Cover Page

Official Title: Buspirone as a Candidate Medication for Methamphetamine Abuse
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1. BACKGROUND

Methamphetamine (MA) abuse is a significant problem. The number of Americans that reported recent MA use nearly doubled from 2008 to 2009 and this number did not change significantly between 2009 and 2010. Treatment admissions for MA use more than doubled from 1998 to 2007 in the United States. While behavioral therapies effectively reduce MA use, many patients are unable to achieve significant periods of abstinence suggesting other strategies like pharmacotherapy are needed. An effective medication has not been identified for MA dependence despite being a high priority for the National Institute on Drug Abuse (NIDA) and extensive efforts by the scientific and treatment communities. MA acts as a substrate for monoamine transporters and is taken into the nerve terminal where it promotes the release of dopamine (DA), serotonin (5-HT) and norepinephrine (NE) into the synapse by preventing the accumulation of neurotransmitter in storage vesicles and by carrier-mediated exchange. MA abuse has been largely attributed to its ability to increase synaptic DA levels. However, targeting DA systems has not identified a broadly effective pharmacotherapy for managing MA abuse. Targeting other monoamine systems implicated in the effects of MA is a vital and innovative strategy for identifying an effective pharmacotherapy. Buspirone (BUSP) is an anxiolytic that lacks the abuse potential and sedation produced by benzodiazepines. BUSP is a $5HT_{1A}$ receptor partial agonist, DA autoreceptor antagonist, and a selective DA D_3 receptor antagonist. Receptor partial agonists have proven effective for managing nicotine and opioid use disorders and may be preferable to full agonists or antagonists because they can stimulate receptors when neurotransmitter tone is low (i.e., during abstinence) and block receptors when neurotransmitter tone is high (i.e., following a lapse). DA autoreceptors (or presynaptic D_2 receptors) stabilize DA tone; antagonists at these receptors increase DA release. DA D_3 receptors play a critical role in motivation to take drugs. BUSP antagonized amphetamine-induced locomotion and stereotypy in rodents. BUSP also attenuated the discriminative effects of amphetamine in monkeys. While BUSP has not yet been tested as a potential pharmacotherapy for MA abuse in a human laboratory experiment or clinical trial to our knowledge, the results of these preclinical experiments suggest it may be a viable option. The results of this “proof-of-concept” study will provide critical information regarding the initial efficacy of BUSP for MA dependence, which will enhance the probability of success when advanced to a clinical trial.

2. OBJECTIVES

The primary objective of this study is to determine the influence of BUSP maintenance on the reinforcing effects of MA. We will also include a battery of subject-rated and physiological measures to more fully characterize the influence of BUSP maintenance on the effects of MA.

3. STUDY DESIGN

A double-blind, placebo-controlled, crossover design will be used in this experiment. A completely within-subject design will be used such that each subject will receive all possible dose conditions, including placebo.

4. STUDY POPULATION

Up to 100 individuals will be screened to participate in this study. We intend to enroll twelve (8 male and 4 female) completers into the study. These individuals must be English-speaking, English-reading subjects 18-55 years of age of varying ethnic backgrounds and they will be recruited to participate in this seven-week experiment. Enrollment in this study will occur between January 1, 2013 and December 31, 2014. Subjects will be required to provide legal proof of age. Subjects must be healthy and without contraindications to MA and BUSP.

Subjects must also report recent use of stimulants and must meet diagnostic criteria for stimulant abuse or dependence using the Structured Clinical Interview for DSM-IV (SCID). Subjects must provide a stimulant positive urine during screening to verify stimulant use status. Screening procedures for all subjects will include a medical history questionnaire, laboratory chemistries (blood chemistry screen, complete blood count, ECG and urinalysis) and a brief psychiatric examination. These procedures will be conducted under our lab's screening protocol (03-0509). Chemistry values and screening outcomes must be deemed normal. If chemistry values or screening outcomes fall outside normal ranges, a study physician must deem them clinically insignificant for a subject to be enrolled. An electrocardiogram must also be within normal limits. Any potential subject with a history of serious physical disease, current physical disease, impaired cardiovascular functioning, chronic obstructive pulmonary disease, history of seizure or current or past histories of serious psychiatric disorder that in the opinion of the study physician would interfere with study participation will be excluded from participation. Subjects with current or past histories of substance abuse or dependence that are deemed by the doctor to interfere with study completion will also be excluded from participation. Female subjects must be using an effective form of birth control (e.g., birth control pills, surgical sterilization, IUD, cervical cap with a spermicide, condoms or abstinence) in order to participate. A urine pregnancy test will be conducted before the start of each experimental session to ensure that female subjects do not continue in the study if pregnant. All study subjects will be judged by one of the study physicians, Dr. Lon R. Hays or Dr. Abner O. Rayapati to be healthy.

