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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.

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 cortisol. Methamphetamine also reverses catecholamine-uptake transporters causing monoamines in the cortisol 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 Brensilver et al., 2013). Medications development studies specifically testing dopamine reuptake inhibitors, releasers or partial agonists have yielded mixed

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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 D_3 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 h 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 h prior to their session. Subjects were also instructed to abstain from food and caffeine for 4 h prior to each session and were given a low-fat breakfast at the beginning of each session.

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