NIDA-CPU-Methylphenidate-0001

DOUBLE-BLIND, PLACEBO-CONTROLLED ASSESSMENT OF POTENTIAL INTERACTIONS BETWEEN INTRAVENOUS METHAMPHETAMINE AND OSMOTIC-RELEASE METHYLPHENIDATE (OROS-MPH)

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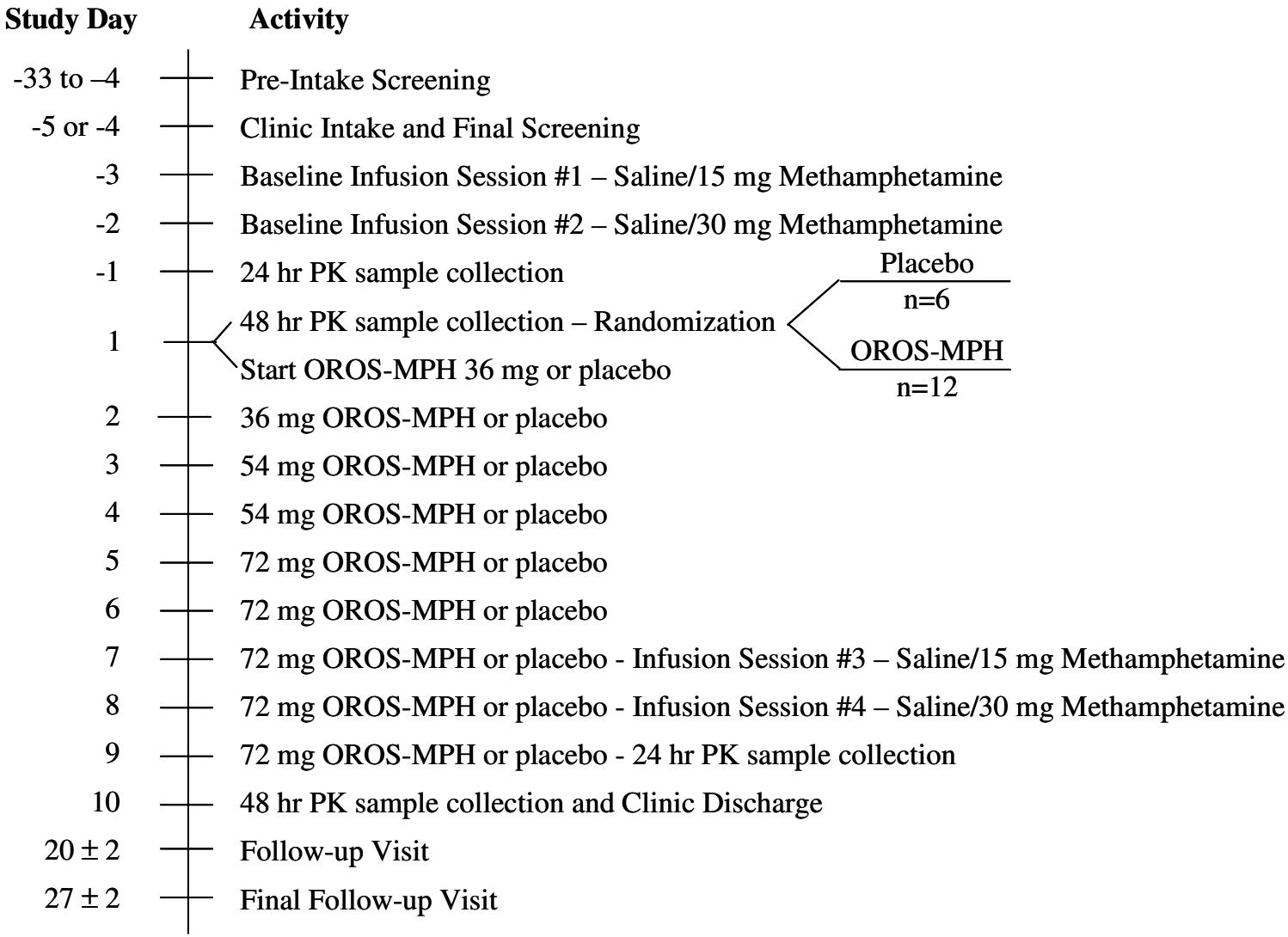
1 ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
λz	terminal exponential coefficient
ADD	Attention Deficit Disorder
ADHD	Attention Deficit Hyperactivity Disorder
AE	adverse event
AGT	angiotensinogen gene
ALP	alkaline phosphatase
ALT/SGPT	alanine aminotransferase/serum glutamic pyruvic transaminase
ANOVA	analysis of variance
ARCI	Addiction Research Center Inventory
ASI-Lite	Addiction Severity Index-Lite
AST/SGOT	aspartate aminotransferase/serum glutamic oxaloacetic transaminase
AUC	area under the concentration- time curve
BUN	blood urea nitrogen
CAP	College of American Pathologists
CL	clearance
CLIA	Clinical Laboratory Improvement Amendment of 1988
Cmax	maximum concentration
CNS	central nervous system
CRF	Case Report Form
CYP2D6	cytochrome P450 2D6 isoform
DA	dopamine
DAT	dopamine transporter
DSMB	Data and Safety Monitoring Board
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders - Fourth Edition
DPMC	Division of Pharmacological and Medical Consequences
ECG	electrocardiogram
EEG	electroencephalograph
FDA	Food and Drug Administration
HIV	human immunodeficiency virus
HR	heart rate

Abbreviation	Definition
IR	immediate-release
IRB	Institutional Review Board
i.v.	intravenous(ly)
LDH	lactate dehydrogenase
MAO	monoamine oxidase
METH	methamphetamine
MINI	Mini International Neuropsychiatric Interview DSM-IV version
MPH	methylphenidate
NIDA	National Institute on Drug Abuse
NMS	neuroleptic malignant syndrome
OROS-MPH	osmotic release methylphenidate
OTC	over-the-counter
PET	positron-emission tomography
PD	pharmacodynamic
PK	pharmacokinetics
PPA	α-phenyl-piperidine acetic acid
PPD	purified protein derivative (test for tuberculosis)
q.d.	once daily
QT	QT interval is the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle measured by ECG
QTc	QTc is the heart-rate corrected QT interval which will be calculated using the Fridericia correction (i.e., observed QT divided by the cube root of the RR interval expressed in seconds)
RDS	Respondent-Driven Sampling
REB	Research Ethics Board
RPR	rapid plasma reagin (test for syphilis)
SAE	serious adverse event
SDV	Subjective Drug Value
SR	sustained release
$t_{1/2}$	half-life
t.i.d.	three times daily
TLFB	timeline followback
VAS	visual analog scale
Vd	volume of distribution

Term	*Definition*
Enrolled	A subject will be considered to be enrolled in the study, upon signing of the informed consent form.
Evaluable	A subject will be considered evaluable if s/he received all doses of OROS-MPH or placebo and had methamphetamine PK blood samples collected up to the 12-hour time point during infusion Session #4. The subject must have received the entire methamphetamine dose during infusion Sessions #2 and #4.
Completed	A subject will be considered to have completed the study if s/he has successfully completed the inpatient phase including all protocol investigational product administrations and has returned for all the outpatient follow-up assessments.

2 STUDY SCHEMA



3 ABSTRACT

STUDY OBJECTIVES: This is a human inpatient clinical pharmacology study to assess potential interactions between intravenous (i.v.) methamphetamine infusion and oral osmotic release methylphenidate (OROS-MPH).

Primary: The primary objective of this study is to determine the safety of the OROS-MPH concurrent with i.v. d-methamphetamine infusions of 15 mg and 30 mg. Safety outcome measures include cardiovascular responses [heart rate (HR), blood pressure (BP), and electrocardiograph (ECG) measurements], oral temperature, adverse events (AEs), and clinical laboratory analyses.

Secondary:

1. To determine plasma levels of MPH during chronic daily administration of OROS-MPH and the effects of methamphetamine administration on OROS-MPH pharmacokinetics (PK).

2. To evaluate whether administration of OROS-MPH alters the PK of d-methamphetamine or its metabolites.

3. To evaluate whether OROS-MPH alters the subjective response to methamphetamine using visual analog scales (VAS), Addiction Research Center Inventory (ARCI) assessments, and a Subjective Drug Value (SDV) test after methamphetamine infusions.

STUDY DESIGN: This is a double blind, placebo-controlled, two-center inpatient study in which subjects will be randomized into one of two groups [placebo (n = 6) or OROS-MPH (n = 12)] with both groups receiving infusions of saline and methamphetamine (15 mg and on a separate day 30 mg) prior to and after OROS-MPH/placebo administration to evaluate interactions between these two drugs. Subjects will undergo an outpatient screening period of not more than 30 days (screening may be repeated if the principal investigator agrees) to determine eligibility for study participation. If eligible during the outpatient screening evaluations, subjects will undergo clinic intake procedures and complete final screening assessments one to two days before baseline infusions of methamphetamine begin. All subjects will undergo two series of two sequential days of saline and methamphetamine infusion sessions. The first day's session will be an i.v. infusion of saline followed one hour later by an i.v. infusion of 15 mg of methamphetamine. The second day's session will be an i.v. infusion of saline followed one hour later by an i.v. infusion of 30 mg of methamphetamine. Baseline sessions #1 and #2 on Study Days -3 and -2 will be conducted before the initiation of daily placebo or OROS-MPH administration which starts on Day 1. On Day 1, subjects will be randomized in a ratio of 1:2 (placebo controls:OROS-MPH dosed subjects) for a total of 18 subjects. The dose of OROS-MPH will be escalated every two days from 36 mg/day to 54 mg/day to 72 mg/day with PK interactions with methamphetamine being tested at the high dose of OROS-MPH. On Study Days 1 and 2, subjects will receive OROS-MPH (36 mg q.d.) or matched placebo. On Days 3 and 4, the OROS-MPH dose will be increased to 54 mg q.d., and on Days 5 through 9, the OROS-MPH dose will be increased to 72 mg q.d. On Days 7 and 8, subjects will undergo saline/

methamphetamine infusion sessions #3 and #4 in a similar fashion to sessions #1 and #2. Infusion sessions after the start of OROS-MPH or placebo dosing will begin after the morning dose. Subjects will not be told the order of methamphetamine and saline infusions. Thus, the study will be single-blind with respect to methamphetamine and saline infusions. Neither the subject nor the investigative staff will know the assignment of subjects to placebo control or OROS-MPH. Thus, the study will be double-blind with respect to these investigational products. Cardiovascular and subjective effects will be measured during all infusion sessions. Blood for methamphetamine PK analyses will be collected during infusion sessions #2 and #4 when subjects receive the 30 mg dose of methamphetamine. Subjects will be discharged from the clinic on Study Day 10, after the final methamphetamine blood PK sample is collected and other safety measures have been assessed. This is one day after the last dose of investigational products. Following clinic discharge, all subjects will be asked to return weekly for 2 weeks for safety follow-up (Study Days 20 ± 2 and 27 ± 2).

STUDY DURATION: The study schedule consists of 30 days or less of outpatient/inpatient screening (some screening assessments will be performed after clinic intake), 13 days of inpatient infusion sessions and assessments (Study Days –3 to 10), and two weekly follow-up visits after discharge. Following clinic discharge, all subjects will be asked to return twice: on Study Days 20 ± 2 and 27 ± 2, preferably as early in each visit window as possible. Study completion is anticipated to be twelve months.

SAMPLE SIZE: Eighteen (18) subjects total; subjects who do not meet the criterion for being evaluable (those procedures scheduled through the 12 hour methamphetamine blood collection PK time point scheduled on Day 9 (after discussions with NIDA and the Sponsor-Investigator) will be replaced.

POPULATION: Volunteer experienced methamphetamine users, 18 to 45 years of age, inclusive, with a diagnosis of methamphetamine abuse or dependence according to DSM-IV criteria and who provide one methamphetamine positive urine sample during screening and satisfy all other eligibility criteria will be included.

STUDY GROUPS: Subjects will be randomized on Day 1 to one of the following groups:

OROS-MPH: Subjects will take 36 mg once daily on Days 1 and 2, 54 mg once daily on Days 3 and 4, and 72 mg once daily on Days 5 through 9. The first dose of 36 mg will be given after the 48 hour PK blood collection on Day 1. Thereafter, OROS-MPH will be given daily at approximately 7:00 am.

Placebo: Subjects will take the equivalent number of placebo tablets once daily on Days 1 through 9 at the same time of day scheduled for administration of OROS-MPH.

Methamphetamine/Saline Infusions: Subjects will receive infusions of saline and methamphetamine as follows:

Days -3 and 7: Saline infusion followed one hour later by infusion of 15 mg of methamphetamine.

Days -2 and 8: Saline infusion followed one hour later by infusion of 30 mg of methamphetamine.

Subjects will not be told the order of the saline and methamphetamine infusions.

ASSESSMENTS: Safety will be evaluated by monitoring AEs, BP, HR, ECG readings, oral temperature, blood chemistry, and hematology. Continuous monitoring of BP, HR, and ECG will be performed during all infusion sessions. Changes in methamphetamine and OROS-MPH PK due to possible interactions will be evaluated using a between- and within-subjects design. Blood samples for methamphetamine PK will be collected over a 48-hour period after infusion sessions #2 and #4 (the 30 mg dose of methamphetamine). To determine peak and trough levels of MPH, PK blood samples will be collected prior to the morning dose of OROS-MPH and 1 and 6 hours after the morning dose on Study Days 2, 4, 6, 7 and 8. Changes in subjective effects in response to i.v. methamphetamine will be assessed using VAS, ARCI, and SDV scores after methamphetamine infusion.

4 INTRODUCTION AND RATIONALE

4.1 Methamphetamine

Methamphetamine (Methedrine, "speed", "ice", "meth", "crank") is used and misused as a central nervous system stimulant. Methamphetamine (N-methylamphetamine) is a non-cathecholamine phenylisopropanolamine that belongs to the ephedrine family of sympathomimetic drugs. The drug is made easily in clandestine laboratories with relatively inexpensive over-the-counter ingredients. These factors combine to make methamphetamine a drug with high potential for widespread abuse.

4.1.1 Pharmacology

Methamphetamine acts primarily by increasing release of stored catecholamines – dopamine (DA), epinephrine, and norepinephrine. It also inhibits monoamine oxidase (MAO), an action that increases its cathecholaminergic activity. Amphetamines affect serotonergic systems as well by increasing the release of serotonin which may act as a direct agonist of serotonin receptors (Weiner 1985); it has been shown to increase serotonergic neurotransmission by inducing the firing rate of serotonergic cells in the raphe nucleus (Groves and Tepper 1983). Methamphetamine abusers demonstrate a significantly lower level of DA D2 receptors, with a difference of 16% in the caudate and 10% in the putamen compared to non-drug abusing controls as assessed by positron emission tomography (PET) with [^{11}C]-raclopride (Volkow, Chang et al. 2001). This low level of DA D2 receptors is associated with a lower level of glucose metabolism in orbitofrontal cortex (assessed by PET with fluorodeoxyglucose) suggesting that D2 receptor-mediated dysregulation of the orbitofrontal cortex could underlie a common mechanism for loss of control and compulsive drug intake in drug addicted subjects (Volkow, Chang et al. 2001).