During the initial screening process, potential subjects will be asked to provide a urine specimen that will be screened for the presence of MA, amphetamine, benzodiazepines, barbiturates, cocaine, tetrahydrocannabinol (THC) and opiates. In order to participate in an experimental session, subjects must provide a urine negative for cocaine, barbiturates, benzodiazepines and opiates on each day of their participation. Subjects will be allowed to continue if they test positive for MA or amphetamine, if it is determined that this drug was given in a recent session and it is likely that the result is positive due to experimental administration. Drs. Hays and Rayapati will be notified of MA- or amphetamine-positive urines on experimental session days and sessions will only proceed if subjects pass the sobriety test and have vital signs within acceptable limits (see below). Subjects will be maintained on a caffeine free diet and will have to abstain from alcohol for the duration of their participation. They will be allowed to smoke cigarettes *ad libitum* except during experimental sessions.

5. SUBJECT RECRUITMENT METHODS AND PRIVACY

Subjects are recruited primarily through formal advertisement (i.e., regular newspaper advertisements placed generally in free newspapers), local flyers posted in public areas (e.g., bars, restaurants, stores) and by word-of-mouth. These advertisements are approved under our screening protocol (IRB # 03-0509). Subjects will make initial contact by phone with one of our recruiters who have completed the research training and HIPAA compliance web-based teaching models. If the subject self-discloses information that would make him/her potentially eligible for the study, they will be invited to come in for a screening appointment. Screening is completed by one of our research assistants at the UK Laboratory of Human Behavioral Pharmacology (LHBP). Study investigators may interact with subjects in this setting and appropriate cautions are in place to ensure privacy during the intake process.

6. INFORMED CONSENT PROCESS

All potential subjects that are identified using the subject recruitment methods noted above will provide informed consent prior to participating in the protocol. Subjects that meet the eligibility criteria noted above will come to the LHBP and will undergo a field sobriety test and provide an expired air sample that will be tested for the presence of alcohol. If the subject passes the field sobriety test (walk and turn, one-leg balance [timed], finger-to-nose and backwards-counting tasks) and the expired air sample is negative, he or she will then be given a copy of the approved informed consent document to read and sign. After reading the consent document, the PI or one of the Co-Is on this protocol will address any questions the subject may have in order to assess the subject's understanding of the protocol. After this, the subject will receive a copy of the informed consent document and will sign a form indicating that they have received a copy of the form they read and signed.

7. RESEARCH PROCEDURES

General Procedures. Subjects that meet the inclusion criteria will participate as inpatients at the University of Kentucky Clinical Services Core (CSC). Subjects will be discharged upon completion of the entire protocol.

This experiment will require each subject to participate for approximately three weeks. Experimental sessions will be conducted as outlined in the table below. We would like to note that the order of the maintenance conditions (i.e., starting with BUSP or placebo) will be counterbalanced across subjects. Moreover, to avoid testing MA on weekends, subjects may be maintained on each condition by up to two more days, so participation may be as long as 25 days.

Day	Experimental Procedures
1	Admission and acclimation to the CSC.
2	Practice Session.
3-12	Placebo maintenance. Placebo administered at 0700, 1500, 2300 hours.
10-12	Experimental Sessions. Reinforcing effects of intranasal MA (0, 10 and 30 mg) determined. Effects of each dose will be determined in a single day.
13-22	BUSP maintenance (45 mg/day). BUSP administered at 0700, 1500 and 2300 hours. The daily BUSP dose will be titrated up to the target dose (i.e., 5 mg three times daily for 1 day, 10 mg three times daily for 2 days, 15 mg daily for remainder of maintenance period).
20-22	Experimental Sessions. Details are the same as for Days 9-11.
23	Discharge

During their participation in the research protocol, subjects will not be allowed to leave the CSC, nor will visitors be allowed, with the exception that subjects can leave for walks under clinical supervision and if approved by physicians. Research subjects will be allowed to make local telephone calls. After completing the research protocol, interested subjects will be offered a referral to an appropriate drug abuse treatment program.

