most recent available data indicate that the total cost for methamphetamine abuse in the United States was over \$23 billion in 2005 (Nicosia et al., 2009). Efforts are ongoing to develop a medication for methamphetamine-use disorders that would reduce this public-health burden, but a widely accepted, effective pharmacotherapy has not been identified (Elkashef et al., 2008; Karila et al. 2010; Rush et al., 2010a; Vocci and Appel, 2007).

Several lines of evidence support the consideration of drugs that are positive modulators of GABA_A receptors, such as benzodiazepines, as medications for disorders associated with the use of stimulants such as methamphetamine. Preclinical and clinical research has uncovered neurobiological perturbations in central GABA_A receptors following chronic stimulant administration. Specifically, repeated administration of cocaine or methamphetamine to rodents results in region-specific changes in the mRNA and protein of certain benzodiazepine receptor subunits (Lilly and Tietz, 2000; Suzuki et al., 2000), as well as the number of benzodiazepine-GABA_A receptor binding sites (Goeders, 1991; Yoo et al., 2010) and GABA_A receptor function (Peris, 1996). These neurobiological changes were associated with differences in the acute behavioral response to these stimulant drugs (Goeders, 1991; Peris, 1996; Suzuki et al., 2000; Yoo et al., 2010). A history of cocaine administration also modified the anxiolytic and locomotor response to benzodiazepines in rodents (Lilly and Tietz, 2000; Lipton and Ellison, 1992), as well as glucose utilization and subject ratings following administration of lorazepam in a clinical PET study (Volkow et al., 1998).

Further support for targeting GABA_A receptors comes from studies demonstrating that GABA_A receptor positive modulation by benzodiazepines attenuates the dopaminergic response to stimulant drugs, which is believed to play a critical role in their abuse-related

effects. Studies using microdialysis techniques in freely moving rats demonstrated that acute lorazepam administration attenuated cocaine-induced increases in dopamine in the striatum (Dewey et al., 1997). Acute imidazinil and diazepam also reduced dopamine content in the dialysates of the nucleus accumbens shell and striatum following cocaine administration (Giorgetti et al., 1998).

GABA_A receptor modulation also attenuates the behavioral response to stimulant drugs. For instance, acutely administered oxazepam blocked the expression of a methamphetamine conditioned place preference in rats (Goeders and Goeders, 2004). Acute pretreatment with chlordiazepoxide (Goeders et al., 1989) and midazolam (Barrett et al., 2005) decreased cocaine self-administration in rats, and in the latter study, benzodiazepine administration did not impact liquid food-maintained responding. Similarly, acutely administered alprazolam selectively and dose-dependently decreased responding maintained by cocaine in baboons (Weerts et al., 2005). A study in rats found that alprazolam initially reduced cocaine and food pellet self-administration, although food intake recovered across the treatment (Goeders et al., 1993). Studies using drug-discrimination procedures are consistent with those results. In rats, chlordiazepoxide and midazolam blocked the discriminative-stimulus effects of methamphetamine and *d*-amphetamine, respectively (Druhan et al., 1991; Gatch et al., 2005). In monkeys trained to discriminate cocaine, acute administration of triazolam and imidazenil attenuated cocaine-appropriate responding (Negus et al., 2000). In humans, concurrent administration of alprazolam attenuated the discriminative-stimulus and some of the positive subject-rated effects of *d*-amphetamine in non-stimulant-dependent subjects (Rush et al., 2004).

Although previous research supports the potential of GABA_A positive modulators for stimulant-use disorders, there do not appear to be any published clinical studies that tested the effects of methamphetamine in stimulant users maintained on a benzodiazepine. In particular, determining the effects of repeated dosing is important because it more closely resembles therapeutic use and because the effects of acute versus chronic dosing could differ (e.g., Lile et al., 2008, 2011). The present experiments tested the hypothesis that intranasal methamphetamine (0, 5, 10, 20 and 30 mg) would be safe and well tolerated during maintenance on extended release alprazolam (i.e., alprazolam XR) and that the subjective and physiological effects of intranasal methamphetamine would be attenuated during alprazolam XR maintenance. Alprazolam was chosen for this initial proof-of-concept study because our previous study demonstrated that it attenuated the response to *d*-amphetamine (Rush et al., 2004). The safety, tolerability and potential effectiveness of alprazolam XR maintenance and the effects of intranasal methamphetamine were assessed using a battery of physiological measures, subject-rated drug-effect questionnaires, side-effects questionnaires and a psychomotor performance task.

