Published in final edited form as:

Pharmacol Biochem Behav. 2016 ; 150-151: 87–93. doi:10.1016/j.pbb.2016.09.009.

ACUTE BUSPIRONE DOSING ENHANCES ABUSE-RELATED SUBJECTIVE EFFECTS OF ORAL METHAMPHETAMINE

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Abstract

There is not an approved pharmacotherapy for treating methamphetamine use disorder. This study sought to determine the effects of acute buspirone treatment on the subjective and cardiovascular effects of oral methamphetamine in order to provide an initial assessment of the utility, safety, and tolerability of buspirone for managing methamphetamine use disorder. We predicted that acute buspirone administration would reduce the subjective effects of methamphetamine. We also predicted that the combination of buspirone and methamphetamine would be safe and well tolerated. Ten subjects completed the protocol, which tested three methamphetamine doses (0, 15, and 30 mg) in combination with two buspirone doses (0 and 30 mg) across 6 experimental sessions. Subjective effects and physiological measures were collected at regular intervals prior to and after dose administration. Methamphetamine produced prototypical subjective and cardiovascular effects. Acute buspirone administration increased some of the abuse-related subjective effects of methamphetamine and also attenuated some cardiovascular effects. The combination of oral methamphetamine and buspirone was safe and well tolerated. Acute buspirone administration may increase the abuse liability of oral methamphetamine. Chronic buspirone dosing studies remain to be conducted, but given preclinical findings and the outcomes of this work, the utility of buspirone for treating methamphetamine use disorder appears limited.

Keywords

methamphetamine; buspirone; acute; subjective effects; cardiovascular effects

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Conflicts of Interest: The authors declare no conflicts of interest.

1. INTRODUCTION

Methamphetamine use is a significant problem. In 2014, an estimated 570,000 Americans age 12 and older reported current use of methamphetamine (Center for Behavioral Health Statistics and Quality, 2015). The number of individuals reporting methamphetamine use in the last year has increased from approximately 1,190,000 in 2013 to approximately 1,300,000 in 2014 (Center for Behavioral Health Statistics and Quality, 2015). The estimated total cost for methamphetamine abuse in the United States was over \$23 billion in 2005, the year with the most recent data available (Nicosia et al., 2009). These costs include premature mortality, crime and lost productivity, environmental damage, and medical conditions such as cardiovascular insults and infectious disease (Pasic et al., 2007; Shoptaw et al., 2009).

Despite the number of individuals using methamphetamine and the cost to society, few interventions are available for those seeking treatment for methamphetamine use disorder. Psychosocial treatments, such as Cognitive Behavioral Therapy, remain one of the few options available for the treatment of methamphetamine use disorder (reviewed in Courtney and Ray, 2014). No pharmacological treatments have been FDA approved for methamphetamine use disorder. Identifying a pharmacological adjunct for reducing methamphetamine use is a research priority.

Methamphetamine produces its behavioral and physiological effects largely via interaction with monoamine transporters (dopamine, serotonin, and norepinephrine; reviewed in Fleckenstein et al., 2000, 2007; Rothman and Glowa, 1995). Methamphetamine acts as a substrate for monoamine transporters and is taken into the nerve terminal where it promotes the release of dopamine, serotonin, and norepinephrine into the synapse (Fleckenstein et al., 2007; Mantle et al., 1976). Methamphetamine interacts with vesicular monoamine transporter-2 to redistribute monoamines from vesicles into the cytosol. Methamphetamine also reverses catecholamine-uptake transporters causing monoamines in the cytosol to move into the synapse. Finally, methamphetamine inhibits monoamine oxidase, which breaks down monoamines in the cell, and increases dopamine synthesis through the promotion of tyrosine hydroxylase. Based on these neuropharmacological effects, medications development research has primarily targeted monoamine systems when evaluating potential pharmacotherapies for methamphetamine use disorder (reviewed in Bressan et al., 2013). Medications development studies specifically testing dopamine reuptake inhibitors, releasers or partial agonists have yielded mixed results (e.g., Anderson et al., 2015; Galloway et al., 2011; Rush et al., 2011; Tiihonen et al., 2007).