Methamphetamine readily enters the central nervous system, and has a marked stimulant effect on mood (Johnson, Ait-Daoud et al. 1999; Johnson, Roache et al. 2005) and alertness (Johnson, Ait-Daoud et al. 2000; Johnson, Roache et al. 2005). Methamphetamine is neurotoxic to DA

terminals when administered to laboratory animals, including monkeys (Wrona, Yang et al. 1997; Cadet, Jayanthi et al. 2003; Kita, Wagner et al. 2003). Studies in methamphetamine abusers have also documented significant loss of DA transporters (used as markers of the DA terminal) that are associated with slower motor function and decreased memory. The extent to which the loss of DA transporters predisposes methamphetamine abusers to neurodegenerative disorders such as Parkinsonism is unclear and may depend in part on the degree of recovery. The effects of protracted abstinence on the loss of DA transporters in striatum has been studied in methamphetamine abusers using PET and [(^{11}C)]d-threo-methylphenidate (DA transporter radioligand) (Volkow, Chang et al. 2001). Brain DA transporters in five methamphetamine abusers evaluated during short abstinence (<6 months) and then retested during protracted abstinence (12-17 months) showed significant increases with protracted abstinence (a difference of 19% in the caudate and 16% in the putamen) that was accompanied by increase in thalamic, but not striatal, glucose metabolism (assessed by PET with fluorodeoxyglucose); however, although the performance in motor and verbal memory tests showed some improvement, this effect was not significant (Volkow, Chang et al. 2001; Wang, Volkow et al. 2004). These data indicate that DA terminals can either recover during protracted abstinence or that remaining viable terminals increase arborization, but it is not sufficient for complete function recovery as there was no improvement in cognitive tests (Volkow, Chang et al. 2001). These findings have treatment implications because they suggest that protracted abstinence may reverse some of the methamphetamine-induced alterations in brain DA terminals, but other deficits persist.

Other studies confirm that methamphetamine use may result in a long-term damage to neurons involved in cognitive function. Thus, brain imaging studies (magnetic resonance spectroscopy) show neuronal damage in basal ganglia and frontal white matter with a concomitant increase in size/number of glial cells in subjects with a history of methamphetamine abuse that have been abstinent for as long as 21 months (Ernst, Chang et al. 2000). The PET studies revealed glucose metabolism abnormalities in limbic and paralimbic regions of recently abstinent methamphetamine abusers that correlated with self-reports of depression and anxiety (London, Simon et al. 2004). Importantly, quantitative electroencephalographic (EEG) abnormalities consistent with generalized encephalopathy, i.e., increased EEG power in the delta and theta bands, have been reported in methamphetamine dependent subjects with 4 days of abstinence providing another evidence to the notion that methamphetamine abuse may be associated with a range of cognitive and psychiatric abnormalities (Newton, Cook et al. 2003). Indeed, a preliminary finding of reduced cognitive function (assessed by Stroop test) in methamphetamine-dependent subjects is consistent with distractibility that they show clinically (Salo, Nordahl et al. 2002). Another study in methamphetamine-dependent subjects that have been abstinent for 8 months showed persistent abnormalities in cerebral flow that was accompanied by reduced cognitive function as tested by California Computerized Assessment Package (Chang, Ernst et al. 2002). Overall, methamphetamine abuse is associated with persistent physiological changes in the brain that are accompanied by reduced cognitive function.

4.1.2 PK

PK of methamphetamine is similar to those of ephedrine: it has high bioavailability and a long duration of action. Following i.v. administration, methamphetamine is eliminated with a $t_{1/2}$ of 12 $\pm$ 3.2 hours.

4.1.3 Metabolism

Methamphetamine is metabolized by N-demethylation to amphetamine (Ling and Shoptaw 1997) and by hydroxylation to 4-OH methamphetamine (Lin, Kumagai et al. 1995). Both of these reactions are catalyzed by cytochrome P450 2D6 (CYP2D6). Approximately 38% of the administered dose is excreted in the urine unchanged (Mendelson, Jones et al. 1995). Methamphetamine and amphetamine also inhibit CYP2D6 with an apparent ki of 25 μM and 26.5 μM, respectively (Wu, Otton et al. 1997). This could shift metabolism during chronic administration towards urinary excretion of the parent compound.

4.1.4 Short-term Effects of Methamphetamine Use

Methamphetamine is a powerful psychostimulant and even in small doses can increase wakefulness, attention and physical activity and decrease fatigue and appetite (Johnson, Roache et al. 1999). Those who smoke or inject methamphetamine report a brief, intense sensation, or rush. Oral ingestion or snorting produces a long lasting high instead of a rush, which reportedly can continue for as long as half a day. Both the rush and the high are the result of dopamine release in cortico-mesolimbic areas of the brain that regulates feeling of pleasure. High doses can elevate body temperature to dangerous, sometimes lethal levels, as well as cause convulsions.

4.1.5 Long-term Effects of Methamphetamine Use

Methamphetamine is an addictive drug. Long-term chronic methamphetamine abusers exhibit symptoms that can include violent behavior, anxiety, confusion, and insomnia. They also can display a number of psychotic features, including paranoia, auditory hallucinations, mood disturbances and delusions (for example, the sensation of insects creeping on the skin, which is called “formication”). The paranoia can result in homicidal as well as suicidal thoughts. With chronic use, tolerance for methamphetamine can develop. In an effort to intensify the desired effects, users may take higher doses of the drug, take it more frequently, or change their method of drug intake. In some cases, abusers forego food and sleep indulging in a form of binging known as “run,” injecting as much as a gram of the drug every 2 to 3 hours over several days until the user runs out of the drug or is too disorganized to continue. Chronic abuse can lead to psychotic behavior, characterized by intense paranoia, visual and auditory hallucinations, and out-of-control rages that can be coupled with extremely violent behavior. These clinical data are confirmed by brain imaging studies that show long-term damage in dopaminergic and serotonergic neurons with a concomitant increase in glial cells in subjects with a history of methamphetamine abuse long after they stopped using methamphetamine (Ernst, Chang et al. 2000).

Methamphetamine abuse has a typical pattern of withdrawal manifested by signs and symptoms opposite to those produced by the drug. Users become sleepy, have a ravenous appetite, are exhausted, and may suffer from mental depression. This syndrome may last for several days after the drug is withdrawn. Tolerance develops quickly, so that abusers may take huge doses compared with those used medically, e.g., as anorexants.

4.1.6 Medical Complications of Methamphetamine Abuse

Methamphetamine toxicity manifests itself at the level of nearly every organ system with the most dramatic changes being observed in the cardiovascular system and brain.

Methamphetamine can cause a variety of cardiovascular problems. These include rapid and sometimes irregular heartbeat (Yu, Larson et al. 2003), increased blood pressure (Johnson, Ait-Daoud et al. 2000), and irreversible, stroke-producing damage to small blood vessels in the brain (McGee, McGee et al. 2004). Hyperthermia and convulsions occur with methamphetamine overdoses, and if not treated immediately, can result in death. Chronic methamphetamine abuse can result in endocarditis, and among users who inject the drug, damaged blood vessels and skin abscesses. Methamphetamine abusers also can have episodes of violent behavior, paranoia, anxiety, confusion, and insomnia. Psychotic symptoms can sometimes persist for months or years after use has ceased. Heavy methamphetamine users show progressive social and occupational deterioration.

4.1.7 Methamphetamine as a Major Health Problem

Methamphetamine has become a major drug of abuse in the United States since the early 1990's. High rates of methamphetamine dependence are also registered in Great Britain, Japan, Australia, and in many other countries (Klee 1992). In Great Britain, the methamphetamine problem is considered of greater public health consequence than cocaine, especially in relation to HIV. In Australia, amphetamines are the second most frequently used drugs, after cannabis.

Methamphetamine abuse, long reported as the dominant drug problem in the San Diego, CA, area, has become a substantial drug problem in other sections of the West and Southwest (NIDAResearchReport 2002). There are indications that it is spreading to other areas of the country, including both rural and urban sections of the South and Midwest. Methamphetamine, traditionally associated with white, male, blue-collar workers, is being used by more diverse population groups that change over time and differ by geographic area (Cho and Melega 2002). According to the 2000 National Household Survey on Drug Abuse, an estimated 8.8 million people (4.0 % of the population) have tried methamphetamine at some time in their lives. Data from the 2000 Drug Abuse Warning Network (DAWN), which collects information on drug-related episodes from hospital emergency departments in 21 metropolitan areas, reported that methamphetamine-related episodes increased from approximately 10,400 in 1999 to 13,500 in 2000, a 30% increase. NIDA's Community and Epidemiology Work Group reported in June 2001, that methamphetamine continues to be a problem in Hawaii and in major Western cities, such as San Francisco, Denver and Los Angeles. Methamphetamine production and availability are being reported in more diverse areas of the country, particularly rural areas prompting concern about more widespread use.

Violence associated with methamphetamine (users under the influence, users who commit violent acts to obtain methamphetamine, and/or distributor-trafficker violence) is also a concern (DAWN 2000). Moreover, a generation of new users is engaging in highly risky sexual activities under the influence of methamphetamine, which raises the possibilities for a new wave of HIV transmission.

The lack of effective treatment for methamphetamine users has far reaching health ramifications both in terms of the consequences from continued drug use and from the potential for increased HIV transmission. As a result, the development of effective treatments for methamphetamine dependence has become a pressing concern for the national and global drug abuse treatment community.

4.1.8 Search for Effective Treatments for Methamphetamine Dependence

Despite a decade of intensive research, an effective pharmacotherapy for stimulant dependence remains elusive with a noted lack of controlled clinical trials in pharmacotherapy for methamphetamine abuse in particular (Ling and Shoptaw 1997). To date, the bulk of the research in the field is oriented toward treatment of cocaine dependence and many of the suggestions on pharmacotherapies for methamphetamine abuse are based upon clinicians' experiences with treating cocaine abuse. The idea of applicability of cocaine treatment strategies for pharmacotherapy of methamphetamine dependence is based on the similarity of their pharmacological actions, i.e., cross-behavioral sensitization and tolerance between these psychostimulants in animal studies (Akimoto, Hamamura et al. 1990; Peltier, Li et al. 1996; Johnson, Chen et al. 1998). The concept of building on knowledge from cocaine dependence studies and applying this knowledge to methamphetamine studies was endorsed by the Methamphetamine Addiction Treatment Think Tank consultants meeting convened at NIDA on January 12, 2000.

4.1.9 Safety of Methamphetamine

Intravenous (i.v.) methamphetamine administration spanning the doses proposed for use in this study have been previously investigated in human laboratory clinical trials. Mendelson and colleagues (personal communication) have employed i.v. methamphetamine doses from 15 mg to 45 mg. These doses were administered safely over 1 to 10 minutes in subjects with prior experience with i.v. methamphetamine use. In these studies, the immediate subjective effects of a 15 mg dose were minimal, almost indistinguishable from placebo. However, after about 10 minutes all subjects were able to distinguish when methamphetamine was administered as compared to placebo. The cardiovascular effects of the 15 mg dose were also minimal.

In a PK and interaction study with alcohol, the cardiovascular effects in 8 subjects following i.v. administration of 30 mg of methamphetamine was accompanied by a peak in blood pressure 2 minutes after administration and a heart rate peak at 10 minutes (Mendelson, Jones et al. 1995). Both measures returned from peak values to a plateau level (20 mm Hg above and about 15 bpm above pre-methamphetamine baseline) 15 minutes following i.v. administration. The plateau levels slowly returned to baseline levels over the rest of the day. HR and BP responses were dramatic in some individuals (50 mm Hg elevations in systolic BP occurred). A few subjects exhibited a baroreceptor reflex response with a brief, relative bradycardia with heart rates of 55 to 60. All subjects had a robust, predictable response to the 30 mg dose with immediate intoxication ratings of about 50 (0=none, 100=max). In the interaction part of this study, methamphetamine (30 mg i.v.) was administered in combination with ethanol (1 gm/kg). Methamphetamine PK was not altered by the concurrent administration of ethanol, with the exception of lowering the apparent volume of distribution at steady state for methamphetamine. Based on these data, Mendelson concluded that doses around 30 mg produced at least half maximal acute subjective and cardiovascular responses.

4.1.10 Methamphetamine Dose Justification

Peak plasma concentrations of 140 ng/mL are observed after i.v. administration of 30 mg doses of methamphetamine in humans (Mendelson, Jones et al. 1995). Thirty mg doses of

methamphetamine translate to an effective dose of 21 mg when delivered by the smoked route (Cook 1991). A peak plasma concentration of 44 ng/ml was observed after 30 mg of methamphetamine was administered by smoking (Cook 1991). Detectable levels of methamphetamine have been documented in the postmortem blood of individuals involved in traffic fatalities (Logan, Fligner et al. 1998). Levels ranged from 50 to 2,600 ng/mL (median 350 ng/mL). Thus, the highest dose of methamphetamine to be used in this study is representative of the levels in blood of methamphetamine users while at the same time being a safe dose to administer in the human laboratory setting.

4.2 Osmotic-Release Methylphenidate (OROS-MPH)

OROS-MPH is approved by the FDA at doses of 18 to 72 mg/day for the treatment of children with Attention Deficit Hyperactivity Disorder (ADHD). Methylphenidate (MPH) and *d,l*-amphetamine have been the mainstay of pharmacologic treatment for ADHD in children, adolescents, and adults. Numerous attempts have been made to develop a longer acting formulation of MPH for the treatment of ADHD to increase medication compliance with once a day dosing, and to provide a longer acting formulation that has lower abuse potential than shorter acting preparations. The OROS delivery system used in OROS-MPH has resulted in the longest delivery system of all psychostimulant formulations. The unique delivery system in OROS-MPH consists of an osmotically active tri-layer core surrounded by a semi-permeable membrane with an immediate-release overcoat that allows for controlled drug delivery throughout the day. OROS-MPH is the only formulation that results in 12 hours of clinical response with once per day dosing (Lopez, Silva et al. 2003; Swanson, Wigal et al. 2004; Wolraich and Doffing 2004).