2. Method

2.1 Subjects

Eight non-treatment-seeking adults with recent histories of illicit stimulant use who met criteria for a stimulant use disorder completed this within-subjects, placebo-controlled study. The Institutional Review Board of the University of Kentucky Medical Center approved this

study and subjects gave their written informed consent prior to participating. Subjects were paid for their participation.

Prior to enrollment, all potential subjects underwent a comprehensive physical-and mental-health screening (see Rush et al., 2011 for details). A psychiatrist (L.R.H., P.E.A.G. or his designee) interviewed and examined each potential participant and deemed him or her to be appropriate for the study. Subjects had to meet the following inclusion criteria: (1) self-reported recent stimulant use, (2) confirmation of recent stimulant use by a positive urine screen during the initial screening process and (3) fulfill diagnostic criteria for stimulant dependence on a computerized version of the Structure Clinical Interview for DSM IV. All subjects were in good health with no contraindications to stimulants or benzodiazepines.

Subjects ranged in age from 36 to 51 years (mean = 43 years) and in weight from 65 to 105 kg (mean = 84 kg). All subjects had a BMI < 30 (mean = 26). Seven subjects were male and one was female. Four subjects reported their race as Black, three reported their race as White and one reported race as Hispanic. All subjects reported current illicit stimulant use in the month prior to screening (6–30 days; mean = 15 days), which was verified by drug urinalysis testing during screening. These subjects all reported the use of cocaine and 5 of the 8 subjects had experience with amphetamine. Subjects reported that their typical route of cocaine administration was smoked, but 6 of the 8 subjects reported regular intranasal use as well. Six subjects reported previous use of benzodiazepines and one of these subjects reported using a benzodiazepine in the month prior to screening. All subjects reported cannabis use in the past month and two subjects reported opioid use in the past month; however all urine samples were required to be negative for substances other than stimulants before alprazolam XR maintenance was initiated. Five subjects reported consuming alcohol (range of 1–28 beverages per week; mean = 11) and scored between 0 and 21 (mean = 11) on the MAST. In addition, all but one subject reported smoking tobacco cigarettes daily (range = 5–25 cigarettes per day; mean = 12 cigarettes). Subjects did not meet criteria for dependence on any substances other than stimulants or tobacco.

2.2 General Procedures

Subjects were enrolled as inpatients at the University of Kentucky Chandler Medical Center Clinical Research Development and Operations Center (CR-DOC) for 14 days and participated in one practice and four experimental sessions. Subjects were informed that they would receive various drugs, administered orally or intranasally, that could include placebo, alprazolam XR or methamphetamine, and that these medications could be administered alone or in combination. Subjects were also told that the purpose of the study was to determine how different drugs affect physiology, mood and behavior. Other than receiving this general information, subjects were blind to the type and dose of drug administered, and were given no instruction of what they were “supposed” to do or of what outcomes might be expected. Following admission, subjects were then allowed to acclimate to the CR-DOC for one day, during which they were observed for signs of drug or alcohol withdrawal. No participant showed signs of withdrawal. After study completion, subjects attended follow-up visits to complete self-reported drug use questionnaires and provide urine samples for illicit drug screening to ensure that their patterns and types of drug use had not changed.

Practice Session—Subjects completed one practice session to familiarize them with experimental measures. Experimental medications were not administered during this session.

Drug Maintenance—Drug maintenance began on the day immediately following the practice session and continued throughout the protocol. Placebo or sustained release alprazolam XR was administered orally at 0700 and 1900 h. The order of drug maintenance was counterbalanced across subjects. After at least four days of maintenance on placebo or alprazolam XR, subjects completed two experimental sessions. After completing these sessions, subjects moved to the other maintenance condition and then completed two more experimental sessions after at least four days of maintenance on that condition. To reduce the likelihood of benzodiazepine withdrawal, subjects received one half of the alprazolam XR dose (i.e., 0.5 mg) on the last day of the active maintenance condition.