Buspirone is an anxiolytic that lacks the abuse potential and sedative effects associated with benzodiazepines (Eison and Temple, 1986). Buspirone is a serotonin 1A receptor partial agonist, a dopamine autoreceptor antagonist, and a selective dopamine D₃ receptor antagonist (Eison and Temple, 1986; Heidbreder, 2008; Kula et al., 1994; Mahmood and Sahajwalla, 1999; Skolnick et al., 1984; Tunnicliff, 1991; Volkow and Skolnick, 2012). The pharmacological actions of buspirone to modulate serotonin and dopamine tone suggest it may be a viable pharmacotherapy for treating methamphetamine use disorder (Kish et al., 2009; Sekine et al., 2003).

Several preclinical studies have investigated the influence of buspirone on the pharmacodynamic effects of amphetamines. Buspirone reduced the locomotor effects of d-amphetamine and antagonized d-amphetamine induced stereotypy in rats (Jackson et al., 1994). Buspirone produced a rightward shift of the d-amphetamine dose-effect curve in rhesus monkeys trained to discriminate d-amphetamine (Nader and Woolverton, 1994). The results of this study are noteworthy because the discriminative-stimulus effects of drugs in laboratory animals are thought to be a model of the subjective effects of drugs in humans. Buspirone did not alter methamphetamine self-administration in rhesus monkeys in a more recent study (John et al., 2015). No other preclinical studies have assessed the influence of buspirone on methamphetamine self-administration, but mixed effects have been observed when evaluating how buspirone impacts cocaine self-administration (Bergman et al., 2013; Czoty and Nader, 2015; Gold and Balster, 1992; John et al., 2015; Mello et al., 2013). Some positive signals with cocaine when this study was designed (i.e., Bergman et al., 2013; Mello et al., 2013) supported the rationale for testing buspirone in combination with methamphetamine. Moreover, no studies have evaluated the influence of buspirone treatment on the effects of methamphetamine, or amphetamines in general, in human subjects.

The purpose of this experiment was to determine the effects of acute buspirone administration on the subjective and cardiovascular effects of oral methamphetamine in order to provide an initial assessment of the utility, safety, and tolerability of buspirone for managing methamphetamine use disorder. Buspirone was administered acutely because this was the first study assessing the combination of methamphetamine and buspirone in humans. Previous research testing medications for cocaine use disorder have shown that acute medication administration produces different effects compared to chronic administration (Haney and Spealman, 2008), but acute administration remains an important first step in evaluating medication combinations. We hypothesized that acute buspirone administration would reduce the subjective effects of oral methamphetamine based on a study that showed buspirone produced a rightward shift in the discriminative effects of d-amphetamine (Nader and Woolverton, 1994), which is thought to model subjective effects in humans. We also hypothesized that the combination of methamphetamine and buspirone would be safe and well tolerated.

2 METHODS

2.1 Study Population, Inclusion/Exclusion Criteria, and Screening

Ten non-treatment seeking adult subjects with who reported current (i.e., past month) stimulant use completed this within-subjects, placebo-controlled study. Six subjects met diagnostic criteria for current stimulant dependence and four met criteria for current stimulant abuse as determined by a computerized version of the Structured Clinical Interview for the *Diagnostic and Statistical Manual of Mental Disorders – IV* (SCID). Two additional subjects were enrolled in the study (i.e., signed the consent document), but did not complete. One subject did not pass the initial health screening and the other decided to enroll in a different research study. The Institutional Review Board of the University of Kentucky Medical Center approved this study and the subjects gave their written informed consent prior to participating. Subjects were informed that during the study they would be

given placebo, a stimulant (i.e., methamphetamine), and an anxiolytic (i.e., buspirone). Subjects were informed that the purpose of the study was to see how drugs affect mood and behavior. Subjects were not informed of the specific drugs they received in individual sessions, possible outcomes, or performance expectations. Subjects were paid for their participation.