Recent reports have suggested that the abuse potential of oral MPH is strongly influenced by the rate of delivery, and not solely by the magnitude of plasma concentration or brain transporter occupancy (Spencer, Biederman et al. 2006; Volkow 2006). Using PET and the dopamine transporter radioligand with [^{11}C]-altropane, Spencer and colleagues (2006) found that immediate release MPH (IR-MPH) at a dose of 40 mg achieved equivalent peak levels of dopamine transporter blockage as a 90 mg dose of OROS-MPH (Spencer, Biederman et al. 2006). Even though peak dopamine transporter blockage was achieved significantly faster with IR-MPH than the OROS-MPH formulation (1.7 hours versus 5 hours, respectively), patients report significantly lower reinforcing effects with the OROS-MPH formulation than with the IR-MPH. It was also observed that at 7 hours after dosing, the level of dopamine transporter blockage for OROS-MPH was 6.5% versus 40% of IR-MPH. Thus, if the rate of dopamine change is positively associated with the reinforcing effects of methylphenidate, its slow clearance from and its long occupancy of dopamine transporter will limit the rate at which it can be administered before producing dopamine transporter saturation. This predicts that delivery systems that maintain steady state plasma levels for longer time periods are less likely to be abused than delivery systems that lead to more abrupt changes (Volkow 2006).

4.2.1 Pharmacology

MPH HCl is a central nervous system stimulant. The mode of therapeutic action in ADHD is not known. MPH is thought to block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space. MPH is a racemic mixture comprised of the d- and l-isomers. The d-isomer is more pharmacologically active than the l-isomer. Animal studies have suggested that MPH is a

dopamine transporter (DAT) inhibitor that rapidly increases vesicular dopamine uptake, vesicular monamine transporter-2 (VMAT-2) ligand binding, and VMAT-2 immunoreactivity in vesicular subcellular fractions (Sandoval, Riddle et al. 2003). MPH has been shown to increase the extracellular dopamine levels by inhibiting DAT and potentiates the action of spontaneously released dopamine acting on D1 receptors in the medium spiny neurons (Fukui, Svenningsson et al. 2003).

4.2.2 PK

MPH is readily absorbed. Following oral administration of OROS-MPH (CONCERTA®) to adults, plasma MPH concentrations increase rapidly reaching an initial maximum at about 1 to 2 hours, then increase gradually over the next several hours. Peak plasma concentrations are achieved at about 6 to 8 hours after which a gradual decrease in plasma levels of MPH begins. OROS-MPH once daily (q.d.) minimizes the fluctuations between peak and trough concentrations associated with immediate-release MPH (IR-MPH) three times daily (t.i.d.) as shown in **Figure 1**. Plasma MPH concentrations in adults decline biexponentially following oral administration. The half-life of MPH in adults following oral administration of OROS-MPH was approximately 3.5 h. In a multiple-dose study in adolescent ADHD patients aged 13 to 16 administered their prescribed dose (18 to 72 mg/day) of CONCERTA®, mean Cmax and AUC_{TAU} of d- and total MPH increased proportionally with respect to dose. The relative bioavailability of OROS-MPH q.d. and IR-MPH t.i.d. in adults is comparable (ConcertaÒ-PackageInsert).

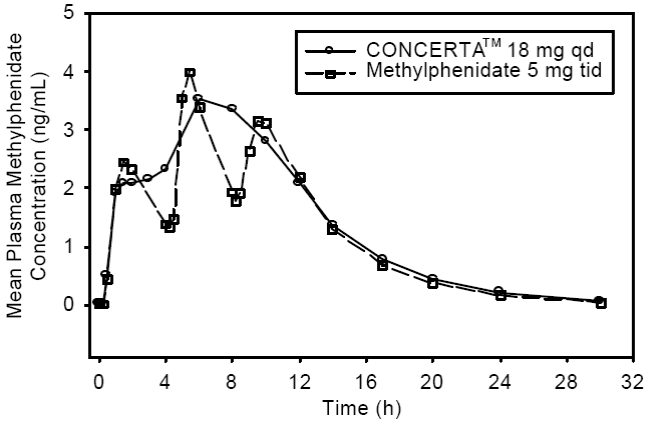


Figure 1. Mean MPH plasma concentrations in 36 adults, following a single dose of OROS-MPH (CONCERTA®) 18 mg q.d. and IR-MPH 5 mg t.i.d. administered every 4 hours.

4.2.3 Metabolism

In humans, MPH is metabolized primarily by deesterification to α-phenyl-piperidine acetic acid (PPA), which has little or no pharmacologic activity. In adults, the metabolism of OROS-MPH q.d. as evaluated by metabolism to PPA is similar to that of MPH t.i.d. The metabolism of single and repeated q.d. doses of OROS-MPH is similar. After oral dosing of radiolabeled MPH in humans, about 90% of the radioactivity was recovered in urine. The main urinary metabolite was PPA, accounting for approximately 80% of the dose.

4.2.4 Previous Human Experience

More than 50 randomized controlled trials (Schachter, Pham et al. 2001), along with decades of clinical experience, has established the safety and efficacy of MPH in the treatment of ADHD (Greenhill, Halperin et al. 1999). Three studies have evaluated the safety and efficacy of OROS-MPH compared to IR-MPH for ADHD. These studies demonstrate low placebo response rates and robust clinical effects of OROS-MPH, equivalent to the clinical effects of IR-MPH in reducing ADHD symptoms in children (Pelham, Gnagy et al. 2001; Wolraich, Greenhill et al. 2001; Swanson, Gupta et al. 2003).

Although there is a large body of clinical experience with MPH in pediatric subjects with ADHD, there are only a limited number of clinical studies in adults. These early studies in adults have yielded equivocal results and the discrepancies have been attributed to low doses, diagnostic uncertainties, and lack of attention to comorbid disorders (Spencer, Wilens et al. 1995). In a small controlled trial of 23 adults with ADHD diagnosis based on clinical assessment and confirmed by structured diagnostic interview, improved responses were shown with higher doses of IR-MPH, 1 mg/kg/day, as opposed to previous reports of adults dosed at 0.6 mg/kg/day (Spencer, Wilens et al. 1995). More recently studies have provided evidence than even higher doses of MPH yield additional benefits for adults with ADHD. Spencer *et al.*, (2005) found marked improvement (76% response versus 19% placebo response) in a larger study of adults with ADHD (146 patients) at an average daily dose of 1.1 mg/kg/day, and in a subsequent study, adults treated with OROS-MPH (141 patients) at doses up to 1.3 mg/kg/day had significantly reduced symptoms of ADHD (Spencer, Biederman et al. 2005; Biederman, Mick et al. 2006). In a separate 6-week, open-label study of adults with late-onset ADHD (36 patients), treatment with OROS-MPH at an oral daily dose of 1.3 mg/kg/day was associated with a clinically and statistically significant response that was of similar magnitude as that observed under double-blind conditions in adults with a full DSM-IV diagnosis of ADHD (Biederman, Mick et al. 2006).

4.2.5 Safety of OROS-MPH

The development program for OROS-MPH (CONCERTA®) included exposures in a total of 2121 participants in clinical trials (1797 patients, 324 healthy adult subjects). These participants received OROS-MPH at 18, 36, 54 and/or 72 mg/day. Children, adolescents, and adults with ADHD were evaluated in four controlled clinical studies, three open-label clinical studies and two clinical pharmacology studies.

In studies on the adult population with ADHD treated with OROS-MPH at doses up to 1.3 mg/kg/day, anorexia, dry mouth, gastrointestinal problems, tension/jitteriness, insomnia, cardiovascular complaints, depression, anxiety, and dizziness were statistically associated with OROS-MPH treatment (Biederman, Mick et al. 2006). OROS-MPH was associated with statistically significant increases in systolic and diastolic blood pressure and heart rate but with statistically significant decrease of ECG QT interval. In the study of adults with late onset ADHD, OROS MPH was associated with small but statistically significant increases in heart rate, QT and QTc intervals (Biederman, Mick et al. 2006). In addition to subjective complaints of decreased appetite, subjects in the OROS MPH group were statistically more likely to lose weight over the course of the 6-week trial. Thus, adults with ADHD, particularly in those with borderline hypertension or those who are underweight, should be monitored for changes in blood

pressure parameters or weight loss when receiving treatment with MPH (Biederman, Mick et al. 2006).

The following summarizes the relevant safety data from the OROS-MPH Package Insert (September, 2006).

Treatment Emergent AEs Among OROS-MPH-Treated Patients. **Table 1** enumerates, for a 4-week placebo-controlled, parallel group trial in children with ADHD at OROS-MPH doses of 18, 36, or 54 mg/day, the incidence of treatment-emergent AEs. The table includes only those events that occurred in 1% or more of patients treated with OROS-MPH where the incidence in patients treated with OROS-MPH was greater than the incidence in placebo-treated patients. **Table 2** lists the incidence of treatment-emergent AEs (AEs that occurred in 2% of more of patients treated with OROS-MPH compared to placebo controls) for a 2-week placebo-controlled trial in adolescents with ADHD at OROS-MPH doses of 18, 36, 54 or 72 mg/day.

Table 1: Incidence of Treatment-Emergent Events[1] in a 4-Week Placebo-Controlled Clinical Trial of OROS-MPH in Children with ADHD

Body System	Preferred Term	OROS-MPH (n=106)	Placebo (n=99)
General	Headache	14%	10%
	Abdominal pain (stomach ache)	7%	1%
Digestive	Vomiting	4%	3%
	Anorexia (loss of appetite)	4%	0%
Nervous	Dizziness	2%	0%
	Insomnia	4%	1%
Respiratory	Upper respiratory tract infection	8%	5%
	Cough increased	4%	2%
	Pharyngitis	4%	3%
	Sinusitis	3%	0%

[1]Events, regardless of causality, for which the incidence for patients treated with OROS-MPH was at least 1% and greater than the incidence among placebo-treated patients. Incidence has been rounded to the nearest whole number.

Table 2: Incidence of Treatment-Emergent Events[1] in a 2-Week Placebo-Controlled Clinical Trial of OROS-MPH in Adolescents with ADHD			
Body System	**Preferred Term**	**OROS-MPH (n=87)**	**Placebo (n=90)**
General	Accidental Injury	6%	3%
	Fever	3%	0%
	Headache	9%	8%
Digestive	Anorexia	2%	0%
	Diarrhea	2%	0%
	Vomiting	3%	0%
Nervous	Insomnia	5%	0%
Respiratory	Pharyngitis	2%	1%
	Rhinitis	3%	2%
Urogenital	Dysmenorrhea	2%	0%
[1]Events, regardless of causality, for which the incidence for patients treated with OROS-MPH was at least 2% and greater than the incidence among placebo-treated patients. Incidence has been rounded to the nearest whole number.			

AEs Associated with Discontinuation of Treatment. In the 4-week placebo-controlled, parallel-group trial one OROS-MPH-treated patient (0.9%; 1/106) and one placebo-treated patient (1.0%; 1/99) discontinued due to an AE (sadness and increase in tics, respectively).

In uncontrolled studies up to 12 months with OROS-MPH, 6.6% (29/441) patients discontinued for AEs. Those events associated with discontinuation of OROS-MPH in more than one patient included the following: twitching (tics, 1.8%); anorexia (loss of appetite, 0.9%); aggravation reaction (0.7%); hostility (0.7%); insomnia (0.7%); and somnolence (0.5%).

Hypertension. In laboratory classroom clinical trials in children, both OROS-MPH q.d. and IR-MPH t.i.d. increased resting pulse by an average of 2-6 bpm and produced average increases of systolic and diastolic blood pressure of roughly 1-4 mm Hg during the day, relative to placebo. In a placebo-controlled adolescent trial, mean increases from baseline in resting pulse rate were observed with OROS-MPH and placebo at the end of the double-blind phase (5 and 3 bpm, respectively). Mean increases from baseline in blood pressure at the end of the double-blind phase for OROS-MPH and placebo-treated patients were 0.7 and 0.7 mm Hg (systolic) and 2.6 and 1.4 mm Hg (diastolic), respectively.

Tics. In a long-term uncontrolled study (n=432 children), the cumulative incidence of new onset of tics was 9% after 27 months of treatment with OROS-MPH. In a second uncontrolled study (n=682 children) the cumulative incidence of new onset tics was 1% (9/682 children). The treatment period was up to 9 months with mean treatment duration of 7.2 months.

AEs with Other MPH HCl Products. Nervousness and insomnia are the most common adverse reactions reported with other MPH products. Other reactions include hypersensitivity (including skin rash, urticaria, fever, arthralgia, exfoliative dermatitis, erythema multiforme with histopathological findings of necrotizing vasculitis, and thrombocytopenic purpura); anorexia; nausea; dizziness; palpitations; headache; dyskinesia; drowsiness; blood pressure and pulse changes, both up and down; tachycardia; angina; cardiac arrhythmia; abdominal pain; and weight loss during prolonged therapy. There have been rare reports of Tourette's syndrome. Toxic

psychosis has been reported. Although a definite causal relationship has not been established, the following have been reported in patients taking this drug: instances of abnormal liver function, ranging from transaminase elevation to hepatic coma; isolated cases of cerebral arteritis and/or occlusion; leukopenia and/or anemia; transient depressed mood; a few instances of scalp hair loss. Very rare reports of neuroleptic malignant syndrome (NMS) have been received, and, in most of these, patients were concurrently receiving therapies associated with NMS. In a single report, a ten-year old boy who had been taking MPH for approximately 18 months experienced an NMS-like event within 45 minutes of ingesting his first dose of venlafaxine. It is uncertain whether this case represented a drug-drug interaction, a response to either drug alone, or some other cause. In children, loss of appetite, abdominal pain, weight loss during prolonged therapy, insomnia, and tachycardia may occur more frequently; however, any of the other adverse reactions listed above may also occur.

Post Marketing Studies. Post-marketing experiences with OROS-MPH have revealed spontaneous reports of: difficulties in visual accommodation, blurred vision, abnormal liver function test (e.g., transaminase elevation), palpitations, arrhythmia, leucopenia, and thrombocytopenia.

4.3 Potential Drug-Drug Interactions

The potential for metabolism-mediated drug-drug interactions of OROS-MPH and the CYP2D6 enzymatic pathway have been investigated. In a study of six adults phenotyped as either extensive or poor metabolizers for CYP2D6, oral doses of MPH on two separate occasions with and without quinidine, a potent CYP2D6 inhibitor had no significant effect on the PK of either MPH or ritalinic acid, its major metabolite, in either group of CYP2D6 metabolizers (DeVane, Markowitz et al. 2000). This is important as methamphetamine is an inhibitor of CYP2D6.

Since psychomotor stimulants like MPH or methamphetamine tend to increase blood pressure and heart rate, it is reasonable to expect patients to develop significant increases in these parameters. Average increases in heart rate were 2.6 beats per minute (3.4%) and 2.6 mmHg (3.4%) for diastolic blood pressure when MPH was administered to adult cocaine dependent patients (Somoza, Winhusen et al. 2004). No differences were observed between baseline and endpoint systolic blood pressure measurements. Both the increase in HR and diastolic BP were statistically significant, however, these increases were not considered to be clinically significant.