Experimental Sessions—Experimental sessions were conducted in two blocks of two sessions each. Subjects received the appropriate maintenance dose at 0700 h on the morning of all experimental sessions. Experimental sessions started at 0800 h and lasted 5.5 h. Three intranasal methamphetamine doses were given in each session in ascending order 1.5 h apart (0 [placebo] 5 and 10 mg for experimental sessions 1 and 3 [i.e., the first session under a maintenance condition] and 0, 20 and 30 mg for experimental sessions 2 and 4 [i.e., the second session under a maintenance condition]). This dosing schedule permitted the administration of a range of methamphetamine doses while minimizing the duration of inpatient participation. An ascending dose order was used for safety purposes. Urine and expired breath samples were collected prior to each session to confirm drug and alcohol abstinence, respectively. Subjects occasionally tested positive for amphetamine and benzodiazepines, which coincided with the administration of the study drugs. Subjects tested negative for all other drug and alcohol use. The female subject received urine pregnancy tests daily, which were negative throughout participation.

Testing Room—The testing room for all sessions consisted of a table and chair for the research assistant and nurse, a hospital bed for the participant, an Apple iBook laptop computer (Apple Computer Inc., Cupertino, CA) and an automated ECG and blood pressure monitor (Dinamap Pro 1000 Vital Signs monitor, Critikon Company L.L.C., Tampa, FL). A crash cart was available in case of a medical emergency.

2.3 Measures

Data were collected in fixed order on a laptop computer, with the exception of physiological measures, which were recorded with pen and paper. Physiological measures were recorded immediately prior to each drug administration and every 15 min for 75 min after each dose. Subject-rated and performance measures were completed prior to initial drug administration, immediately after each drug administration and every 15 min for 75 min after each dose.

Physiological—Outcomes included heart rate, blood pressure and oral temperature. Cardiac rhythmicity was recorded throughout experimental sessions. If heart rate exceeded 130 beats per minute, systolic blood pressure exceeded 180 mmHg, diastolic blood pressure

exceeded 120 mmHg or clinically significant ECG changes occurred following administration of methamphetamine at any point during the experiment, participation was discontinued. One subject was discharged for exceeding these criteria. The data from that subject were not included in the statistical analysis.

Subject-Rated Measures—Questionnaires consisted of the Drug-Effect Questionnaire (Lile et al., 2010) and the Adjective-Rating Scale (Oliveto et al., 1992). CRDOC nursing staff also completed the Udvalg for Kliniske Undersøgelser (UKU) Side Effects Rating Scale daily (Lingjaerde et al., 1987). Although not analyzed statistically, unit physicians monitored side effects reported on these scales regularly.

Performance Task—The Digit-Symbol-Substitution Test (DSST) was used to assess changes in psychomotor performance following drug administration (see Rush et al., 2011 for details).

2.4 Drug Administration

All drugs were administered in a double-blind fashion. Sustained release alprazolam (0.5 mg alprazolam XR, b.i.d.) doses were prepared by over-encapsulating commercially available drug (Greenstone, Ltd, Peapack, NJ). Methamphetamine doses (0 mg [placebo], 5, 10, 20 and 30 mg) were prepared by combining the appropriate amount of methamphetamine HCl (National Institute on Drug Abuse, Rockville, MD) with lactose to equal a total of 100 mg powder. Capsule preparation and intranasal dose administration are described in detail in Rush et al., 2011.

References below to methamphetamine alone pertain to those instances in which an active dose was administered during maintenance on 0 mg alprazolam XR. References to placebo pertain to sessions in which 0 mg methamphetamine (i.e., placebo) was administered during maintenance on 0 mg alprazolam XR.

2.5 Data Analysis

Data were analyzed as area-under-the-curve (AUC; calculated using the trapezoidal method) using a two factor repeated-measures ANOVA with alprazolam XR maintenance condition (0 and 1 mg/day) and Methamphetamine dose (0 [placebo, averaged across the two administrations within a maintenance condition], 5, 10, 20 and 30 mg) as the factors (StatView, SAS Institute, Cary, NC). AUC data were divided by the coefficient used in the AUC calculation (5, which corresponds to the number of post-methamphetamine time points), in an effort to incorporate data from the entire post-drug time period, while presenting the data in a number range that is more easily interpreted. Data were also analyzed as peak effect, but the results were nearly identical, so only the AUC results are presented. If a significant main effect of methamphetamine was detected, Fisher's PLSD *post-hoc* tests were conducted to compare each of the active drug conditions with placebo. If a dose of methamphetamine alone differed significantly from placebo, additional *post-hoc* tests were conducted to compare the effects of these doses of methamphetamine alone and during maintenance on alprazolam XR. Effects were considered significant for $p \leq 0.05$.