Prior to enrollment in the experimental protocol, all subjects underwent a comprehensive physical and mental health screening as described previously (Sevak et al., 2011). Subjects had to meet the following inclusion criteria: self-reported stimulant use, confirmation of recent stimulant use by a stimulant positive urine sample, and fulfillment of the diagnostic criteria for current stimulant abuse or dependence on a computerized version of the SCID that was reviewed by a psychologist or psychiatrist. Potential subjects with histories of serious physical disease or current physical disease (e.g., impaired cardiovascular functioning, chronic obstructive pulmonary disease, seizure, head trauma or central nervous system tumors) current or past histories of serious psychiatric disorder, (i.e., Axis I of *DSM-IV*) other than substance abuse or dependence, or who reported physical withdrawal symptoms from alcohol or drugs that was determined by medical staff to potentially interfere with participation were excluded from participation. All subjects were physically and psychologically healthy, as determined by the medical staff, with no contraindications to the study medications.

Subjects ranged in age from 26 to 54 years (mean 42 years) and in weight from 64 to 103 kg (mean 78 kg). Eight subjects were male and two were female. Six subjects were black and four were white (one Hispanic). Subjects reported use of a range of drugs for recreational purposes including stimulants, nicotine, alcohol, caffeine, marijuana, opiates, hallucinogens, and sedatives (current use shown in Table 1). All subjects reported current cocaine use and one subject also reported current amphetamine use. Six of the enrolled subjects reported lifetime illicit amphetamine use.

2.2 Study Procedures

The experiment consisted of 7 total outpatient sessions (1 practice and 6 experimental) that were separated by at least 24 hours to minimize carryover effects. For all sessions, subjects arrived at the University of Kentucky Laboratory of Human Behavioral Pharmacology at approximately 8:00 AM. Subjects completed a field sobriety test and provided an expired breath sample that was tested for the presence of alcohol using a handheld Alco-Sensor Breathalyzer (Intoximeters, St. Louis, MO) prior to the beginning of each session. Subjects also provided a urine sample that was tested for drugs of abuse, as well as pregnancy for female subjects. Both female subjects tested negative for pregnancy throughout their participation. Subjects were instructed to abstain from drugs and alcohol for 12 hours prior to their session. Subjects were also instructed to abstain from food and caffeine for four hours prior to each session and were given a low-fat breakfast at the beginning of each session.

2.3 Practice Session

Subjects completed a practice session to familiarize them with the subjective effects questionnaires, performance task, and timeline of experimental sessions, as described below. No medications were administered during the practice session.

2.4 Experimental Sessions

Experimental sessions started at 8:00 AM and lasted approximately 6 hours. At 9:00 AM, subjects received the dose condition (i.e., methamphetamine and/or buspirone) for the session. Subjects were instructed to swallow the capsules and a research assistant performed a mouth check to ensure that the capsules were swallowed. Subjects had vital signs recorded and completed subjective effects questionnaires approximately 30 minutes before dose administration and 1, 2, 3, 4, and 5 hours following dose administration. Subjects completed the End of Day and Street Value Questionnaires at the 5-hour time point.

Urine and breath samples were collected before each session to confirm drug and alcohol abstinence, respectively. Subjects occasionally tested positive for methamphetamine, which was likely attributable to the administration of the experimental medications. Subjects also occasionally tested positive for cocaine and THC. Subjects were asked at the beginning of their sessions when they last used any substances to verify that they were not acutely intoxicated.

All subjects who reported smoking were allowed to smoke one cigarette in the morning and one cigarette at lunch during sessions. All subjects were required to keep their smoking behavior consistent throughout the experiment in order to keep nicotine exposure constant within subjects.

2.5 Subjective Effect Questionnaires and Performance Measure

Two subjective effect questionnaires were administered using an Apple computer with a mouse attached in a fixed order throughout the session: the Adjective Rating Scale (Oliveto et al., 1992) and the Drug Effect Questionnaire (Rush et al., 2011). The Adjective Rating Scale was a 32-item computer based questionnaire that contained items that load into two subscales: Sedative and Stimulant. Subjects rated each item on a 5-point Likert-type scale as “Not at All,” “A Little Bit,” “Moderately,” “Quite a Bit,” or “Very Much” (scored numerically from 0 to 4, respectively). The Drug Effect Questionnaire contained 13 items and subjects rated responses along a 100 mm visual analog scale anchored at each end with “Not at All” (i.e., 0) and “Extremely” (i.e., 100). Subjects also completed the Digit-Symbol-Substitution Task (DSST; McLeod et al., 1982) on an Apple computer with an attached nine-digit keypad. In the DSST, subjects used a numeric keypad to recreate patterns shown on the computer screen over a period of 90 seconds. These measures were selected because they are sensitive to the effects of stimulants (Rush et al., 2004, 2011; Sevak et al., 2011; Stoops et al., 2015). At the end of each session, subjects completed two additional subjective effects questionnaires: the End of Day and Street Value Questionnaires. The End of Day Questionnaire assessed drug-effects experienced throughout the session with six questions and subjects rated each item along a 100 mm visual analog scale anchored at each end with

“Not at All” (i.e., 0) and “Extremely” (i.e., 100). On the Street Value Questionnaire subjects wrote in the street value of the dose received.