4.4 Rationale for MPH Treatment for Methamphetamine Dependence

A variety of neuropharmacological strategies are being pursued in the search for an effective treatment for methamphetamine abuse. One approach has been to target the dopaminergic neurotransmitter system involved in the reward mechanism to interrupt the reinforcing action of methamphetamine and thus reduce its use and prevent relapse to use (Hyman and Nestler 1996; Mendelson and Mello 1996; Ling and Shoptaw 1997). Methamphetamine is known to produce its major effects through dopaminergic mechanisms in the midbrain. Methamphetamine causes DA release and blocks the reuptake of DA; the consequent excess of DA stimulates the midbrain reward centers. One therapeutic strategy is to develop and test DA antagonists, to see if blocking DA can reduce methamphetamine abuse. A second, and diametrically opposed therapeutic strategy, is to develop and test DA agonists -- agents that increase DA release or dopaminergic activity to see if they can reduce methamphetamine abuse. This second strategy is based on a

combination of theory and data suggesting that chronic methamphetamine use depletes brain DA and that this depletion is experienced as methamphetamine craving; the aim here is to reduce methamphetamine craving and use by restoring the depleted DA system to normality.

MPH treatment has successfully suppressed the ADD symptoms in cocaine dependent adults with a history of long term sobriety (Castaneda, Sussman et al. 1999). In a subgroup of cocaine-dependent adults experiencing a positive therapeutic effects from cocaine during their initial phases of their addiction, several patients (10/19) achieved continued cocaine abstinence by treatment with various formulations of MPH (Ritalin, and Ritalin-SR) alone, or in combination with anti-depressants. Combinations of dextroamphetamine sulfate and anti-depressants were among the other medications that were efficacious in the subjects that were not using MPH formulations. These formulations were efficacious in suppressing the ADD symptoms and enabling patients to remain cocaine abstinent for an additional 12 months in all but one patient. A recent open-label pilot study of MPH in the treatment of cocaine dependent patients with ADHD described statistically significant improvements in subjective efficacy measures of cocaine dependence and ADHD symptoms in both compliant and non-compliant subjects (Somoza, Winhusen et al. 2004). This study demonstrated that MPH could be a safe and effective treatment for individuals with comorbid diagnoses of cocaine dependence and ADHD. As with the supporting studies described here, it is hoped that similar positive responses can be achieved with MPH treatment of methamphetamine dependent patients who also struggle in achieving abstinence due to either ADD or ADHD comorbidities.

5 STUDY OBJECTIVES

5.1 Primary Objectives

The primary objective of this study is to determine the safety of the OROS-MPH concurrent with i.v. d-methamphetamine infusions of 15 mg and 30 mg. Safety outcome measures include cardiovascular responses (HR, BP, and ECG) measurements, oral temperature, AEs, and clinical laboratory analyses.

5.2 Secondary Objectives

Secondary objectives include:

1. Determining plasma levels of MPH during chronic daily administration of OROS-MPH and the effects of methamphetamine on OROS-MPH PK.
2. Evaluating whether administration of OROS-MPH alters the PK of d-methamphetamine or its metabolites.
3. Evaluating whether OROS-MPH alters the subjective response to methamphetamine using VAS, ARCI, and SDV assessments after methamphetamine infusions.

6 STUDY SPONSOR

This study will be conducted under an Investigational New Drug Application (IND) held by the Sponsor-Investigator, Dr. Eugene Somoza. Dr. Edward Sellers will be the Sponsor of a Clinical Trial Application with Health Canada for the Canadian Site (DecisionLine).

7 STUDY SITES

This study will be conducted at two sites, including the Cincinnati Addiction Research Center (CinARC) of the College of Medicine University of Cincinnati, under the direction of the Sponsor-Investigator, Eugene Somoza, M.D., Ph.D., who is also the site Principal Investigator of CinARC, and at DecisionLine Clinical Research Corporation under the direction of the Site Principal Investigator, Edward Sellers, M.D., Ph.D. It is expected that the DecisionLine site will complete the study with approximately twice as many participants as CinARC (12 versus 6).

8 STUDY DESIGN

This is a double-blind, placebo-controlled, two-center inpatient study in which subjects will be randomized into one of two study groups [placebo (n = 6) or OROS-MPH (n = 12)] with both groups receiving infusions of methamphetamine (15 mg and on a separate day 30 mg) prior to and after OROS-MPH/placebo administration to evaluate interactions between these two drugs. Subjects will undergo an outpatient screening period of not more than 30 days (screening may be repeated if the principal investigator agrees) to determine eligibility for study participation. If eligible during the outpatient screening evaluations, subjects will undergo clinic intake procedures and complete final screening assessments one to two days before baseline infusions of methamphetamine begin. If eligible after completion of all outpatient and inpatient screening assessments, subjects will start the first infusion session. All subjects will undergo two series of two sequential days of saline and methamphetamine infusion sessions. The first day's session will be an i.v. infusion of saline followed one hour later by an i.v. infusion of 15 mg of methamphetamine. The second day's session will be an i.v. infusion of saline followed one hour later by an i.v. infusion of 30 mg of methamphetamine. Baseline sessions #1 and #2 on Study Days -3 and -2 will be conducted before the initiation of daily placebo or OROS-MPH administration which starts on Day 1. On Day 1, subjects will be randomized in a ratio of 1:2 (placebo controls:OROS-MPH dosed subjects) for a total of 18 total subjects. The dose of OROS-MPH will be escalated every two days from 36 mg/day to 54 mg/day to 72 mg/day with PK interactions with methamphetamine being tested at the high dose of OROS-MPH. On Study Days 1 and 2, subjects will receive OROS-MPH (36 mg q.d.) or matched placebo. On Days 3 and 4, the OROS-MPH dose will be increased to 54 mg q.d., and on Days 5 through 9, the OROS-MPH dose will be increased to 72 mg q.d.

On Days 7 and 8, subjects will undergo saline and methamphetamine infusion sessions #3 and #4 in a similar fashion to sessions #1 and #2. Infusion sessions after the start of OROS-MPH or placebo dosing will begin after the morning dose. Subjects will not be told the order of methamphetamine and saline infusions. Thus, the study will be single-blind with respect to methamphetamine and saline infusions. Neither the subject nor the investigative staff will know the assignment of subjects to placebo control or OROS-MPH. Thus, the study will be double-blind with respect to these investigational products. Cardiovascular and subjective effects will be measured during all infusion sessions. Blood for methamphetamine PK analyses will be collected during infusion sessions #2 and #4 when subjects receive the 30 mg dose of methamphetamine. Subjects will be discharged from the clinic on Study Day 10, after the final methamphetamine blood PK sample is collected and other safety measures have been assessed. This is one day after the last dose of investigational products. Following clinic discharge, all

subjects will be asked to return twice: on Study Days 20 ± 2 and 27 ± 2, preferably as early in each visit window as possible.

9 SUBJECT SELECTION

9.1 Inclusion Criteria

In order to participate in the study, subjects must:

1. Be volunteers who meet DSM-IV criteria for methamphetamine abuse or dependence determined using the Mini-International Neuropsychiatric Interview (MINI) and be non-treatment seeking at time of study and have a positive urine test for methamphetamine (≥ 500 ng/mL) during screening.

2. Be males or females, 18 to 45 years of age, inclusive.

3. Be able to verbalize understanding of consent form, able to provide written informed consent, and verbalize willingness to complete study procedures.

4. Have a negative urine test for methamphetamine and other drugs of abuse (opiates, cocaine, and benzodiazepines) after clinic intake before the first infusion session.

   NOTE: Recent intermittent alcohol or other illicit drug use without physical dependence is allowable (however an opiate, cocaine, and benzodiazepine-free urine should be produced to document absence of recent use). A positive urine drug screen for marijuana is not exclusionary.

5. Have a history and physical examination that demonstrate no clinically significant contraindication for participating in the study, in the judgment of the admitting physician and the site Principal Investigator

6. Have vital signs as follows: resting heart rate between 45 and 100 bpm, systolic BP below 140 mm Hg and diastolic BP below 90 mm Hg.

7. Have electrolytes (Na, K, Cl, HCO_3) and hematocrit that is clinically normal (+/- 10% of laboratory limits).

8. Have liver function tests (total bilirubin, ALT, AST, and alkaline phosphatase) less than three times the upper limit of normal.

9. Have kidney function tests (creatinine and BUN) less than twice the upper limit of normal.

10. Have an ECG performed that demonstrates sinus rhythm between 45 and 100 beats per minute (bpm), normal conduction, and no clinically significant arrhythmias.

11. Be able to swallow whole tablets of OROS-MPH due to the controlled release formulation.

12. If female, have a negative pregnancy test and agree to use one of the following methods of birth control, or be postmenopausal, have had a hysterectomy or have been sterilized. Birth control must be in effect starting at least 7 days (14 days for hormone-based methods used alone) prior to clinic intake, and should extend at least until the last follow-up visit.

    a. oral contraceptives
    b. contraceptive sponge or patch
    c. barrier (diaphragm or condom) with spermicide
    d. intrauterine progesterone, or non-hormonal contraceptive system
    e. levonorgestrel implant
    f. medroxyprogesterone acetate contraceptive injection
    g. complete abstinence from sexual intercourse

9.2 Exclusion criteria

In order to participate in the study, subjects must <u>not</u>:

1. Have a current or past history of seizure disorder, including alcohol- or stimulant-related seizure, febrile seizure, or significant family history of idiopathic seizure disorder.

2. Have a history of clinically significant head trauma that resulted in neurological sequelae (e.g., loss of memory for greater than 5 minutes or that required hospitalization).

3. Have physiological dependence on alcohol, an opioid analgesic, or a sedative-hypnotic, (e.g., a benzodiazepine) that requires medical detoxification or have diagnosis of dependence, in accordance with DSM-IV criteria, on other substances of abuse except marijuana, nicotine, or alcohol.

4. Have any previous medically serious adverse reaction to methamphetamine including loss of consciousness, chest pain, or epileptic seizure resulting in hospitalization.

5. Meet the diagnostic criteria (DSM-IV) for the following Axis I disorders: psychosis, bipolar I disorder, organic brain disease, dementia, major depression, schizoaffective disorder, schizophrenia, anorexia nervosa, or bulimia disorder.

6. Exhibit marked anxiety, tension, or agitation, since the OROS-MPH may aggravate these symptoms.

7. Report becoming violent, or have homicidal or have suicidal thoughts when taking methamphetamine by medical/psychiatric history.

8. Have evidence of clinically significant heart disease as evidenced by a history of arrhythmia requiring medication, angina pectoris, or myocardial infarction or a clinically significant ECG abnormality (such as defined below), or any history of cardiac disease or current ECG

abnormality which the investigator feels may make participation in this study dangerous for the participant such as:

a. ST segment elevations in two or more contiguous leads of greater than 0.1 mV.
b. ST segment depression of greater than 1 mm that are flat or down-sloping at 80 msec after the J point.
c. A bundle branch block.
d. Mobtiz II second or third degree heart block.
e. Atrial fibrillation or atrial flutter or activation of any tachyarrhythmia for greater than 10 seconds.
f. A QT of >470 msec or a QTc of >440 msec for males and >450 msec for females.

9. Have any history of hypersensitivity to MPH, glaucoma, motor tics or with a family history or diagnosis of Tourette's syndrome.

10. Have severe gastrointestinal narrowing (pathologic or iatrogenic, for example: esophageal motility disorders, small bowel inflammatory disease, "short gut" syndrome due to adhesions or decreased transit time, past history of peritonitis, cystic fibrosis, chronic intestinal pseudo-obstruction, or Meckel's diverticulum).

11. Have an overactive thyroid gland.

12. Have any legal or other issues that would interfere with study participation.

13. Be pregnant or lactating.

14. Have a significant family history of early cardiovascular morbidity or mortality in the opinion of the site Principal Investigator.

15. Have any illness, condition, and/or use of medications that in the opinion of the site Principal Investigator and the admitting physician would preclude safe and/or successful completion of the study.

16. Have active syphilis that has not been treated or refuse treatment for syphilis (see note).

17. Be undergoing HIV treatment with antiviral and/or non-antiviral therapy.

18. Have AIDS according to the current CDC criteria for AIDS - MMWR 1999;48 (no. RR-13:29-31).

19. Have neurological disorders including Parkinson's disease.

20. Be using OROS-MPH or any form of MPH HCl (Ritalin, Ritalin SR, Methylin, Methylphen, Metadate ER) during the past 30 days, or any medication that could interact adversely with MPH, within the following times of beginning of administration of MPH based on the longest time interval of A, B, or C, below or as otherwise specified:

    A) Five half lives of other medication or active metabolite(s), whichever is longer

B) Two weeks
C) Interval recommended by other medication's product labeling

Medications that fall into this category include:

1. Amphetamines (e.g., Adderall, Dexedrine, Dextrostat, and other amphetamine formulations), atomoxetine, modafinil, buproprion, ephedrine (including pseudoephedrine, and herbal/dietary supplements containing Ephedra, i.e., Ma huang), or any other stimulant formulations
2. Antidepressants including monoamine oxidase (MAO) inhibitors (MAO inhibitors should be stopped 14-days before starting OROS-MPH).
3. Coumarin anticoagulants.
4. Anticonvulsants (e.g., phenobarbital, phenytoin, primidone).
5. Antidepressants including tricyclics and selective serotonin reuptake inhibitors.
6. Clonidine.
7. Neuroleptics
8. Psychotropics
9. Systemic corticosteroids
10. Xanthines, i.e., theophilline, theophilline sodium glycinate and aminophylline
11. Drugs that lower seizure threshold
12. Drugs that are vasopressor agents should be used cautiously

Notes on inclusion/exclusion criterion: Although AIDS is an exclusion criteria, a positive antibody titer to HIV is not. Prospective subjects will be offered HIV testing during screening. This test is offered as a courtesy to the prospective subject along with HIV education.

Prospective subjects who are positive for syphilis by the rapid plasma reagin (RPR) test will have a fluorescent treponemal antibody absorbant assay (FTP-abs) or microhemagglutinin assay-Treponema pallidum (MHA-TP) confirmatory test performed. If this test is positive, prospective subjects must be treated for syphilis to be eligible for the study or provide evidence of previous successful treatment for syphilis.

The infectious disease panel for hepatitis is performed as an aid to determine if the prospective subject has been exposed to a hepatitis virus. Positive hepatitis results do not exclude a prospective subject from participation unless there is an indication of active liver disease (by clinical laboratory result, medical history, or physical exam). Similarly, a positive tuberculin (PPD) result does not exclude a prospective subject from participation, but if diagnostic tests (e.g., chest x-ray) indicate that active disease is present, subjects will be excluded from participation.

If any test results are positive, the subject will be notified of positive and confirmatory test results and will be referred for treatment.

History of methamphetamine-induced psychosis does not exclude a prospective subject from the study; however, the presence of current methamphetamine-induced psychosis will exclude a prospective subject from the study until clinically stabilized.