3. Results

3.1 Physiological Measures

ANOVA revealed a significant effect of methamphetamine on systolic ($F_{4,28} = 8.9$, $p = 0.001$) and diastolic blood pressure ($F_{4,28} = 4.9$, $p = 0.01$) and heart rate ($F_{4,28} = 8.4$, $p = 0.001$). Post-hoc comparisons indicated that intranasal methamphetamine dose-dependently elevated blood pressure and heart rate above placebo levels. One exception is that heart rate following administration of the 5 mg methamphetamine dose was significantly lower than placebo during placebo alprazolam XR maintenance. Alprazolam XR maintenance reduced heart rate and systolic pressure at the 10 mg dose of methamphetamine (Figure 1). There was no effect of methamphetamine on oral temperature (data not shown).

3.2 Digit-Symbol-Substitution Test (DSST)

A significant interaction of methamphetamine and alprazolam XR was found for the number of trials attempted ($F_{4,28} = 3.1$, $p = 0.05$) and number of trials correct ($F_{4,28} = 4.4$, $p = 0.01$) on the DSST. DSST performance is presented in Figure 1. Post-hoc comparisons revealed that during placebo maintenance, 20 and 30 mg methamphetamine significantly increased the number of trials attempted and trials correct relative to placebo. During maintenance on 1 mg/day alprazolam XR, the number of trials attempted was significantly less than placebo at the 5, 10 and 30 mg dose and the number of trials correct was significantly reduced at the 5 and 30 mg dose of methamphetamine. In addition, when performance across maintenance conditions was compared for a given dose of methamphetamine, the number of trials attempted and correct was significantly lower during alprazolam XR maintenance at every dose, including placebo.

3.3 Drug-Effect Questionnaire

A significant main effect of methamphetamine was observed for thirteen items on the Drug-Effect Questionnaire: Active-Alert-Energetic, Any Effect, Good Effects, High, Irregular-Racing Heartbeat, Like Drug, Nauseated, Pay For, Rush, Shaky-Jittery, Sluggish-Fatigued-Lazy, Stimulated, Talkative-Friendly and Willing to Take Again, ($F_{4,28}$ values = 2.8–5.5, $p = 0.05$). Methamphetamine generally increased ratings in a dose dependent manner. During active alprazolam XR maintenance, ratings for the items Any Effect, Stimulated, Rush and High were significantly decreased relative to placebo at the 30 mg dose of methamphetamine (Figure 2). An interaction of methamphetamine and alprazolam XR was found for the Drug-Effect Questionnaire items Nervous-Anxious ($F_{4,28} = 3.0$, $p = 0.05$) and Shaky-Jittery ($F_{4,28} = 5.0$, $p = 0.01$). For the item Nervous-Anxious, ratings were significantly decreased relative to placebo at the 30 mg dose of methamphetamine during active alprazolam XR maintenance. For the item Shaky-Jittery, maintenance on 1 mg/day alprazolam XR increased ratings at the 5 and 10 mg dose of methamphetamine, but attenuated ratings following administration of the 20 mg dose.

3.4 Adjective-Rating Scale

ANOVA revealed a significant effect of methamphetamine on the Stimulant Scale of the Adjective-Rating Scale ($F_{4,28} = 4.9$, $p = 0.01$). Intranasal methamphetamine increased scores

on this scale significantly above placebo levels at all active doses, and alprazolam XR maintenance attenuated scores at the 30 mg methamphetamine dose (Figure 2). No effects of methamphetamine or alprazolam XR were detected on the Sedative Scale of the Adjective-Rating Scale (data not shown).