All subjects will provide urine and expired air samples before and periodically during study participation. The presence of non-nicotine drugs of abuse or alcohol not administered experimentally in the research protocol will result in immediate termination from the research study.

This experiment will consist of 6 experimental sessions conducted according to the timeline in Table 1, above. After admission, subjects will be allowed to acclimate to the CSC for two days before beginning the study. During this time, subjects will receive instructions concerning the details of the daily research procedures and general rules of the psychiatry inpatient research unit and complete a "practice" session to familiarize them with the experimental routine and tasks.

Each day after the practice session, subjects will be awakened at 0700 hours and will receive maintenance medication (see Table 2, below). Medications will not be administered if a subject's heart rate is ≥100 bpm, systolic pressure is ≥150 mmHg or diastolic pressure is ≥100 mmHg. Maintenance medication will be administered again at 1500 and 2300 h, as long as the aforementioned physiological dosing criteria are met. The UKU side effects scale will be completed daily to monitor for the emergence of side effects.

Time	Table 2-Daily Activities for Maintenance Days
0700	Patient awakened. Vital signs recorded. Medication administered if vitals are within range. Subject eats breakfast.
1200	Lunch is served.
1300	Nursing staff completes UKU.
1500	Vital signs recorded. Medication administered if vitals are within range.
1800	Dinner is served.
2300	Vital signs recorded. Medication administered if vitals are within range. Lights out.

On experimental session days, after receiving maintenance medication, subjects will then be allowed to eat a standard, fat-free breakfast (cereal with skimmed milk, 2 pieces of toast with jam or jelly and 8 ounces of fruit juice). Tables 3, below, outlines the activities of experimental sessions. Experimental sessions will begin at 0900 hours and will last approximately 5.5 hours. Medications will not be administered if a subject's heart rate is ≥100 bpm, systolic pressure is ≥150 mmHg or diastolic pressure is ≥100 mmHg or if clinically significant and/or prolonged ECG abnormalities are detected.

Subjects will be excluded from further research participation if at any time during the experimental sessions MA increases heart rate above 130 bpm, systolic pressure above 180 mmHg, diastolic pressure above 120 mmHg or if clinically significant and/or prolonged ECG abnormalities are noted. Subjects will remain seated for the duration of the experimental session. No experimental activities will be scheduled for the remainder of the day after an experimental session, but subjects will receive their appropriate maintenance medication at 1500 and 2300. Subjects will be free to engage in recreational activities (e.g., watch television, read, listen to music, arts and crafts, play video or board games). Research subjects will be required to be in bed with the lights out by 2300 hours.

Time	Table 3-Daily Activities for Experimental Days
0700	Patient awakened. Vital signs recorded. Medication administered if vitals are within range and no indication of sedation or withdrawal. Subject eats breakfast.
0900	Vital signs recorded. Computerized tasks completed. ECG monitoring begins.
0930	Vital signs recorded. 0 [placebo], 10 or 30 mg intranasal METH administered if vitals are within range. Measures completed 0, 15, 30, 45, 60, 90 and 120 minutes after drug administration.
1130	Session ends. Lunch is served. Nursing staff completes UKU.

1230	Vital signs recorded. Computerized tasks completed (including progressive-ratio task). ECG monitoring begins.
1330	Vital signs recorded. Portion of intranasal dose earned is administered if vitals are within range. Measures completed 0, 15, 30, 45, 60, 90 and 120 minutes after drug administration
1530	Session ends. Remainder of daily activities identical to those listed in Table 2.

All drugs will be administered under double-blind conditions and under medical supervision. Test doses of MA will be 0, 10 and 30 mg, administered in random order. These doses were chosen based on prior work and have safely been administered to human subjects (Lile et al., 2011; Marks et al., In Preparation; Pike et al., In Preparation). The maintenance conditions will be placebo and a maximum of 45 mg BUSP/day. Doses will be administered 3 times/day (i.e., the maximum individual BUSP dose is 15 mg) at 0700, 1500 and 2300. Subjects will be maintained on these doses for at least four days before beginning experimental sessions. The dose of BUSP was selected based on results of previous clinical trial research, which have shown that higher doses can be safely administered to active stimulant users (Moeller et al, 2001). Placebo powder and capsules will contain only lactose or cornstarch, but will be visually identical to the powder and capsules that contain active drug.