2.6 Physiological Measures

Heart rate and blood pressure were measured at regular intervals throughout session. Medications were held if systolic pressure was 150 mmHg or higher, diastolic pressure was 100 mmHg or higher, or heart rate was 100 bpm or higher. No medications were held for exceeding these parameters. If systolic blood pressure, diastolic blood pressure, or heart rate exceeded 180, 120, or 130, respectively, participation was discontinued. No subjects were excluded from participation for exceeding these parameters.

2.7 Drug Administration

All medications were administered in a double blind fashion. The doses of methamphetamine were 0, 15, and 30 mg and the doses of buspirone were 0 and 30 mg. The doses of methamphetamine were selected based on previous studies showing that doses within this range were well tolerated and produced increases in subjective effects compared to placebo (Hart et al., 2001; Kirkpatrick et al., 2012; Sevak, et al., 2011). Methamphetamine and buspirone were administered simultaneously at approximately 9:00 AM. Placebo capsules contained only cornstarch and were visibly identical to the capsules that contained active medications. Following dose administration, the research assistant conducted a mouth check to verify that the subject swallowed the capsules. The order of dose administration was random (i.e., dose order was determined with a random number generator) and all subjects received all possible dose combinations (i.e., 0 mg buspirone with 0, 15, and 30 mg methamphetamine; 30 mg buspirone with 0, 15, and 30 mg methamphetamine) across the six sessions.

2.8 Statistical Methods

For all statistical analyses, effects with $p < 0.05$ were considered significant. Data were analyzed as peak effect (i.e., the maximum response observed after dosing) using a two-factor repeated-measures analysis of variance (ANOVA; Statview, Cary, NC). The factors were Methamphetamine (i.e., 0, 15, and 30 mg) and Buspirone (i.e., 0 or 30 mg). Fisher's Least Significant Difference (LSD) *post hoc* tests were used to interpret ANOVA outcomes for significant main effects or interactions. Comparisons were made for each dose combination back to placebo (i.e., 0 mg methamphetamine and 0 mg buspirone) and for each methamphetamine dose between buspirone conditions (e.g., 30 mg methamphetamine with 0 mg buspirone compared to 30 mg methamphetamine with 30 mg buspirone).

3 RESULTS

3.1 Subjective Effects

3.1.1 Adjective Rating Scale—ANOVA revealed only a main effect of methamphetamine for scores on the Stimulant scale of the Adjective Rating Scale ($F_{2,18} = 7.0$, $p = .01$). Fisher's LSD *post hoc* test showed that the 30 mg methamphetamine dose significantly increased ratings relative to placebo (i.e., 0 mg methamphetamine combined

with 0 mg buspirone) regardless of buspirone condition (Figure 1). There were no significant effects on the Sedative scale of the Adjective Rating Scale (data not shown).

3.1.2 Visual Analog Scales—ANOVA revealed main effects of methamphetamine and buspirone ($F_{2,18} = 4.0$, $p = 0.04$; $F_{1,18} = 6.5$, $p = 0.03$, respectively), but not an interaction of these factors, for ratings of *High*. Fisher's LSD *post hoc* test showed that the 30 mg methamphetamine dose significantly increased ratings on this item relative to placebo (i.e., 0 mg methamphetamine combined with 0 mg buspirone), regardless of buspirone condition (Figure 1). For all doses of methamphetamine, ratings were increased under the 30 mg buspirone dose condition relative to the 0 mg buspirone dose condition.