10 INVESTIGATIONAL PRODUCTS

10.1 OROS-MPH AND MATCHED PLACEBO

OROS-MPH is an extended-release tablet for once-a-day oral administration designed to have a 12-hour duration of effect. Tablets containing 18 mg, 27 mg, and 36 mg of MPH will be used for this study. CONCERTA® is manufactured by ALZA Corporation, Mountain View, CA 94043 and is marketed and distributed by McNeil Pediatrics (Division of McNeil-PPC Inc., Fort Washington, PA 19034) in the United States. CONCERTA® is licensed by ALZA Corporation under New Drug Application (NDA) Number 021121 in the United States.

Murty Pharmaceuticals Inc., will over encapsulate placebo tablets and the 18 mg, 27 mg, and 36 mg OROS-MPH tablets to blind investigational products for the study. Supplies of the over encapsulated tablets will be provided to each clinical site's research pharmacist for dispensing the daily dose for each subject to maintain the blind. The total daily dose will be administered by dispensing the appropriate combination of 18 mg, 27 mg, and 36 mg tablets to deliver the total daily dose.

The same number of over encapsulated placebo tablets will be administered to subjects randomized to the placebo control group to mimic the number of tablets of OROS MPH being administered on each study day. The research pharmacist will be unblinded, but the remaining study staff will be blinded with respect to OROS-MPH or placebo capsule identification.

Controlled Substance Class: OROS-MPH, like other methylphenidate products, is classified as a Schedule II controlled substance by U.S. federal regulation.

10.2 Methamphetamine

Sterile i.v. human use methamphetamine HCl at 10 mg/mL in 1 mL ampules will be provided by NIDA. The compound will be stored in the pharmacy vault. Standard narcotics control procedures will govern access to the drug. Aliquots of 0, 15 or 30 mg will be drawn into a syringe for i.v. administration. Methamphetamine will be administered by i.v. infusion over 2 minutes by the study physician. Any unused drug will be disposed of according to standard practices.

10.3 Saline

Sterile preservative-free saline (0.9% sodium chloride) for injection will be obtained from a local supplier.

10.4 Storage

Investigational products should be stored at room temperature [15-30°C (59-86°F)], be protected from moisture, and be maintained in a secure area.

10.5 Investigational Product Accountability

The site Principal Investigator or designated study personnel will maintain a log of all investigational products administered to subjects throughout the trial. In addition, supplies of OROS-MPH or placebo control and methamphetamine ampules will be inventoried and audited against administration records.

10.6 Used/Unused Supplies

At the end of the study, all unused investigational products must be inventoried. If any investigational product is lost or damaged, its disposition should be documented. Unused investigational products will be retained at the clinic sites pending instructions for disposition by the NIDA at the end of the study.

11 INVESTIGATIONAL PRODUCT ADMINISTRATION

OROS-MPH or Placebo: Blinded OROS-MPH or matched placebo capsules will be administered once daily at 36 mg/day for 2 days (Study Days 1 and 2), once daily at 54 mg/day for 2 days (Study days 3 and 4), and once daily at 72 mg/day for 5 days (Study Days 5 to 9). OROS-MPH or placebo will be given at the same time each day and should be given at approximately 7 a.m., 5 hours before the start of the saline infusion on infusion days. On the first day of dosing, OROS-MPH or placebo will be given slightly later in the day, i.e., after the 48-hour blood collection for methamphetamine PK assessments after baseline infusion session #2 has been completed.

Subjects should be informed that CONCERTA® should be swallowed whole with the aid of liquids. Tablets should not be chewed, divided, or crushed. The medication is contained within a nonabsorbable shell designed to release the drug at a controlled rate. The tablet shell, along with insoluble core components, is eliminated from the body; subjects should not be concerned if they occasionally notice in their stool something that looks like a tablet.

This timing of administration of OROS-MPH and infusions was planned to achieve the C_{max} for OROS-MPH (6 hours after administration) to coincide with the start of the methamphetamine infusion. The once daily morning dosing schedule with OROS-MPH was also designed to minimize insomnia or effects on subject's sleep cycles.

Methamphetamine or Saline (All Subjects):

Infusion Sessions #1 and #3 (saline i.v. followed one hour later by 15 mg methamphetamine i.v.): Infusion sessions #1 and #3 are scheduled on Study Day -3 (baseline infusion) and Day 7 (infusion during OROS-MPH dosing), respectively. The start of the saline infusion is 5 hours after OROS-MPH/placebo dosing followed one hour later by the 15 mg methamphetamine infusion.

Infusion Sessions #2 and #4 (saline i.v. followed one hour later by 30 mg methamphetamine i.v.): Infusion sessions #2 and #4 are scheduled on Study Day - 2 (baseline infusion) and Day 8 (infusion during OROS-MPH dosing), respectively. The start of the saline infusion is 5 hours

after OROS-MPH/placebo dosing followed one hour later by the 30 mg methamphetamine infusion.

12 STUDY PROCEDURES

12.1 Subject Recruitment

Interested candidates who are methamphetamine users but not seeking treatment and are available to stay in the clinic for up to 15 days will meet with the investigator or a designated investigational staff member and receive an explanation of the study purpose and requirements. If still interested after receiving an explanation of the study, the candidate will be given an opportunity to review, inquire about, and sign the informed consent form.

Recruitment strategies may include flyers, newspaper advertisements, or radio advertisements. Chain-referral or "snowball" recruitment methods may also be used, in which study participants may refer potentially eligible friends or acquaintances to the study. "Respondent-Driven Sampling" (RDS) is a type of "snowball" recruitment that offers additional incentives to study participants who refer friends/peers who are consented for baseline eligibility screening (Abdul-Quader, Heckathorn et al. 2006; Abdul-Quader, Heckathorn et al. 2006). RDS will only be performed at the CinARC site that must obtain specific local IRB approval prior to implementation. Study participants may be provided with information to provide to their peers and a means of identifying the referral source. Interested referred individuals must contact the study site for additional information and pre-screening. If the referred individuals complete the consent process, the referring participant will be given up to $30 per referral.

The responsible Institutional Review Board (IRB), Research Ethics Board (REB), and NIDA will approve all advertising materials used for subject recruitment.

12.2 Screening Assessments (Outpatient and Inpatient)

Screening of subjects to establish eligibility will occur within 30 days before clinic intake. If the potential subject does not complete the screening within this time period, screening may be repeated if the principal investigator agrees. Some screening assessments will be completed after intake. Assessments performed before intake include collection of demographic information and completion of a subject locator form, a timeline followback (TLFB) for methamphetamine use for the prior 6 weeks, drug use and treatment history, urine test for methamphetamine (will be repeated until a positive test is obtained within 30 days prior to intake), a 12-lead ECG, a physical exam including vital signs (BP, HR, oral temperature and respiration rate), medical/psychiatric history, prior medication use in past 30 days from the start of signing the informed consent form up to the time of the start of the baseline infusion session. Laboratory analyses during screening include hematology, blood chemistries, medical urinalysis, an infectious disease panel, an HIV antibody test (optional), urine drug screen, and the MINI for DSM-IV diagnosis of methamphetamine dependence or abuse. Axis I Disorders will be assessed using the medical/psychiatric history. All women will have a serum pregnancy test performed during screening. Subjects meeting initial eligibility criteria will be asked to stop using methamphetamine at least 3-days before the scheduled clinic intake, so that a negative urine sample can be obtained prior to the baseline infusion session.

If the subject is still eligible after completing the outpatient screening procedures, s/he will be scheduled for clinic intake one to two days prior to the first infusion session. Final intake screening assessments include repeat pregnancy test for all women (a urine test will be performed in the clinic), review of medical history, vital signs (BP and HR), medication use, TLFB for methamphetamine use, and a urine drug screen. If the subject's urine test is positive for methamphetamine (≥ 500 ng/mL) at intake, they will be retested or released from the clinic and rescheduled for intake, if possible within the window allowed for screening procedures to be completed. The baseline infusion session can be performed on the day after clinic intake, or an additional day of acclimation and screening can occur at the discretion of the site Principal Investigator.

All drug-abusing applicants will receive counseling about drug dependence and be advised that treatment for drug abuse is indicated and available. Applicants not participating in the study will receive treatment referral information as appropriate. At the completion of their participation, study participants will again be advised that treatment is indicated and available, and will be given treatment referral information and assistance.

12.3 Subject Randomization

Randomization into study groups (OROS-MPH or placebo) will not occur until the completion of the baseline infusion sessions. The Data Management Center will be responsible for preparing the Master Randomization list and coordinating the reassignment of subjects to the appropriate study group between the two clinical sites in the event that each site does not randomize the expected number of subjects assigned to that site.

To randomize a subject, if still continuing in the study after the baseline infusion sessions are completed, the site Principal Investigator or a study coordinator will contact the Research Pharmacist for randomization and group assignment. Subjects will be randomized to either the OROS-MPH or placebo group within each clinical site in a ratio of 1 placebo subject for each 2 OROS-MPH-treated subjects. CinARC is projected to randomize and complete 6 evaluable subjects. DecisionLine is projected to randomize and complete 12 evaluable subjects. Blinded envelopes will be provided to Research Pharmacist within each site containing subject group assignments by the Data Management Center. The research pharmacist will maintain the envelopes and list of subject group assignments and will prepare all investigational products in a blind-coded manner.

If subjects are terminated before completing all of the methamphetamine infusion sessions and methamphetamine PK sample collection, a replacement subject may be included (after discussions with the NIDA and the Sponsor-Investigator) to ensure that there are 18 evaluable subjects. A replacement subject will be assigned to the same medication group as the terminated subject being replaced.

12.4 Saline and Methamphetamine Infusion Sessions

12.4.1 Schedule

Saline and methamphetamine i.v. infusion sessions will be conducted according to the schedule shown in **Table 3.** Infusion sessions at baseline and during OROS-MPH/placebo administration will consist of two sessions on two successive days. Each infusion session consists of a saline infusion followed one hour later by either a 15 or 30 mg methamphetamine infusion. The fixed ascending sequence of methamphetamine infusions is a safety precaution. However, the subjects will not be told the order of the saline and methamphetamine infusions.

During the baseline infusion session, the subject's responses to methamphetamine without concomitant OROS-MPH or placebo administration will be assessed. The baseline series of infusions (sessions #1 and #2) provide baseline cardiovascular response data, physiological and psychological responses to methamphetamine, and methamphetamine PK data before OROS-MPH administration for the within subjects analysis. These sessions also provide the investigator will the opportunity to ensure that volunteers can safely tolerate the methamphetamine test doses. Only subjects safely tolerating both test doses of methamphetamine will continue in the study.

During the OROS-MPH/placebo administration phase, the subject's responses to methamphetamine with concomitant OROS-MPH or placebo administration will be assessed. This data will be used for both between-subject and within-subject analyses.

Table 3. Saline/Methamphetamine Infusion Session Schedule			
Study Phase	**Session Number**	**Study Day**	**Infusion**
Baseline	Session 1	-3	Saline followed by 15 mg methamphetamine
Baseline	Session 2	-2	Saline followed by 30 mg methamphetamine
OROS-MPH 72 mg or Placebo Control Daily Administration	Session 3	7	Saline followed by 15 mg methamphetamine
OROS-MPH 72 mg or Placebo Control Daily Administration	Session 4	8	Saline followed by 30 mg methamphetamine

12.4.2 Conduct of Methamphetamine/Saline Infusion Sessions

Each i.v. infusion will be administered over a 2-minute duration by a study physician. The saline infusion will occur at approximately 12:00 noon. The timing of the infusion session should be scheduled to occur as close to 5 hours after the morning dose of OROS-MPH/placebo as possible. The methamphetamine infusion, 15 or 30 mg, will occur one hour after the saline infusion. The timing of the dosing of the OROS-MPH/placebo and methamphetamine infusions should remain the same for each series of sessions for an individual.

Subjects will receive a clinic meal prior to test session initiation, but will not be allowed to eat within the hour prior to the infusion until after the entire session. Cigarette-smoking is permitted in the DecisionLine facility but will be actively discouraged at the CinARC facility. Cigarette-smoking subjects may not smoke from 1-hour prior to infusion session initiation until 90 minutes after the infusion. Smoking is not permitted within 15 minutes of scheduled vital sign measurements. Cigarette smoking subjects at CinARC will be offered the nicotine patch, which will be removed from 1-hour prior to infusion session initiation until 90 minutes after the infusion, and 15 minutes before scheduled vital sign measurements outside infusion sessions.

Before and after each i.v. infusion, the subject's physiologic responses will be closely monitored using either continuous or repeated HR, BP, and ECG readings. In addition, for 4 hours after the completion of each methamphetamine infusion, a cardiologist (or other designated physician during the final hour) must be available who can respond if medical intervention is warranted. Blood for methamphetamine PK will be drawn during infusion sessions #2 and #4. A complete schedule of activities for infusion sessions is presented in **Table 4**. Blood draws for PK samples should be drawn as close as possible to the scheduled times provided in **Table 4**. The times indicated in this table are target times and the associated activities should be performed as close as possible to the target times. The actual times will be recorded on the study CRFs.

Table 4. Saline/Methamphetamine Infusion Sessions Daily Schedule								
Approximate Time Point	**BP, HR**	**Oral Temp**	**12-lead ECG**	**VAS**	**ARCI**	**SDV**	**Blood for OROS-MPH level[a]**	**Blood for Meth PK[b]**
Between 6 and 7 a.m.	Insert catheter (catheter can be left in place between sessions)							
	X						X	
7 a.m.	Administer OROS-MPH or placebo **(sessions #3 and #4)** Note: OROS-MPH administration should be scheduled to occur 5 hours before the time planned to start the saline infusion.							
8 a.m.							X	
8:05 a.m.	Urine Drug Screen							
The following should start at approximately 11:35 a.m. Times shown are relative to the start of saline administration. The order in which assessments occur when scheduled for the same approximate time are: HR > BP > ECG > Oral Temperature > VAS > ARCI > SDV > Blood draw.								
	Start continuous monitoring of ECG, BP, and HR							
-25 min	X	X						
-15 min	X		X	X	X			
Time 0 12:00 p.m.	Inject saline 2 min i.v. infusion							
3 min	X							
5 min								
6 min	X							
9 min	X							
10 min				X				
12 min	X							
15 min	X							
20 min	X			X				
30 min	X	X	X	X	X			
45 min	X							
50 min				X				
55 min	X	X					X	X
The methamphetamine infusion should begin one hour after the start of the saline infusion. Times that follow are relative to the start of the methamphetamine infusion.								
0 min 1:00 p.m.	Inject methamphetamine 2 min i.v. infusion							
3 min	X							
5 min								X
6 min	X							
9 min	X							
10 min				X				
12 min	X							
15 min	X							X

Table 4. Saline/Methamphetamine Infusion Sessions Daily Schedule								
Approximate Time Point	**BP, HR**	**Oral Temp**	**12-lead ECG**	**VAS**	**ARCI**	**SDV**	**Blood for OROS-MPH level[a]**	**Blood for Meth PK[b]**
20 min	X			X				
30 min	X	X	X	X	X			X
45 min	X							
60 min	X	X	X	X				X
End continuous monitoring of ECG, BP, and HR								
90 min	X			X				
120 min	X			X				X
150 min	X			X				
180 min	X			X				X
210 min	X			X				
240 min	X			X				X
300 min	X			X				
360 min	X			X				X
420 min	X			X				
480 min	X			X		X		X
10 hr 11:00 p.m.	X							
12 hr 1:00 a.m.	X							X
24 hr 1:00 p.m.	X[c]							X
36 hr 1:00 a.m.								X
48 hr 1:00 p.m.	X[c]							X

[a]Blood for OROS-MPH level PK will only be drawn during sessions #3 and #4.
[b]Blood for Methamphetamine PK will only be drawn during sessions #2 and #4.
[c]These measurements only made during sessions #2 and #4.