Apparatus. Behavioral testing will be conducted at the CSC. Subjects will be tested using an individual Macintosh laptop computer that automates behavioral tasks.

Progressive-Ratio Procedure. During each afternoon self-administration session, subjects will be given 10 opportunities to work on a computer to earn all, or some, of the powder that was administered during the preceding sampling session. Prior to each of the 10 opportunities to earn a drug, subjects will be asked if they want to work for a portion (i.e., $1/10^{th}$) of the drug administered during the sampling session. Subjects will respond by clicking on one of two buttons on the computer screen labeled YES or NO. If the subject responds YES, they will then be required to click the computer mouse a predetermined number of times to earn a portion of the sampled dose. To earn the first portion, subjects will have to click the mouse 400 times. The number of clicks required to earn each additional capsule increases by 100 (i.e., 500, 600, 700, 800, 900, 1000, 1100, 1200 and 1300 responses). To receive a full dose, subjects will have to click the mouse a total of 8500 times. If the subject responds NO at any time when they are asked if they want to work for one of the capsules, the task is terminated. While completing each component of the progressive-ratio schedule, subjects are also able to terminate the task by clicking on a button labeled STOP. The dependent measure on this task is the break point (i.e., the last ratio completed).

Subject-Rated Questionnaires. A battery of subject-rated questionnaires will also be used to assess drug effects. These measures have previously been shown to be sensitive to the effects of stimulants (Rush et al., 2009). These experimental measures will be taken on all experimental session days. The measures described below will be recorded as described in the tables above. The subjective-effects measures are included in Appendix A.

Vital Signs. Heart rate, blood pressure, oral temperature and heart rhythmicity (*via* ECG) will be recorded using a Dinamap digital monitor (Critikon, Pro 1000, Tampa, FL). These measures will be completed at as described in the tables above. Telemetry-certified nurses will interpret the results of the ECG with instructions to contact Dr. Hays or Rayapati regarding abnormalities.

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Drug Dose and Administration. All drugs will be administered under double-blind conditions and under medical supervision. Doses of MA will be prepared by weighing out the appropriate amount of powdered drug (NIDA, Rockville, MD). The MA will be mixed with lactose monohydrate powder, N.F. to make a total of 100 mg powder. Doses of MA will be prepared individually for each subject. These MA doses are behaviorally active and well tolerated under controlled conditions (e.g., Lile et al., 2011; Marks et al., In Preparation; Pike et al. In Preparation). For afternoon doses, drug will be labeled from 1-10, indicating the portion of drug earned on the progressive-ratio procedure. Subjects will only be administered the dose they earned (i.e., if they earned 3/10ths of the morning drug dose, they will be given the dose labeled 3). Intranasal MA administrations within an experimental session will be separated by at least 2 hours.

Maintenance Dosing. BUSP (0 and 45 mg/day) will be prepared by over-encapsulating commercially available doses in a size 0 capsule. All capsules will then be filled with lactose monohydrate powder, N.F. Placebo capsules will be identical, but will contain only lactose. BUSP will be administered thrice daily (i.e., 0700, 1500 and 2300 hours). The BUSP dose was selected based upon clinical dosing recommendations for anxiety (i.e. 15-60 mg/day in 2-3 divided doses). Subjects will be maintained on BUSP for at least 7 days, with at least 4 days at the target dose, before experimental sessions, which is sufficient to reach steady-state blood levels (Sakr and Andheria, 2001). The daily dose is clinically effective and well-tolerated when administered acutely or chronically (Evans and Levin, 2002; McRae-Clark et al., 2009; Moeller et al., 2001; Rush and Griffiths, 1997; Sakr and Andheria, 2001). The daily BUSP dose will be titrated upward until the target dose is achieved (i.e., 15 mg/day for 1 day [5 mg thrice daily]; 30 mg/day for 2 days [10 mg thrice daily]; and 45 mg/day for 4 days [15 mg thrice daily]). Subjects that are unable to tolerate BUSP, alone or in combination with MA, will be discharged from the study. Subjects that are dismissed will be replaced so that 12 subjects complete the study to ensure adequate statistical power to detect changes in the reinforcing effects of MA as a function of BUSP. Subjects will be blind to the maintenance drug administered.