ANOVA revealed only a main effect of buspirone for ratings of *Good Effect* ($F_{1,18} = 5.4$, $p = 0.05$). The 30 mg methamphetamine dose increased ratings on this item when combined with 30 mg buspirone compared to placebo (i.e., 0 mg methamphetamine combined with 0 mg buspirone). Ratings for the 15 mg methamphetamine dose were increased by the 30 mg buspirone dose compared to this dose of methamphetamine combined with 0 mg buspirone based on the results from Fisher's LSD *post hoc* tests (Figure 1).

3.1.3 End of Day Questionnaire—ANOVA revealed main effects of both methamphetamine and buspirone ($F_{2,18} = 4.7$, $p = 0.02$; $F_{1,18} = 6.1$, $p = 0.04$, respectively), but not an interaction of these factors, for ratings of *Take Again*. Fisher's LSD *post hoc* test showed that the 15 mg methamphetamine dose significantly increased ratings compared to placebo (i.e., 0 mg methamphetamine combined with 0 mg buspirone) when combined with 30 mg buspirone. The 30 mg methamphetamine dose significantly increased ratings compared to placebo (i.e., 0 mg methamphetamine combined with 0 mg buspirone), regardless of buspirone condition (Figure 1).

ANOVA revealed only a main effect of methamphetamine for ratings of *Drug Strength*, *Good Effects*, and *Like Drug* ($F_{2,18}$ values > 4.1 , p values < 0.03). For ratings of *Drug Strength*, there were no significant *post hoc* differences observed. For ratings of *Good Effects*, Fisher's LSD *post hoc* test showed that the 30 mg methamphetamine dose significantly increased ratings compared to placebo (i.e., 0 mg methamphetamine combined with 0 mg buspirone) when combined with 0 mg buspirone. Both the 15 and 30 mg methamphetamine doses significantly increased ratings on this item compared to placebo (i.e., 0 mg methamphetamine combined with 0 mg buspirone) when combined with 30 mg buspirone. Ratings following the 15 mg methamphetamine dose were increased when combined with 30 mg buspirone compared to 0 mg buspirone. For ratings of *Like Drug*, Fisher's LSD *post hoc* test showed that the 30 mg methamphetamine dose significantly increased ratings compared to placebo (i.e., 0 mg methamphetamine combined with 0 mg buspirone) regardless of buspirone condition. Ratings following the 15 mg methamphetamine dose were increased when combined with 30 mg buspirone compared to 0 mg buspirone (Figure 1).

3.1.4 Digit-Symbol-Substitution Task—ANOVA revealed no significant effects of methamphetamine or buspirone on percent correct on the DSST (data not shown).

3.2 Physiological Effects

ANOVA revealed main effects of methamphetamine and buspirone, but not an interaction of these factors, for diastolic blood pressure ($F_{2,18} = 10.2$, $p = 0.001$; $F_{1,18} = 6.3$, $p = 0.03$, respectively). Fisher's LSD *post hoc* test showed that the 30 mg methamphetamine dose significantly increased diastolic blood pressure relative to placebo (i.e., 0 mg methamphetamine combined with 0 mg buspirone) when combined with 0 mg buspirone (Figure 2). The 30 mg dose of buspirone attenuated the pressor increasing effects of the 30 mg methamphetamine dose.

ANOVA revealed only a main effect of methamphetamine for systolic blood pressure and heart rate ($F_{2,18} = 8.5$, $p = 0.003$; $F_{2,18} = 4.0$, $p = 0.04$, respectively). When combined with 0 mg buspirone, both the 15 and 30 mg methamphetamine doses significantly increased systolic blood pressure compared to placebo (i.e., 0 mg methamphetamine combined with 0 mg buspirone) as determined by Fisher's LSD *post hoc* test. When combined with 30 mg buspirone, only the 30 mg methamphetamine dose significantly increased systolic blood pressure relative to placebo (i.e., 0 mg methamphetamine combined with 0 mg buspirone). The increase in systolic blood pressure following the 30 mg methamphetamine dose was attenuated when combined with 30 mg buspirone relative to 0 mg buspirone. Both the 15 and 30 mg methamphetamine doses significantly increased heart rate compared to placebo (i.e., 0 mg methamphetamine combined with 0 mg buspirone) when combined with 0 mg buspirone but not 30 mg buspirone (Figure 2) as determined by Fisher's LSD *post hoc* test.