4. Discussion

Previous research has demonstrated that there are neurobiological changes to GABA_A receptor activity following repeated administration of stimulant drugs such as methamphetamine and cocaine. Furthermore, positive modulation of GABA_A receptors with benzodiazepines has been shown to attenuate the neurochemical and behavioral response to stimulants. These data suggest that targeting GABA_A could be a useful strategy to develop medications for stimulant-use disorders. The present study appears to be the first to have evaluated the safety, tolerability and potential efficacy of treatment with a GABA_A positive modulator in stimulant users who received methamphetamine.

Intranasal methamphetamine produced prototypical stimulant-like subject-rated drug effects and increased heart rate and blood pressure as a function of dose. Alprazolam XR produced small, but orderly, reductions in some of the subjective effects of methamphetamine. Specifically, ratings on some questionnaire items (e.g., VAS ratings of Any Effect, Stimulated, Rush and High; Stimulant scale of Adjective Rating Scale) were significantly attenuated following administration of the 30 mg dose of methamphetamine during alprazolam XR maintenance. Intranasal methamphetamine produced subjective drug effects typical of stimulant drugs that were generally dose dependent, significantly greater than placebo, and of a magnitude comparable to what has been reported in previous studies (Harris et al., 2003; Hart et al., 2008; Rush et al., 2011). Collectively, these studies have tested a range of doses from 2.5–50 mg. Moderate doses of intranasal methamphetamine (i.e., 20–30 mg) have frequently produced peak self-reported effects in the range of 30–50 out of 100 on a visual analog scale. Hart and colleagues (2008) tested the highest acute dose, 50-mg/70 kg intranasal methamphetamine (up to a maximum of 60 mg), which produced substantially larger subjective ratings (i.e., nearly 80 on a 100-unit VAS). Intranasal methamphetamine also increased heart rate and blood pressure during both placebo and alprazolam XR maintenance, generally in a dose dependent manner, and consistent with previous studies with intranasal methamphetamine (Harris et al., 2003; Hart et al., 2008; Rush et al., 2011). Together these results demonstrate the ability of intranasal methamphetamine to reliably engender abuse-related subjective and physiological effects within a dose range that is safe and tolerable for laboratory screening of potential medications for methamphetamine-use disorders.

Maintenance on 1 mg/day alprazolam XR significantly decreased the number of symbols attempted and correct on the DSST when compared to placebo maintenance. The largest impact on performance was observed following administration of the 30 mg methamphetamine and active alprazolam XR dose combination, resulting in a decrease of approximately 9% in the number of correct trials completed compared to placebo. In addition, although subjects did not report significant sedative-like drug effects on the questionnaires administered during experimental sessions during active alprazolam XR

treatment, review of the twice-daily side-effect questionnaires administered by the medical staff indicated that occasionally subjects responded that they had experienced increased duration of sleep or sleepiness/sedation (5 of 8 subjects). The target dose range for clinical indications of alprazolam XR is 3–6 mg/day. That sedation and performance decrements were observed at a sub-therapeutic dose might be considered surprising, although other studies have demonstrated similar effects at lower doses (e.g., Kaplan et al., 1998; Kelly et al., 1997). Tolerance to the effects of benzodiazepines, such as sedation and performance impairment, is frequently observed with repeated use (e.g., Seidel et al., 1985; Stoops and Rush, 2003). In the present study, the length of the maintenance period was chosen to attain steady state blood levels of alprazolam prior to methamphetamine testing, but might not have been long enough for subjects to develop tolerance to its sedating and performance impairing effects.

Maintenance on alprazolam XR resulted in relatively small reductions in the effects of intranasal methamphetamine, and for only a subset of the subjective-effects questionnaire items, whereas some previous laboratory research has yielded more robust findings (Druhan et al., 1991; Gatch et al., 2005; Negus et al., 2000; Rush et al., 2004). One possibility for these differences is that previous research has typically used acute pretreatment with a benzodiazepine, whereas the present study administered alprazolam XR twice a day for four days prior to testing. The acute versus maintenance dosing could account for the differential response to alprazolam XR. For example, clinical studies that have tested the atypical antipsychotic aripiprazole in combination with stimulant drugs have found that acute pretreatment attenuated the discriminative-stimulus and self-reported effects of cocaine and d-amphetamine (Lile et al., 2005, 2010; Stoops et al., 2006), but that the reinforcing and self-reported effects of cocaine were enhanced following repeated dosing with aripiprazole (Haney et al., 2011; Lile et al., 2008; Stoops et al., 2007). Similarly, clinical research has demonstrated that acute pretreatment with another indirect dopamine agonist enhanced the discriminative-stimulus and self-reported effects of cocaine and methamphetamine (Johanson et al., 2007; Vansickel et al., unpublished data) whereas maintenance dosing attenuated the abuse-related effects of the stimulant drug (Collins et al., 2006; Rush et al., 2009, 2010b, 2011; Winhusen et al., 2006). In those examples, however, the putative pharmacotherapy and the abused drug were acting upon the same neurotransmitter systems. The relative impact of acute vs. chronic dosing when the pretreatment agent acts at a distinct neurotransmitter system (i.e., GABA) remains unclear and deserves further investigation.