12.4.3 Safety Precautions

A physician will perform the infusions and will be present at least 60 minutes after the methamphetamine infusions and will remain until vital signs are stabilized. The physician may leave the room, if the subject's vital signs are stabilized, but will remain nearby and available by pager for prompt response, if needed, for at least four hours post-infusion. If a subject demonstrates a significant adverse reaction to methamphetamine, he or she will be evaluated according to the stopping criteria outlined in sections 12.4.4 and 12.4.5 and appropriate action taken.

12.4.4 Stopping Criteria for Further Methamphetamine Infusion

A given methamphetamine i.v. administration will be discontinued if any of the following events occurs:

1. Systolic BP > 185 mm Hg;
2. Diastolic BP > 110 mm Hg;
3. Heart rate > 130 bpm;
4. Behavioral manifestation of methamphetamine toxicity, e.g., agitation, psychosis, inability to comply with study procedures.
5. A QT of >470 msec or a QTc of >470 msec for both males and females.

If the infusion is stopped during sessions #1 and #3, when the 15 mg dose of methamphetamine is being administered, safety data and psychological measures will be collected as scheduled (if possible) and the subject may continue in the study, at the discretion of the investigator, unless criteria for stopping further study participation are met. If the infusion is stopped during sessions #2 and #4, when the 30 mg dose of methamphetamine is being administered, blood for PK assessments will not be collected, but appropriate safety monitoring will be conducted until the subject has been stabilized. Subjects who do not receive the full dose of methamphetamine during infusion sessions #2 and #4, will be replaced.

12.4.5 Stopping Criteria for Further Study Participation

Subject participation will be terminated if any of the following events occur:

1. Stopping criteria for further methamphetamine infusion do not return to acceptable limits listed in the previous section (**Section 12.4.4**) within an appropriate time frame (e.g., 30 minutes).
2. Stopping criteria for further methamphetamine infusion are met for a second infusion within the protocol.
3. The subject does not receive the full 30 mg dose of methamphetamine during infusion sessions #2 and #4.
4. Systolic BP > 200 mm Hg sustained for 5 minutes or more.
5. Diastolic BP > 120 mm Hg sustained for 5 minutes or more.
6. Heart rate > (220 – age) x 0.85 bpm sustained for 5 minutes or more.
7. A clinically significant ECG abnormality, such as:
    - ST segment elevations in two or more contiguous leads of greater than 0.1 mV.
    - ST segment depression of greater than 1 mm that are flat or down-sloping at 80 msec after the J point.
    - New bundle branch block.
    - Mobitz II second or third degree heart block.
    - Atrial fibrillation or atrial flutter or activation of any tachyarrhythmia for greater than 10 seconds.
    - A QT of >470 msec or a QTc of >470 msec for both males and females.
    - Three or more consecutive ectopic ventricular complexes at a rate of greater than 100 per minute

8. Any condition that in the clinical judgment of the investigator is of sufficient magnitude to present a danger to the subject.
9. The subject cannot tolerate all doses of OROS-MPH.

12.4.6 Concomitant Medication Use

Subjects will not be allowed to take concomitant medications, whether prescription or over the counter (OTC), without the permission of a Study Physician. Specific medications that will be excluded are:

- Antidepressants including MAO inhibitors, tricyclics and selective serotonin reuptake inhibitors
- Amphetamine (Adderall, Dexedrine, Dextrostat, and other amphetamine formulations), atomoxetine, modafinil, buproprion, ephedrine (including pseudoephedrine, and herbal/dietary supplements containing Ephedra, i.e., Ma huang), or any other stimulant formulations
- Coumarin anticoagulants
- Clonidine
- Anticonvulsants (e.g., phenobarbital, phenytoin, primidone)
- Neuroleptics
- Psychotropics
- Systemic corticosteroids
- Xanthines (i.e., theophilline, theophilline sodium glycinate and aminophylline)
- Stimulants and medications that interfere with methamphetamine detection in urine samples (e.g. ephedrine and pseudoephedrine)
- Drugs that lower seizure threshold

Drugs that are vasopressor agents should be used cautiously. If the participant is using a hormone-based contraceptive, medications that may affect its action should be used cautiously.

12.4.7 Clinic Discharge and Follow-up

Subjects will be discharged from the clinic on Study Day 10. Subjects will be asked to return to the clinic for two follow-up visits following completion of the residential phase of the study, on Days 20 ± 2 and 27 ± 2, preferably as early in each visit window as possible. These visits will permit monitoring of safety outcomes.

12.4.8 Volunteer Discontinuation

Subjects will be excluded or discharged if their behavior is disruptive, noncompliant with study procedures, or otherwise not consistent with remaining in the clinic. Subjects will be discontinued if the urine drug screen indicates illicit use of illegal or legal drugs that are not allowed on this study during participation in this protocol. Subjects who do not tolerate investigational products in accordance with the criteria in Sections 12.4.4 and 12.4.5 will be discontinued from the study and a replacement subject will be randomized. In addition, subjects will be discontinued, if in the opinion of the site Principal Investigator, continued participation in

the study puts the subject at risk due to AEs or other medical conditions that emerge during the study.

12.4.9 Off-unit Passes

Subjects will normally reside full-time in the clinic throughout the inpatient portion of their study participation. In extraordinary cases, subjects may be allowed a pass for the shortest period feasible at the investigator's discretion. Subjects must agree to provide urine for drug screening upon return. Any trips outside the clinic should be in the company of a study staff member.

12.4.10 Subject Payment

Subject payment will be determined by local site IRB/REB requirements, which can change and are likely be combinations of cash and vouchers. A specific amount will be paid for the initial screen, completion of the intake screening assessments, and a completion bonus if all follow-up visits have been met. A daily rate of compensation will be approved by the local IRB/REB for the inpatient portion of the study. A completion bonus may be included to encourage subjects to complete the study and to remain for the full duration of safety monitoring. Subjects who drop out or are discontinued after initiating the study, i.e., beginning the inpatient portion of the study, will be paid on a prorated basis according to the length of their stay in the clinic and any follow-up visit attended, but will not receive the completion bonus.

Subjects will not receive the entire payment for the in-patient portion of the study at one time, but in several payments over several days or weeks after study completion. The full payment will be completed within a month after discharge.

13 CLINICAL AND LABORATORY EVALUATIONS

Table 5 summarizes the timing of the clinical activities and assessments to be conducted over the entire study period.

13.1 Screening

Screening evaluations will be performed initially before clinic intake with some assessments conducted after intake.

Outpatient Screening Assessments:

1. Informed consent;
2. Locator form;
3. Demographics information;
4. TLFB for methamphetamine use for the prior 6 weeks;
5. Drug use and treatment history;
6. Urine drug screen for benzodiazepines, opiates, cocaine, and methamphetamine (this test will be repeated until a methamphetamine positive test is obtained within 30 days prior to intake);
7. 12-lead ECG, vital signs (HR, BP, oral temperature, and respiratory rate);
8. Serum pregnancy test for all women;
9. Physical exam (including height and weight) and medical/psychiatric history;

10. Prior medication use for the 30 days prior to signing consent;
11. Hematology;
12. Blood chemistries;
13. Medical urinalysis;
14. MINI for methamphetamine abuse/dependence;
15. HIV test (optional);
16. Infectious disease panel.

Inpatient Screening Assessments:

1. Intake form;
2. Review of medical history;
3. Review of prior medication use;
4. Urine drug screen for benzodiazepines, opiates, cocaine, and methamphetamine;
5. TLFB for methamphetamine use for interval between first assessment and intake;
6. Urine pregnancy test for all women.
7. Vital signs (BP and HR).

13.2 Evaluations During the Inpatient Phase of Study

The following describes the inpatient assessments to be performed during the study, with the exception of those addressed in **Table 4** that are performed during the infusion sessions.

1. A urine drug screen use will be performed once daily (approximately 8 a.m.) to monitor illicit drug use other than investigational methamphetamine administration.
2. AEs will be monitored daily starting immediately after the placement of the catheter for the first saline infusion at baseline and continuing daily while in the clinic.
3. Blood chemistries, hematology, and medical urinalysis will be performed on Days 2 and 10.
4. Vital signs (HR and BP) will be monitored (daily).
5. Vital signs (HR, BP, oral temperature, and respiration rate) and 12-lead ECG will be taken before clinic discharge, Day 10.
6. Concomitant medication use will be recorded daily.
7. Blood will be collected for OROS-MPH levels (no more than one hour before OROS-MPH dosing and 1 and 6 hours after dosing) on Days 2, 4, 6, 7, and 8.
8. Women will have a urine pregnancy test performed on Day 1 prior to dosing and before clinic discharge, Day 10.
9. Locator form is updated on Day 10, before clinic discharge.
10. Training and practice for the (self-administered) pharmacodynamic measures (VAS, SDV, and ARCI) will be administered on day -5 or day -4.

13.3 Tabulation of Blood Collections During the Study

Table 6 summarizes the timing, types of specimens collected, and the volume of blood collected throughout the entire study from screening through clinic discharge. Additional blood may be collected to repeat clinical laboratory studies, if needed.

Table 5: Time and Events Schedule																	
Study Phase	**Screening**	**CI[a]**	**Baseline Infusions**			**OROS-MPH Dosing Infusions**										**Follow-up**	
Study Day	**-33 to -4**	**-5 or -4**	**-3**	**-2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**20 ± 2**	**27 ± 2**
Informed Consent	X																
Locator Form	X														X		
Demographics	X																
TLFB for Methamphetamine Use	X	X															
Drug Use and Treatment History	X																
12-lead ECG	X														X		
MINI	X																
Medical/Psychiatric History	X	X															
Physical Exam	X																
Height and Weight	X														X	X	X
Vital Signs (BP & HR)	X	X	X[c]	X[c]	X	X	X	X	X	X	X	X[c]	X[c]	X	X		
Vital Signs (Oral temp. & Respiration Rate)	X														X		
Blood Chemistries and Hematology	X						X								X		
Medical Urinalysis	X						X								X		
Pregnancy Test[b]	X	X				X									X	X	
Infectious Disease Panel/ HIV Test (optional)	X																
Urine Drug Screen	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Training/Practice on PD Assessments[d]		X															
Randomization						**X**											
OROS-MPH or Placebo Administration						X	X	X	X	X	X	X	X	X			
OROS-MPH Blood levels							3X		3X		3X	3X	3X				
Adverse Events			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prior and Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Methamphetamine Infusion Sessions			**1**	**2**								**3**	**4**				
Saline then 15 mg Methamphetamine i.v.			X									X					
Saline then 30 mg Methamphetamine i.v.				X									X				
VAS			19X	19X								19X	19X				

Table 5: Time and Events Schedule																	
Study Phase	**Screening**	**CI[a]**	**Baseline Infusions**			**OROS-MPH Dosing Infusions**										**Follow-up**	
Study Day	**-33 to -4**	**-5 or -4**	**-3**	**-2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**20 ± 2**	**27 ± 2**
ARCI			3X	3X								3X	3X				
SDV			X	X								X	X				
Continuous BP, HR, ECG Monitoring			X	X								X	X				
Intermittent ECG Data Recording			4X	4X								4X	4X				
Intermittent BP, HR Data Recording			32X	33X	2X	1X						32X	33X	2X	1X		
Oral Temperature			4X	4X								4X	4X				
Methamphetamine Blood PK				10X[e]	2X[e]	2X[e]							10X[e]	2X[e]	2X[e]		

[a] Clinic intake.
[b] A serum pregnancy test is performed during screening with a urine test performed thereafter.
[c] The first vital signs measurement taken on infusion days will be summarized as part of the daily reporting of vital signs.
[d] The Training and Practice session on PD assessments (VAS, ARCI, SDV) will be administered before the first baseline infusion (Day -5 or Day -4).
[e] Blood for methamphetamine PK is collected approximately 5 min before and 5, 15, 30, 60 min, and 2 hr, 3 hr, 4 hr, 6 hr, 8 hr, 12 hr, 24 hr, 36 hr, and 48 hr the start of the methamphetamine infusion.

Table 6: Schedule of Blood Collections[a]											
Assessment	**Estimated Blood Volume**	**Type**	**Screening**	**Baseline Infusion Day -2 to Day -1**	**Day 2**	**Day 4**	**Day 6**	**Day 7**	**OROS-MPH Dosing Infusion Day 8 to Day 10**	**Discharge Day 10**	**Total Blood Volume**
Hematology	8 mL	E	1X	ND	1X	ND	ND	ND	ND	1X	24 mL
Chemistry	8 mL	S	1X	ND	1X	ND	ND	ND	ND	1X	24 mL
Infectious Disease Screen	8 mL	S	1X	ND	ND	ND	ND	ND	ND	ND	8 mL
Serum pregnancy test	5 mL	S	1X								5 mL
OROS-MPH Blood Level[b]	5 mL	H	ND	ND	3X	3X	3X	3X	D8 - 3X [b]	ND	75 mL
Methamphetamine PK[c]	3 mL	H	ND	D-2 to D-1 14X	ND	ND	ND	ND	D8 to D10 14X	ND	84 mL
										Grand Total	**220 mL**

[a] Abbreviations: E= EDTA; H = heparin; S = serum; ND = No sample collected; D = Study Day

[b] Three samples per day: 1) approximately 7:00 a.m. before OROS-MPH administration for trough levels; 2) approximately 8:00, one hour after OROS-MPH administration; and 3) approximately 12:55 p.m., six hours after for peak levels.

[c] Blood for methamphetamine PK is collected at 55 min after the saline infusion, then at 5 min, 15 min, 30 min, 60 min, 120 min, 180 min, 240 min, 360 min, 480 min and 12 hr, 24 hr, 36 hr, and 48 hr after the methamphetamine infusion on Days – 2 to -1 and 8 to 10.

13.4 Evaluations at Follow-up

AEs and medication use will be recorded at both follow-up visits. In addition, a urine pregnancy test will be performed at one of the follow-up visits.