4 DISCUSSION

The purpose of this study was to assess the influence of acute buspirone administration on the subjective and cardiovascular effects of oral methamphetamine. We hypothesized that acute buspirone administration would reduce the subjective effects of oral methamphetamine. Oral methamphetamine increased subject ratings, which has been shown previously and is indicative of abuse potential (Hart et al., 2001; Kirkpatrick et al., 2012; Sevak et al., 2011). Oral methamphetamine also increased cardiovascular effects, which is consistent with previous studies (Hart et al., 2001; Kirkpatrick et al., 2012; Sevak et al., 2011).

Acute buspirone administration enhanced the abuse-related subjective effects of oral methamphetamine. The enhancement of subjective effects observed following combination of buspirone and methamphetamine is discordant with previous research showing that buspirone attenuates the locomotor effects of amphetamine in rats (Jackson et al., 1994) and the discriminative-stimulus effects of amphetamine in monkeys (Nader and Woolverton, 1994). In monkeys, 0.3–1.0 mg/kg buspirone attenuated the discriminative effects of d-amphetamine, as shown by a rightward shift of the dose-effect curve (Nader and Woolverton, 1994). The reason for the discordance between previous research and the present study is unknown, but may be due to the selected buspirone dose. Preclinical studies are able to test higher doses than is possible in humans. The dose tested in monkeys (in mg/kg) was much higher than could safely be administered acutely to humans in this study. Moreover, in monkeys, the effect of buspirone on the discriminative effects of d-amphetamine was surmountable by higher doses of amphetamine (Nader and Woolverton,

1994). Consistent with this finding, the dose of methamphetamine in the present study may have surmounted the effects of the low dose of buspirone tested here. Another possible reason for the discordance observed is that relationship between reinforcing and subjective effects is not isomorphic. In two previous studies, for example, cocaine self-administration was decreased by a potential pharmacotherapy, but subjective effects were increased (Foltin and Fischman, 1994; Stoops et al., 2012). Subjects may decrease drug intake in response to enhanced subjective effects.

This study was also designed to test the safety and tolerability of the combination of methamphetamine and buspirone. We hypothesized that the combination of methamphetamine and buspirone would be safe and well tolerated. Acute buspirone administration attenuated the cardiovascular effects of oral methamphetamine. The attenuation of cardiovascular effects supports our hypothesis and demonstrates that the combination oral buspirone and methamphetamine at the doses tested can be safely combined in the laboratory.

Medications development for methamphetamine use disorder has primarily tested dopamine reuptake inhibitors releasers or partial agonists because the abuse liability for methamphetamine has been primarily attributed to its ability to increase synaptic levels of dopamine (e.g., Anderson et al., 2015; Galloway et al., 2011; Rush et al., 2011; Tiitonen et al., 2007; reviewed in Rush et al., 2009). Clinical trials and human laboratory studies targeting dopamine systems have yielded mixed results. Methylphenidate, a dopamine reuptake inhibitor, decreased both amphetamine and methamphetamine use (Tiitonen et al., 2007; Ling et al., 2014, respectively). Bupropion, a dopamine reuptake inhibitor, reduced use in a subset of methamphetamine dependent patients (Elkashef et al., 2008; Shoptaw et al., 2008), but did not reduce methamphetamine use in a later study (Anderson et al., 2015). In the human laboratory, bupropion maintenance did not alter methamphetamine self-administration or subjective effects in one study (Stoops et al., 2015), but attenuated some subjective effects of methamphetamine in another (Newton et al., 2006). D-amphetamine, a dopamine releaser, did not promote methamphetamine abstinence (Galloway et al., 2011). D-amphetamine decreased some of the subjective effects of methamphetamine, but did not reduce self-administration in the human laboratory (Rush et al., 2011; Pike et al., 2014, respectively). Aripiprazole, a dopamine partial agonist, increased amphetamine use (Tiitonen et al., 2007). As may be surmised from these results, targeting dopamine systems has not resulted in an FDA approved pharmacotherapy.