Data Analysis. Data will be analyzed as raw scores. Statistical significance refers to $p \leq 0.05$. Progressive-ratio data (i.e., break point and number of MA doses earned) will be analyzed with two-factor repeated measure ANOVA to test the primary hypotheses. Factors for these analyses will be MA (0, 10 and 30 mg), and BUSP (0 and 45 mg/day). A significant attenuation (i.e., rightward shift in the dose-response) of the effects of MA will be inferred if the main effect of BUSP or the interaction of MA and BUSP attains statistical significance in the ANOVA. If the MA-BUSP interaction attains statistical significance, the mean square error term will be used to conduct Tukey's HSD *post-hoc* test to make appropriate pair-wise comparisons between means. Peak effect and area-under-the-time-action curve (AUC) data for the subjective-effects

measures and physiological indices obtained during the sampling phase will be analyzed in the same fashion as data from the progressive-ratio procedure in order to test the secondary hypotheses. Subjective-effects and physiological data from the self-administration phase will not be analyzed statistically because participants will likely ingest varying amounts of MA making these data difficult to interpret.

8. RESOURCES

This study will take place at the CSC. Study sessions will only be conducted on weekdays. All drug administration will take place at the UK CSC in a room equipped with all the necessary physiologic and computer equipment for the study. Dr. Hays is an adult psychiatrist who has worked extensively with individuals with substance use disorders in both the clinical and research setting and he is the responsible medical investigator for this study. Dr. Rayapati is a psychiatrist who has worked extensively with individuals with substance use disorders in both the clinical and research setting and he is the back up medical investigator for this study. They will be available to attend to medical problems as well as any psychological or psychiatric issues that may arise. Drs. Rush, Stoops and Lile will provide scientific oversight for the study and have safely completed numerous human behavioral pharmacology studies. Overall, the study team and resources described above are well equipped to protect subjects and successfully implement, carry out and complete this study protocol.

9. POTENTIAL RISKS

The subject-rated drug-effect questionnaires and physiological measures employed in these studies are benign. The risks to the study subjects are those related to the ingestion of the drugs under study. All of the drugs to be administered in the proposed research are commercially available. The relative safety as well as the contraindications and possible side effects of these compounds are well known and documented. However, the administration of any drug involves some risks simply because individuals differ in their reactions to drugs. The main risk is that subjects will experience side effects that may be unpleasant.

Side-effects of MA include nausea, abdominal pain, loss of appetite, dry mouth, weight loss, changes in mood, headache, tremor, difficulty sleeping, nervousness, restlessness, increases in temperature, changes in heart rate or blood pressure (including irregular heart rate and blood pressure), palpitations, anxiety, dizziness, hallucinations, forgetfulness, sleepiness and performance impairment. The severity and likelihood of these side effects usually varies with dosage and chronic administration. More serious side effects could include allergic reaction, chest pain, heart attack or other heart related problems, changes in blood platelet levels, stroke, psychotic episodes, seizures, Tourette's Syndrome and sudden unexplained death. These side effects may be more frequent and larger in magnitude when testing the BUSP-MA combinations.

Common side effects of BUSP include dizziness, nausea, headache, nervousness, lightheadedness, excitement and insomnia. Less common side effects include unsteady gait, diarrhea, weakness, hostility, skin rash and tremors.

The doses to be administered in the present experiment were chosen to minimize, if not eliminate, the chance of these side effects occurring since these side effects are related to dose. Thus, it is unlikely that subjects will experience side effects during the experimental protocol. All sessions proposed in this application will be conducted at the CSC and under medical supervision. Side effects of the drugs are temporary, usually dissipating in less than 24 hours. The principal investigator on this project, Dr. Rush, has had extensive experience over more than 20 years administering therapeutic and supratherapeutic doses of stimulant

drugs to subjects in both inpatient and outpatient settings and has never observed a serious, unexpected adverse effect. Dr. Rush will train all staff on this project.

To avoid potential drug interactions, subjects taking any prescribed medication chronically, except birth control, will be excluded. The medical personnel on this protocol will determine if it is safe for a potential subject to discontinue taking their medication during their participation.

There is some theoretical risk that subjects might choose to seek out illicit sources of drugs they received experimentally and liked. However, this risk is minimal since all drugs are administered under blind conditions and in a setting that is not conducive to the development of dependence.