14 ASSESSMENT METHODS

14.1 Locator Form

A locator form will be used to assist in finding subjects at follow-up. This form asks subjects to give consent for follow-up and to provide names, addresses, and phone numbers of several friends and family members. This information is essential and will be collected during screening, and will be updated throughout the study as necessary. The information will be checked prior to clinic discharge on Day 10.

14.2 Timeline Followback (TLFB)

Detailed histories of methamphetamine use over the past 6 weeks prior to screening as well as during the period between the initial clinic screening assessment and the time of clinic intake will be obtained using the TLFB method. The TLFB method was described and validated for reporting alcohol use (Sobell, Sobell et al. 1986). It has also been found to be a reliable method for assessing the history of psychoactive substance use in drug-abusing populations (Fals-Stewart, O'Farrell et al. 2000).

14.3 MINI

The Mini-International Neuropsychiatric Interview (MINI) is a short structured diagnostic interview, developed jointly by psychiatrists and clinicians in the United States and Europe, for DSM-IV and ICD-10 psychiatric disorders (Sheehan, Lecrubier et al. 1998). With an administration time of approximately 15 minutes, it was designed to meet the need for a short but accurate structured psychiatric interview for multicenter clinical trials and epidemiology studies and to be used as a first step in outcome tracking in nonresearch clinical settings.

14.4 Physical Exam

A physical exam of the oral cavity, head, eyes, ears, nose, and throat, cardiovascular system, lungs, abdomen (liver/spleen), extremities, skin, neuropsychiatric mental status and sensory/motor status, musculoskeletal system and general appearance will be performed during screening. Height and weight will be recorded during screening, at clinic discharge, and at follow-up.

14.5 Medical/Psychiatric History

To monitor the physical and mental health of all potential study subjects, health profiles and medical/psychiatric history will be collected during screening and reviewed again at clinic intake. Subjects will specifically be asked about history of violence, or homicidal or suicidal thoughts, including those which occur only after taking methamphetamine.

14.6 Vital Signs

Vital signs to be assessed during screening and discharge include oral temperature, sitting BP, HR, and respiratory rate. In addition, BP and HR will be taken daily after clinic intake. **Table 4** shows the schedule for collection of vital signs (BP, HR, and oral temperature) during infusion sessions.

14.7 Eligibility Checklist

The Eligibility Checklist must be completed prior to the subject receiving the first study infusion. This form will document final eligibility and, if applicable, the reason the subject was not eligible for study participation.

14.8 Urine Drug Screen

A urine drug screen for opiates, cocaine, benzodiazepines, and methamphetamine will be performed during screening and will be monitored once daily (preferably in the morning) using an onsite qualitative urine test device. The daily assessments should occur at approximately the same time each day, i.e., within a two-hour interval. The onsite test device indicates the presence/absence of all those abused drugs at once using a non-quantitative antibody test. There are circumstances (use of over the counter drugs or carryover after methamphetamine infusions) that lead to false positives. Therefore, methamphetamine positive tests can be sent to analytical lab for chemical determination of the amount of drug present if the investigator suspects that the subject has used methamphetamine outside of infusion sessions. The test will be considered positive if methamphetamine is $\geq$ 500 ng/mL.

14.9 Hematology

Blood will be collected in anticoagulant containing tubes (e.g., Vacutainer^{TM}) for hematologic assessments. Analysis of hemoglobin, hematocrit, mean corpuscular volume, white blood cell count, differential white blood cell count, and platelet count will be performed. Analyses will be performed in the institution's clinical laboratory. The laboratory performing these assessments should be either directly regulated by the College of Pathologists (CAP) or the Clinical Laboratory Improvement Act of 1988 (CLIA) or indirectly according to CLIA guidelines. The laboratory will need to provide a copy of current certification.

14.10 Blood Chemistries

Blood will be collected in a serum separation evacuated venous blood collection tubes (e.g., Vacutainer^{TM}) and serum separated according to standard procedures. Quantitative analysis will be performed for the following analytes: creatinine, blood urea nitrogen (BUN), glucose, creatinine phosphokinase (CPK), lactate dehydrogenase (LDH), electrolytes (Na, K, Cl, HCO_3), and liver function tests [total bilirubin, aspartate aminotransferase (AST/SGOT), alanine aminotransferase (ALT/SGPT), and alkaline phosphatase]. The laboratory performing these assessments should be either directly regulated by CAP or CLIA or indirectly according to CLIA guidelines. The laboratory will need to provide a copy of current certification.

14.11 Medical Urinalysis

Urine will be collected and analyzed for specific gravity, pH, blood, protein, glucose, ketones, leukocytes, and nitrites at the local site's clinical laboratory.

14.12 Pregnancy Test

An FDA approved serum (screening) or urine (all other time points) pregnancy test designed to measure human chorionic gonadotropin will be used.

14.13 HIV Test

During screening all subjects will be offered the opportunity to have an HIV test performed. This test is not requisite for study participation. Subjects may be tested at the clinical site or may be referred to another clinic for testing and education on HIV risk-behaviors. If the test is to be performed by the clinical site, a separate HIV test informed consent must be obtained before collecting blood for this test. An HIV antibody test will be performed on a serum sample collected from the subject after the HIV informed consent form is signed. This serum sample could be part of the infectious disease panel sample.

14.14 Infectious Disease Panel

During screening, blood will be collected in a serum separation evacuated venous blood collection tubes (e.g., Vacutainer^{TM}) and serum separated according to standard procedures. Qualitative analysis reporting positive/negative results will be performed for the following analytes: Hepatitis B surface antigen, Hepatitis B surface antibody, Hepatitis B core antibody, and Hepatitis C virus antibody. A purified protein derivative (PPD) skin test for tuberculosis will be performed, and if positive, a chest x-ray is required to assess active tuberculosis. If the subject reports that they have been previously positive for the PPD test, the PPD test will not be performed and a chest x-ray will be required. An RPR test for syphilis will be performed. If positive, subjects must be referred for appropriate follow-up and/or treatment. If treatment is required, it must be completed prior to the start of the inpatient phase of the study. Documentation of appropriate follow-up and/or treatment is required for subjects to be considered eligible for the study. Subjects may continue to be screened while the evaluation process is ongoing.

14.15 Monitoring and Assessments During Methamphetamine Infusions

14.15.1 Blood Sample Collections

A schedule of blood collections and volumes is provided in **Table 6** including collection of samples for methamphetamine PK, OROS-MPH blood levels, hematology, blood chemistry, serum pregnancy, and infectious disease screening assays. Blood samples collected for methamphetamine and OROS-MPH PK analysis will be prepared and shipped according to the instructions in **Appendix I** for analysis at a central laboratory.

An i.v. catheter will be inserted for each infusion session, and maintained in place for the duration of the infusion sessions, if the subject wishes. Two i.v. catheters will be placed for infusion sessions that involve repeated blood draws: one will be for methamphetamine or saline administration, the other for blood sample collection.

Samples will be collected for assessment of methamphetamine PK at baseline and during infusion sessions when OROS-MPH is administered and for MPH peak and trough levels during days when MPH is administered (Study Days 2, 4, 6, 7, and 8).

14.15.2 ECG, BP, and HR Monitoring

Before and after each i.v. infusion, the subject's physiologic response will be closely monitored using continuous and intermittent HR, BP, and ECG readings. Continuous monitoring by telemetry will start approximately 25 minutes before and will continue for 60 minutes after the last infusion of the day. BP and HR will be recorded at 25 and 15 minutes before, and 3, 6, 9, 12, 15, 20, 30, 45, and 55 minutes after saline infusion, and 3, 6, 9, 12, 15, 20, 30, 45, 60 minutes following the methamphetamine infusion. In addition, BP and HR will be taken and recorded at 90, 120, 150, 180, 210, 240, 300, 360, 420, 480 minutes, and 10 and 12 hours following methamphetamine infusions. ECG will be monitored continuously beginning 15 minutes before the saline infusion and will continue for until 60 minutes after the start of the methamphetamine infusion. ECG parameters will be recorded 15 minutes before the start of the saline infusion, 30 minutes after the saline and methamphetamine infusions, and finally 60 minutes after the methamphetamine infusion.

14.15.3 Pharmacodynamic (PD) Measures (VAS, ARCI, and SDV)

During and after the infusions, subject's subjective response to the methamphetamine will be closely monitored. Pharmacodynamic self-administered assessments will be performed using lap-top computers and validated software (Scheduled Measurement System (SMS) Version 6.2, DecisionLine Clinical Research Corporation). All subjects will receive training and practice on the PD measures.

VAS: Computerized VAS will be administered 15 minutes before, and 10, 20, 30, and 50 minutes after the start of the saline infusion, and 10, 20, 30, 60, 90, 120, 150, 180, 210, 240, 300, 360, 420, 480 minutes following the start of the methamphetamine infusion. For the VAS scales, subjects will report the degree to which they feel "any effects", "high", "good effects", "bad effects", "like methamphetamine", "desire for methamphetamine", "depression", "anxiety", "over stimulated", and "drug liking" on a continuous scale digitized between 0 to 100 for computing a score. Note that scales that refer specifically to drug (i.e., Good Drug Effects, Bad Drug Effects, Any Drugs Effects, Drug Liking; Anxiety; Like methamphetamine; Desire for methamphetamine) are not administered pre-dose. Details of the VAS are provided in **Appendix IV**.

ARCI: A computerized ARCI will be administered 15 minutes before the start of the saline infusion and at 30 minutes after each saline and methamphetamine infusion. The ARCI consists of 49 statements in a true/false format.(Martin, Sloan et al. 1971) In the computerized version, the subject selects the appropriate response with a mouse click. Details of the ARCI are provided in **Appendix V**.

SDV: The SDV involves a series of independent, theoretical forced choices between the drug administered and different monetary values. Subjects are asked to choose between receiving another dose of the same drug to take home or an envelope containing a specified amount of money, but they do not receive either the drug or the money described in the choices. Depending

on the answer to each question, the monetary value in the next question is either higher or lower. At the end of the procedure (generally 6 questions), the procedure estimates the crossover point at which the subject is indifferent between choosing drug and choosing money. The crossover point is the proxy index of reinforcing efficacy that will be used as an outcome measure for estimating abuse potential. This test is adapted from a similar procedure utilized by Griffiths and colleagues (Griffiths, Troisi et al. 1993; Griffiths, Rush et al. 1996). Details of the SDV are provided in **Appendix VI**. The SDV will be administered approximately 8 hours after the start of methamphetamine infusions (Study Days -3, -2, 7, and 8).

14.15.4 Adverse Events (AEs)

AEs will be assessed once the subject signs informed consent. In addition, once a subject has been randomized and a catheter is inserted to start the saline infusions, AEs will be assessed throughout the inpatient period at least once a day. If an AE is reported to a nurse that requires medical attention, it should be reported to a study physician immediately. The investigator or study physician will assess subjects for any medical or psychiatric side effects.

14.15.5 Prior and Concomitant Medications

Prior medication use in the 30 days before the start of screening up to the day of clinic intake and concomitant medication use throughout the study will be assessed by an investigative staff member. Any medications to be taken during the study must be approved by a study physician.

14.15.6 Clinic Discharge Form

The Clinic Discharge CRF will document all data relevant to subject discharge from the clinic: reason for discharge (i.e., completion of in-patient portion of the study, or early termination from the study), date of discharge, and study day of discharge.

15 REGULATORY AND REPORTING REQUIREMENTS

15.1 GOOD CLINICAL PRACTICES

This study will be conducted in accordance with the most current version of the International Conference on Harmonization Guidance Document E6: Good Clinical Practices: Consolidated Guideline. An Operations Manual will be provided to all investigational sites as a study quality assurance tool.

15.2 FDA FORM 1572

Each site's Principal Investigator will sign a Statement of Investigator (FDA Form 1572) prior to initiating this study which will be updated as needed.

15.3 IRB/REB APPROVAL

Prior to initiating the study, each site's Principal Investigator will obtain written approval from the appropriate IRB or REB to conduct the study. Should changes to the study protocol become necessary, protocol amendments will be submitted in writing to the local IRB/REB by the site Principal Investigator for IRB/REB approval prior to implementation. In addition, NIDA and the local IRB/REB will approve all advertising materials used for subject recruitment and any

educational materials given to the subject. Progress reports will be submitted to the local IRB/REB annually or at a frequency requested by the IRB/REB.

15.4 INFORMED CONSENT

All potential subjects for the study will be given a current copy of the Informed Consent Form to read and take home. All aspects of the study will be explained in lay language. Subjects who refuse to participate or who withdraw from the study also will be assisted in finding other sources of treatment without prejudice. All study subjects will be given a copy of the signed informed consent(s).

15.5 DRUG ACCOUNTABILITY

Upon receipt, the investigator/research pharmacist is responsible for taking inventory of the investigational products. A record of this inventory must be kept and usage must be documented. Any unused or expired investigational products shall be returned to NIDA (or designee) unless otherwise instructed. OROS-MPH is a Schedule II controlled substance and will be handled appropriately. In addition, standard narcotics control procedures will govern access to and appropriate disposal procedures for methamphetamine.

15.6 OUTSIDE MONITORING

Data and Safety Monitoring Board: Quarterly safety data will be submitted to the Data and Safety Monitoring Board (DSMB) for review or more often if the board deems necessary. The board will be blinded to subjects' actual group assignments but may request that the blind be broken by the data center, if concerns arise from the blinded data.

Medical Monitor: A medical monitor has been appointed for the study. The medical monitor will be available for making recommendations to the investigator and the Sponsor-Investigator on the severity of any SAEs, the relatedness to the study interventions, and for determining if the SAE should be reported to the FDA and Health Canada in a 7 or 15 day expedited report or an annual report. The medical monitor will also be responsible for tracking and assessing trends in the AEs reported. In the event that the medical monitor and investigator do not concur on SAE evaluations, both opinions will be reported to the FDA/Health Canada.

Clinical Monitors: All investigators will allow representatives of the Sponsor-Investigator and NIDA to periodically monitor, at mutually convenient times during and after the study, all CRFs and corresponding source documents for each subject. These monitoring visits provide the Sponsor-Investigator with the opportunity to evaluate the progress of the study and to inform the Sponsor-Investigator of potential problems. The monitors will assure that submitted data are accurate and in agreement with source documentation; verify that investigational products are properly stored and accounted for, verify that subjects' consent for study participation has been properly obtained and documented, confirm that research subjects entered into the study meet inclusion and exclusion criteria, and assure that all essential documentation required by Good Clinical Practices (GCP) guidelines are appropriately filed.

Monitors will conduct a site initiation visit prior to the start of the study. At this visit, they will assure that proper study-related documentation exists, assist in training investigators and other

site personnel in study procedures and GCP guidelines, confirm receipt of study supplies, and assure that acceptable facilities and staff are available to conduct the study.