The present study has a few limitations worth noting, which should be used to direct future research. First, the present study used acute administration of a moderate dose of buspirone. Chronic administration of buspirone may be more effective for reducing the subjective effects of methamphetamine. Previous research testing medications for cocaine use disorders has provided evidence for differential effects based on acute compared to chronic dose administration (Haney and Spealman, 2008). Ecopipam, for example, administered acutely decreased the positive subjective effects of cocaine, but chronic dosing increased cocaine self-administration (Romach et al., 1999; Haney et al., 2001, respectively). Second, this study tested the influence of buspirone on the effects of oral methamphetamine. Future studies should also assess the effect of buspirone on methamphetamine administered via a

route more frequently associated with abuse (e.g., smoked or injected; National Institute on Drug Abuse, 2014). Third, this study only assessed the influence of buspirone on the cardiovascular and subjective effects of methamphetamine. Self-administration outcomes better predict pharmacotherapy efficacy (Comer et al., 2008; Haney and Spealman, 2008). Future studies should include a measure of drug reinforcement to assess buspirone-methamphetamine combinations. Buspirone administration did not decrease methamphetamine self-administration in one study with monkeys, but the literature on the effects of buspirone on methamphetamine self-administration is limited to one study (John et al., 2015). Fourth, the sample size of the present study was relatively small ($n = 10$) and the number of women was limited ($n = 2$). This sample size limited the ability to investigate differences in responding within the sample, which may have contributed to the outcomes observed.

The present study addressed a gap in the literature by assessing the initial efficacy, safety, and tolerability of the combination of methamphetamine and buspirone in humans. The results showed that the combination of methamphetamine and buspirone could be safely administered in the laboratory at the doses tested. Acute buspirone administration enhanced some subjective effects of oral methamphetamine. When considering these results with findings from preclinical literature showing buspirone did not reduce methamphetamine self-administration in monkeys (John et al., 2015) the potential utility of buspirone for managing methamphetamine use disorder appears to be limited.

5 Conclusions

Acute buspirone administration enhanced some subjective effects of oral methamphetamine, but also attenuated some of the cardiovascular effects. Acute buspirone administration may increase the abuse liability of methamphetamine. Chronic administration of buspirone may be more effective and should be assessed in future studies, especially because any pharmacotherapy for methamphetamine would be administered chronically. Overall, few treatment options are available to treat methamphetamine use disorder and more research is needed to identify potential pharmacotherapies to improve treatment outcomes.

Acknowledgments

We would like to thank the staff of the University of Kentucky Laboratory of Human Behavioral Pharmacology for assistance in screening and running sessions with subjects in this study.

Source of Funding: This research and the preparation of this manuscript were supported by grants from the National Institute on Drug Abuse R01DA025032 and R01DA025591 awarded to Dr. Craig Rush. This funding source had no further role in study design; the collection, analysis, or interpretation of the data; writing of the report; or in the decision to submit the paper for publication.

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Highlights

- A pharmacotherapy has not been identified for treating methamphetamine use disorder
- The influence of acute buspirone on the effects of methamphetamine was tested
- Methamphetamine produced prototypical subject-rated and cardiovascular effects
- Acute buspirone increased some subject-rated effects of methamphetamine
- Acute buspirone attenuated some cardiovascular effects of methamphetamine

Fig. 1.

Subjective effect data are shown for mean peak values (N=10) following administration of oral placebo and methamphetamine (15 and 30 mg; x-axes) following administration of placebo (squares) or 30 mg oral buspirone (circles). Filled symbols indicate a significant difference from placebo using Fisher's LSD *post hoc* test. Asterisks indicate a significant difference between corresponding doses using Fisher's LSD *post hoc* test.

Fig. 2.

Physiological data are shown for mean peak values (N=10) following administration of oral placebo and methamphetamine (15 and 30 mg; x-axes) following administration of placebo (squares) or 30 mg oral buspirone (circles). Filled symbols indicate a significant difference from placebo using Fisher's LSD *post hoc* test. Asterisks indicate a significant difference between corresponding doses using Fisher's LSD *post hoc* test.

Table 1

Subject self-reported current substance use

Substance	Number Reporting Use	Mean	Range
Cigarettes per Day	7	13	3 – 20
Alcohol Drinks per Week	6	19	2 – 42
Caffeine Milligrams per Day	5	330	27 – 816
Illicit Drug Use in the Last Month			
Cocaine	10	12	3 – 17
Amphetamines	1	1	1
Marijuana	10	15	2 – 31
Opiates	4	3	1 – 5
Benzodiazepines	2	2	1 – 3