10. SAFETY PRECAUTIONS

Subjects are carefully screened (history and physical exam, routine labs such as CBC, complete metabolic panel and urinalysis, ECG and psychiatric assessment) to exclude those with potential increased risk of adverse effects, such as personal or family histories of heart disease, histories of seizure or head injury associated with more than a brief loss of consciousness, hypertension, psychosis, etc. During sessions subjects remain under careful medical observation and are monitored continuously by on-site medical staff. Vital signs will be collected throughout the dosing period. Staff is familiar with the acceptable physiological parameters for these studies and this information is posted in every experimental session room. In addition, Dr. Rush has substantial experience administering medications to human subjects under a variety of dosing conditions. Lastly, female subjects are also given pregnancy tests prior to each session to ensure that we do not administer active medications to a pregnant woman.

Legal risks including loss of confidentiality: All intake documentation that contains personal information is handled separately from the actual data collected during the study. All information of a personal nature (intake assessments, medical test results) is kept locked either on password-protected computers or in secure filing cabinets all behind locked doors and accessible only to key personnel involved in the research. A Certificate of Confidentiality will be obtained from NIDA.

11. BENEFIT vs. RISK

The degree of risk to which individual study subjects are exposed as a consequence of their research participation is slight. In contrast, the potential and probable benefits to be derived by society in general and by patients as a group appear to be considerable. The major benefits of these studies are clinical and scientific ones related to the knowledge gained about putative medications for MA use disorders. The data from this project will contribute to a better understanding of drug abuse and will ultimately contribute to the development of improved prevention, control and treatment procedures. Individual study subjects are expected to benefit personally from the medical and psychiatric evaluations and from referrals for medical and psychiatric treatment that are provided whenever appropriate. Overall, the risk/benefit ratio appears favorable and the conduct of this research seems well justified.

12. AVAILABLE ALTERNATIVE TREATMENTS

There are no available alternative treatments as this is not a treatment study. If subjects express the desire for treatment they will be given referrals for treatment and not be allowed to participate in this study.

13. RESEARCH MATERIALS, RECORDS AND PRIVACY

Urine and blood samples will be collected at screening prior to a subject's participation in the experimental protocol under another IRB approved protocol (Number 03-0509). These urine

samples will be tested for the presence of a full range of drugs of abuse. Blood samples will be used for the laboratory chemistries. Females will also be given a pregnancy test at the time of screening (via the urine sample). Urine drug and pregnancy tests will be conducted prior to the conduct of each experimental session. Other data obtained from the subjects will involve subjective effects based on questionnaires, various computer-based tasks and non-intrusive staff observations and ratings. The consent form states that subject's confidentiality will be protected.

14. CONFIDENTIALITY

Identifying information will be stored in a separate, locked area from all other de-identified data and codes linking the two will be kept under lock and key or on password protected computers. Incidental materials containing subject identifiers will be shredded or incinerated. Identification and access of identified data/specimens will be available only to study investigators when it is detrimental to subject safety or the conduct of the research protocol. For example, if a subject has an adverse event, we will want to obtain a quantitative drug screen to identify whether there may have been illicit drug use while in the study versus a true adverse event related to the study procedures. In the future, data/specimens may be shared with non-UK affiliations in a HIPAA compliant manner.

15. PAYMENT

Subjects will be paid $40 for each day they reside on the CSC and will receive a $40 completion allowance for these days if they complete the entire experiment. The amount earned by the subject will be disbursed to them upon completion of the study. Payments will be disbursed in amounts up to $500 dollars and will be given once per week following discharge until the subject is paid in full. When subjects return on a weekly basis to receive their payments, we will survey them regarding their drug use since being discharged from the study. A subject can earn a maximum of $2000 for participating in this study.

16. COSTS TO SUBJECTS

There will be no cost to the subject for participating. Costs for the screening procedures (i.e., medical history questionnaire, physical examination including laboratory chemistries (blood chemistry screen, complete blood count, urinalysis) and a psychiatric examination will be paid by the Laboratory of Human Behavioral Pharmacology.