In addition to their potential for blocking the effects of stimulant drugs, there are at least three other reasons that GABA_A positive modulators could be useful as medications for stimulant-use disorders. First, cocaine use activates the hypothalamic-pituitary-adrenal (HPA) axis, resulting in the secretion of stress hormones such as cortisol and ACTH (Baumann et al., 1995; Mendelson et al., 1989). Benzodiazepines reduce plasma corticosteroid concentrations in humans, and animal research has demonstrated that they attenuate the neuroendocrine response to amphetamine (reviewed in DeSouza, 1990). Second, and related to HPA axis activation, is that anxiety is a frequently reported symptom of withdrawal from stimulant drugs (e.g., Cruickshank and Dyer, 2009; McGregor et al., 2005), and many benzodiazepines are indicated for the relief of anxiety. Third, there is a risk of seizure associated with stimulant drug use (e.g., Myers and Earnest, 1984; Sommers et

al., 2006; Washton and Tatarsky, 1984) and benzodiazepines are well known for their ability to elevate seizure thresholds and to arrest seizures. In these ways, alprazolam XR or another GABA_A positive modulator could be useful as adjunct component of combination behavioral and/or drug treatment, despite the lack of a large positive signal in the present study. Furthermore, there are several instances in which one or both components of a proposed treatment were ineffective or produced small magnitude effects alone, but exhibited significant therapeutic efficacy when combined. For example, pharmacotherapy with the opioid antagonist naltrexone and behavioral therapy in the form of relapse prevention training significantly reduced cocaine use in dependent patients when combined, but not when administered individually (Schmitz et al., 2001). Future studies could evaluate GABA_A positive modulators for their ability to enhance the therapeutic efficacy of another treatment.

In summary, alprazolam XR maintenance was safe and well tolerated when combined with intranasal methamphetamine, but resulted in relatively small reductions in some of the subjective effects of methamphetamine. However, given the overall positive findings from other laboratory studies that have tested benzodiazepines for their ability to attenuate the effects of stimulants, and their potential to manage other aspects of stimulant abuse and dependence that were not tested here (i.e., drug-induced seizures, anxiety and stress), additional research with GABA_A positive modulators appears worthy of further pursuit, although these compounds might be best suited as adjunct components of combined treatment with behavioral therapies or other drugs.

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Figure 1.

AUC dose-response functions for methamphetamine during maintenance on placebo (squares) and 1 mg/day alprazolam XR (circles) for the number of symbols attempted and correct on the DSST, systolic pressure and heart rate. Data were divided by the coefficient used for AUC calculation (5, which corresponds to the number of post-methamphetamine time points). X-axis: Intranasal methamphetamine dose. PL denotes placebo. Data points represent means for eight subjects. Filled symbols indicate the data point differs significantly from the placebo condition (i.e., 0 mg methamphetamine during maintenance on 0 mg alprazolam XR). An asterisk indicates that the data point is significantly different

from the corresponding dose of methamphetamine during maintenance on 0 mg alprazolam XR. Error bars represent 1 S.E.M.

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Figure 2.

Area-under-the-curve (AUC) dose-response functions for methamphetamine during maintenance on placebo (squares) and 1 mg/day alprazolam XR (circles) for VAS ratings of Any Effect, Stimulated and High on the Drug-Effect Questionnaire and scores from the Stimulant scale of the Adjective Rating Scale. Other details are as in Figure 1.