17. DATA AND SAFETY MONITORING

Data Monitoring Plan

Data will be collected using a computerized data collection and management system wherever possible. This system automates the collection of data, which ensures the accuracy and completeness of data collection. The data are stored in a unique file on the hard drive of the computer and are printed after all the tasks are completed. In all instances, the data files do not contain the name of the subject, but instead, each subject is identified by a unique four-digit number. A computer file linking the unique number with the subject's name will be kept on a stand-alone, password-protected computer. All data requiring hand entry (e.g., cardiovascular measures) will be entered by two separate staff members and comparison macros will be run to ensure accuracy. Data files for experimental tasks and physiological measures from each experimental session will be manipulated and combined into a single electronic spreadsheet for each subject by one of the investigators. Data for all subjects will then be combined into a single electronic spreadsheet and separated by experimental measure for statistical analysis using Statview (SAS Institute Inc., Cary, NC).

In this protocol the primary outcome measure will be the influence of BUSP maintenance on the reinforcing effects of MA. The alpha level will be set at 5%.

As noted above, wherever possible, data are collected using an automated computer system, which increases the accuracy and completeness of data collection and ensures the validity and integrity of the data. The initial data manipulation described above will be conducted twice and compared. The quality of manipulated data and data analyses will be monitored by random inspection by the PI and/or Co-Investigators.

Safety Monitoring Plan

Potential subjects will provide information regarding their drug use history and undergo an extensive physical and psychiatric health screening to determine their eligibility and safety of their participation. Any potential subject with a history of clinically significant physical disease, current physical disease (e.g., impaired cardiovascular functioning, histories of seizure, head trauma or CNS tumors) or current or past histories of psychiatric disorder that in the opinion of the study physician would interfere with study participation, other than substance abuse or dependence, will be excluded from research participation. Females must be using an effective form of birth control in order to participate and must not be pregnant. Methods for monitoring adverse events (AEs) will include observations by the medical and research staff, spontaneous report by the subjects and, regular measurement of cardiovascular function. Subjects will not receive study drug if they have any signs or symptoms that may contraindicate its administration (e.g., HR and BP outside of predetermined range, development of serious side effects).

All AEs occurring during the course of the study will be collected, documented and reported to the PI. The occurrence of AEs will be assessed for the duration of participation. Each week a study investigator will review the AE forms from the previous week for events that were reported as new or continuing. The study investigators will follow all AEs to the point of a satisfactory resolution. Subjects may be withdrawn from the study if the medically responsible investigator determines it is the best decision in order to protect the safety of the subject. All AEs will be assessed to determine if they meet criteria for a serious adverse event (SAE).

Serious Adverse Events, as defined by the FDA, will be systematically evaluated for the duration of participation and during the follow-up visits at 2 and 4 weeks following study completion. Any SAE, whether or not related to the study drug, will be reported to the IRB, CSC, NIDA and the FDA. The initial SAE report will be followed by submission of a completed SAE report to all three institutions.

In the event that a subject either withdraws from the study or the investigator decides to discontinue a subject due to an SAE, the subject will have appropriate follow-up medical monitoring. Monitoring will continue until the problem requiring hospitalization has resolved or stabilized with no further change expected, is clearly unrelated to the study drugs or results in death. Outcome of SAEs will be periodically reported to the IRB, CSC, NIDA and the FDA. A summary of the SAEs that occurred during the previous year will be included in the annual progress report to NIDA, the IRB, CSC and FDA.

18. SUBJECT COMPLAINTS

Subjects may at any time ask study personnel questions about the study procedures or make complaints. All staff will be aware to notify Drs. Rush, Stoops, Lile, Hays or Rayapati about any subject concern or complaint as it arises. Subjects will be allowed the opportunity to discuss any concerns or questions with an investigator promptly, in person and in confidence. It should be noted, however, that subjects will be told that some concerns and complaints will not be

kept private such as an adverse event, protocol deviation or threat to the safety of subjects or integrity of the research study. In these cases, all information will be made available to the Principal Investigator in order to determine any further course of action. Drs. Hays and Rayapati will also communicate with the nursing or laboratory staff on at least a weekly basis in order to discuss any concerns regarding particular subjects or with respect to the conduct of the study.

19. RESEARCH INVOLVING NON-ENGLISH SPEAKING SUBJECTS OR SUBJECTS FROM A FOREIGN CULTURE Not Applicable.

20. HIV/AIDS RESEARCH POLICY Not applicable.

21. PI SPONSORED FDA-Regulated Research

Dr. Rush currently holds an IND for intranasal MA (#104,829). This application will be modified to combining intranasal MA with oral BUSP. Dr. Rush has held INDs for behavioral pharmacology research with a number of drugs for over twelve years and is well aware of the necessary reporting requirements and other responsibilities associate with IND sponsorship. As required by the FDA, Dr. Rush will submit annual reports on the progress of the IND and will also report serious adverse events in accordance with published guidelines. Dr. Rush has trained all study staff on their responsibilities regarding the IND.

APPENDIX A

Subject-Rated Drug-Effect Questionnaires Descriptions

Adjectives Rating Scale (ARS)

Individual questions are presented sequentially, one at a time. Subjects rate their response to each question on a 5-point scale (0 = Not at all, 1 = A little, 2 = Moderately, 3 = Quite a bit, 4 = Extremely).

(1) How "**ACTIVE**" do you feel right now? (2) How "**AGITATED**" do you feel right now? (3) How "**CLUMSY**" do you feel right now? (4) How "**ALERT**" do you feel right now" (5) How "**DIZZY**" do you feel right now? (6) How "**CONFUSED**" do you feel right now? (7) How "**ENERGETIC**" do you feel right now? (8) Are you in a "**GOOD MOOD**" right now? (9) How "**DAZED**" do you feel right now? (10) How "**EXCITED**" do you feel right now? (11) How "**SLEEPY**" do you feel right now? (12) How "**DEPRESSED**" do you feel right now? (13) How "**EUPHORIC**" do you feel right now? (14) Are you experiencing an "**IRREGULAR HEARTBEAT**" right now? (15) Do you feel as if you would have "**DIFFICULTY WALKING**" right now? (16) How "**TALKATIVE**" do you feel right now? (17) Are your "**MUSCLES TWITCHING**" right now? (18) How "**DROWSY**" do you feel right now? (19) How "**NAUSEOUS**" do you feel right now? (20) How "**DRUNK**" do you feel right now? (21) How "**NERVOUS**" do you feel right now? (22) How "**FATIGUED**" do you feel right now? (23) Is your "**HEART RACING**" right now? (24) How "**IRRITABLE**" do you feel right now? (25) How "**RESTLESS**" do you feel right now? (26) How "**LAZY**" do you feel right now? (27) How "**SHAKY**" do you feel right now? (28) How "**RELAXED**" do you feel right now? (29) How "**TIRED**" do you feel right now? (30) How "**SLUGGISH**" do you feel right now? (31) How "**SWEATY**" are you right now? (32) How "**SPACED OUT**" do you feel right now?

Drug Effect-Questionnaire (DEQ)-VAS

Individual questions are presented sequentially, one at a time. Subjects rate their response to each question by marking a 100-unit line anchored with "Not at All" on the left side and "Extremely" on the right side.

(1) Is the drug producing "**ANY EFFECT**" right now? (2) Is the drug producing any "**BAD EFFECTS**" right now? (3) Is the drug producing any "**GOOD EFFECTS**" right now? (4) Is the drug making you feel "**HIGH**" right now? (5) Are you experiencing a "**RUSH**" from the drug right now"? (6) How much do you "**LIKE**" the drug right now? (7) Is the drug making you feel "**STIMULATED"** right now? (8) Is the drug "**IMPAIRING YOUR PERFORMANCE**" right now? (9) Is the drug "**IMPROVING YOUR PERFORMANCE**" right now? (10) Based on how the drug effect feels right now, would you be willing to "**TAKE THIS DRUG AGAIN**"? (11) Based on how the drug effect feels right now, would you be willing to "**PAY FOR THIS DRUG**"? (12) Is the drug making you feel "**ACTIVE, ALERT OR ENERGETIC**" right now? (13) Is the drug making you feel "**EUPHORIC**" right now? (14) Is the drug making you experience an "**IRREGULAR OR RACING HEARTBEAT**" right now? (15) Is the drug making you "**TALKATIVE OR FRIENDLY**" right now? (16) Is the drug making you feel "**NAUSEATED, QUEAZY OR SICK TO YOUR STOMACH**" right now? (17) Is the drug making you feel "**SHAKY OR JITTERY**" right now? (18) Is the drug making you feel **"NERVOUS OR ANXIOUS"** right now? (19) Is the drug

making you feel "**RESTLESS**" right now? (20) Is the drug making you feel "**SLUGGISH, FATIGUED OR LAZY**" right now?