Routine monitoring visits by NIDA and/or the Sponsor-Investigator's representatives will be scheduled at appropriate intervals but probably more frequently at the beginning of the study. A monitoring visit soon after the first two subjects have been randomized is recommended. At these visits, the monitors will verify that study procedures are being conducted according to the protocol guidelines and will review AEs and SAEs and drug accountability. At the end of the study, they will advise on storage of study records and return of unused investigational products. All sites should anticipate visits by NIDA, the Sponsor-Investigator, and the FDA.

15.7 ADVERSE EVENTS REPORTING

In accordance with FDA reporting requirements, all AEs occurring during the course of the clinical trial will be collected, documented, and reported by the investigator or sub-investigators according to the specific instructions detailed in this section of the protocol and in **Appendix II**. The occurrence of AEs will be assessed starting when the subject is enrolled in the study (when the subject signs informed consent) and daily during the inpatient portion of the study, and at each follow-up visit.

An AE is defined as any reaction, side effect, or untoward event that occurs during the course of the clinical trial, whether or not the event is considered related to the investigational product or clinically significant. For this study, events reported by the subject, as well as clinically significant abnormal findings on physical examination or laboratory evaluation will be recorded on the AE CRF. A new illness, symptom, sign or clinically significant clinical laboratory abnormality or worsening of a pre-existing condition or abnormality is considered an AE. Stable chronic conditions, such as arthritis, which are present prior to clinical trial entry and do not worsen are not considered AEs. The AE CRF is also used to record follow-up information for unresolved events reported on previous visits.

At least once a week, a study physician must review the AE CRF(s) completed for the previous week for any events that were reported as continuing. All AEs, recorded during the inpatient portion of the study, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed by study physicians until satisfactory resolution. AEs must be reported up to 2 weeks following clinic discharge. At the follow-up visits, AEs will be recorded and followed; they will be followed to resolution only if they are serious, or if the study physician assesses them to be clinically significant.

15.8 SERIOUS ADVERSE EVENTS

Each adverse event or reaction will be classified by a study physician as being serious or non-serious. Based on the seriousness of the adverse event or reaction, appropriate reporting procedures will be followed. The Code of Federal Regulations Title 21 part 312.32 and International Conference on Harmonization (ICH) Guideline for Industry: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, ICH-E2A March 1995, as implemented by the U.S. Food and Drug Administration and Health Canada, defines a serious

adverse event (SAE) or serious adverse drug experience as any untoward medical occurrence at any dose that:

- results in death;
- is life-threatening; *(NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.)*
- requires inpatient hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability/incapacity; or
- is a congenital anomaly/birth defect.

In addition, important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug reaction, when based on appropriate medical judgment that may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in the above definition.

An unexpected adverse event is one that is not described with respect to nature, severity, or frequency in the current Investigator's Brochure or product package insert.

Reporting of AEs and SAEs is described in **Appendix II.** There can be serious consequences including ultimately, criminal and/or civil penalties for sponsors who fail to comply with FDA and Health Canada regulations governing the reporting of SAEs. The investigators in this study have the responsibility of promptly reporting all SAEs to NIDA and the Sponsor-Investigator in order that the Sponsor-Investigator can comply with these regulations.

If a study subject withdraws from the study or if an investigator decides to discontinue the subject from the study because of an SAE, the subject must have appropriate follow-up medical monitoring including, if necessary, hospitalization. Monitoring will continue until the problem prompting hospitalization has resolved or stabilized with no further change expected or is discovered to be clearly unrelated to study medication or progresses to death.

16 ANALYTICAL PLAN

16.1 Outcome Measures

16.1.1 Primary Outcome Measures

The primary objective of this study is to determine the safety of the OROS-MPH concurrent with d-methamphetamine infusions of 15 mg and 30 mg i.v. Safety outcome measures include cardiovascular responses (HR, BP, ECG), oral temperature, AEs, and clinical laboratory analyses.

16.1.2 Secondary Outcome Measures

Secondary outcome measures are intended to further explore the safety of OROS-MPH administration in combination with methamphetamine, by evaluating interactions that result in

significant changes in OROS-MPH or methamphetamine PK and to assess the effects of OROS-MPH on a variety of subjective measures. Secondary outcome measures include:

1. Peak and trough plasma levels of MPH during chronic daily administration of OROS-MPH.
2. Change in plasma levels of MPH after methamphetamine administration.
3. Blood PK parameters of d-methamphetamine including Cmax, Tmax, $AUC_{0-\infty}$, apparent $t_{½}$, CL, Vd (volume of distribution), and λz (terminal exponential coefficient).
4. Pharmacodynamic measures including VAS, ARCI, and SDV.

16.2 Analysis Plan

16.2.1 Primary Outcome Measures

Baseline (pre-methamphetamine) resting HR and BP measures will be compared to HR and BP after each infusion of saline or methamphetamine. Changes (from baseline) in HR and BP induced by methamphetamine injection along with OROS-MPH will be compared to those without OROS-MPH, by methamphetamine dose level [0 mg (saline infusion), 15 mg, and 30 mg doses), using repeated measures ANOVA in a within and between-subjects analysis. Changes in ECG parameters and oral temperature will be reported as summary statistics.

AEs will be coded using Medical Dictionary of Regulatory Affairs (MedDRA) preferred terms and presented as summary statistics organized by system, organ, and class designated of the preferred terms.

16.2.2 Secondary Outcome Measures

Plasma concentration-time profiles of d-methamphetamine after the 30 mg methamphetamine infusion will be analyzed to obtain PK parameter estimates of methamphetamine (Cmax, Tmax, $AUC_{0-\infty}$, apparent $t_{½}$, CL, Vd, and λz) by individual and means computed by group. Comparisons of PK parameter estimates of d-methamphetamine between the placebo control and OROS-MPH dosed groups will be performed using ANOVA. Comparison of the PK parameters within subjects will be also be compared using the data collected during the baseline series of infusions as compared to that collected during the infusions during OROS-MPH administration. Confidence intervals (90%) for each parameter will be determined.

Peak and trough levels in MPH will be compared using a between-subjects analysis by t-test.

Psychological outcome measures (including VAS, ARCI, and SDV) obtained during baseline infusions will be compared, by methamphetamine dose level, to those during OROS-MPH administration to determine the extent to which these measures are modified by the administration of OROS-MPH using repeated measures ANOVA (Study Days -2 and -1 versus Days 7 and 8).

Population demographics will be compiled for both groups and presented in tabular form.

16.3 Sample Size

No formal sample size analysis was performed. The number of subjects is hypothesized to provide an indication of the safety and potential interactions between OROS-MPH and methamphetamine.

17 DATA MANAGEMENT AND CASE REPORT FORMS

Data management activities and statistical analytical support will be coordinated through the Data Management Center.

17.1 Data Collection

Data will be collected at the study sites and transcribed onto CRFs. CRFs should be completed according to the instructions in the study operations manual. The site Principal Investigator is responsible for maintaining accurate, complete and up-to-date records for each subject. The site Principal Investigator is also responsible for maintaining any source documentation related to the study, including any films, tracings, computer discs or tapes.

Some assessments will be collected via computer applications (i.e., VAS, ARCI, and SDV). Electronic files will be submitted to the Data Management Center in accordance with procedures detailed in the study Procedures Manual.

17.2 Data Editing and Control

CRFs received at the Data Management Center will be reviewed. If incomplete or inaccurate data are found, a data clarification request will be forwarded to the clinical site for a response. The site will resolve data inconsistencies and errors prior to returning CRFs to the data-coordinating center. All corrections and changes to the data will be reviewed prior to being entered into the main study database.

Study monitors will routinely visit the study sites to assure that data submitted on the appropriate forms are in agreement with source documents. They will also verify that the investigational products have been properly stored and accounted for, subject informed consent for study participation has been obtained and documented, all essential documents required by Good Clinical Practice regulations are on file, and sites are conducting the study according to the research protocol. Any inconsistencies will be resolved, and any changes to the data forms will be made using the Data Management Center procedures.

17.3 Data Processing and Analyses

When the study is completed and all data have been entered into the clinical database and the database has been checked by Quality Assurance and is locked, statistical analysis of the data will be performed by the Data Management Center statisticians in accordance with the analytical plan section of this protocol. Periodically, during the investigation, data sets will be submitted to the NIDA DPMC central data repository according to procedures specified in the study operations manual.

17.4 Study Documentation and Records Retention

Study documentation includes all CRFs, data correction forms, workbooks, source documents, monitoring logs and appointment schedules, sponsor and investigator correspondence and regulatory documents (e.g., signed protocol and amendments, IRB correspondence and approved consent form and signed informed consent forms, Statement of Investigator form, and clinical supplies receipt and distribution records).

Source documents include all original recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study. Accordingly, source documents include, but are not limited to, laboratory reports, ECG tracings, X-rays, radiologist reports, subject diaries, biopsy reports, ultrasound photographs, subject progress notes, hospital charts or pharmacy records and any other similar reports or records of any procedure performed in accordance with the protocol.

Whenever possible, the original recording of an observation should be retained as the source document; however, a photocopy is acceptable provided that it is a clear, legible, and exact duplication of the original document.

Government agency regulations and directives require that the investigator must retain all study documentation pertaining to the conduct of a clinical trial. These documents must be kept for a minimum of two years after discontinuation of the IND or 2 years after the approval of an NDA.

17.5 Confidentiality

17.5.1 Confidentiality of Data

Particular attention is drawn to the regulations promulgated by the Food and Drug Administration (FDA) under the Freedom of Information Act providing, in part, that proprietary information furnished to clinical investigators and IRBs will be kept confidential by the FDA only if maintained in confidence by the clinical investigator and IRB.

By signing this protocol the investigator affirms to NIDA that information furnished to the investigator by NIDA will be maintained in confidence and such information will be divulged to the IRB, REB, or similar or expert committee; affiliated institution; and employees only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees.

17.5.2 Confidentiality of Subject Records

To maintain subject confidentiality, all laboratory specimens, CRFs, reports and other records will be identified by a coded study subject number only. Research and clinical records will be stored in a locked cabinet. Only research staff and NIDA program officials will have access to the records. Subject information will not be released without written permission, except as necessary for monitoring by the FDA, the NIDA monitoring contractor, or NIDA. NIDA will file for a certificate of confidentiality that will cover all sites participating in the study.

By signing the protocol the investigator agrees that within local regulatory restrictions and ethical considerations, NIDA or any regulatory agency may consult and/or copy study documents in order to verify CRF data.

The procedure for applying for a certificate of confidentiality is provided in **Appendix III**.

18 PUBLICATIONS OF THE STUDY RESULTS

NIDA and the investigative group agree that data will be made available to individual investigators to encourage other publications, either by a group or by an individual investigator provided that: manuscripts based on OROS-MPH interactions with methamphetamine may not be submitted for publication until the main findings of the study have been published or are in press and this study has been accepted by the FDA for filing to the IND or NDA. Review of manuscripts resulting from this study or from data generated during this study must occur according to the NIDA DPMC Publications Policy prior to submission for publication. Authorship shall be consistent with NIDA and DPMC policies.

19 SIGNATURES

NIDA REPRESENTATIVES

Typed Name	Signature	Date
Ahmed Elkashef, M.D. NIDA Investigator	_____	_____
Nora Chiang, Ph.D. NIDA Investigator	_____	_____
Ann Anderson, M.D. NIDA Investigator	_____	_____
Roberta Kahn, M.D. NIDA Medical Monitor	_____	_____
Jurij Mojsiak, M.S. NIDA Project Officer/Manager	_____	_____

INVESTIGATOR (S)

I agree to conduct this clinical study in accordance with the design and specific provisions of this protocol; deviations from the protocol are acceptable only with a mutually agreed upon protocol amendment with the IRB approval. I also agree to report all information or data in accordance with the protocol, and in particular I agree to report any serious adverse experiences as defined in section 15.8 of this protocol.

Typed Name	Signature	Date
Eugene Somoza, M.D., Ph.D.	_____	_____
Edward Sellers, M.D., Ph.D., FRCPC	_____	_____

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APPENDIX I: Procedure for Collection, Storage, and Shipping of Blood Samples for Methamphetamine/Methamphetamine Metabolite Levels and MPH Levels

Any questions about blood collection should be addressed to Dr. Nora Chiang at NIDA (301-443-5280).

Blood Drawing Procedure:

Blood drawn from all subjects should be considered infectious and extreme caution should be used to avoid needle sticks and direct contact with blood or plasma.

Using 3 cc (methamphetamine PK) or 5 cc (MPH PK) green-stoppered Vacutainer (heparinized) tubes:

(1) draw one tube of blood, filling it as completely as possible;
(2) invert 8-10 times;
(3) centrifuge the blood (3,000 x g for 15 min.) immediately to prevent hemolysis;
(4) using a disposable pipet, immediately transfer the plasma from the tubes to a single plastic plasma storage vial, and secure the cap tightly;
(5) label the vial as described below, and;
(6) freeze sample at -20 degrees C immediately afterwards in an upright position. Keep frozen until shipment.

Labeling Procedure:

Fill out a shipping/specimen inventory form. Use labels to label tubes. Use indelible black ink to write on labels. The label should include:

(1) the clinic's (site) identification or name,
(2) subject identification number, and
(3) date and time of collection.

After affixing the label to the vial, cover it with transparent tape. A record (shipping/specimen inventory form) containing the same information on the plasma samples shall be generated.

Shipping: Remember to only ship on Monday thru Wednesday. When ready to ship:

(1) line the container with an open plastic bag (12 gallon waste-container size);
(2) place approximately 10 pounds of dry ice (roughly two slabs) in the Styrofoam container, place the ice in the bottom, and compress with a hammer (Caution, do not touch dry ice with your bare hands);
(3) cover the dry ice with a layer of newspaper (2-3 sheets folded);
(4) put each vial of plasma into a ziplock bag, each of which should contain an absorbent pack;
(5) place the plasma vials in the Styrofoam container;
(6) then fill the remaining space with crumpled newspaper or other shipping filler;
(7) close the container and place it into the outer cardboard container;
(8) place completed sample I.D. list in envelope and include in cardboard container;
(9) ship to the University of Utah; and
(10) notify personnel (Ms. Bobbie Smith or Dr. David Moody) at the Center for Human Toxicology, University of Utah (801) 581-5117 before samples are shipped.

Shipping Address:

Attn: Bobbie Smith
Center for Human Toxicology
417 Wakara Way, Suite 2111
University of Utah
Salt Lake City, UT 84108

Supplies Needed:

- Outer shipping container (a insulated styrofoam container)
- Cardboard box to place container into
- 3 cc heparinized blood drawing tubes
- 5 cc heparinized blood drawing tubes
- Disposable transfer pipettes
- 3-5 cc plastic vial to store plasma
- Adhesive labels for vials
- ziplock bag with absorbent pad for each vial
- newspaper and dry ice (day of shipping)

APPENDIX II:

Instructions for Evaluating and Reporting Adverse Events and Serious Adverse Events

A. GENERAL INSTRUCTIONS

1. AEs will be recorded once the subject signs informed consent.

2. AEs will be recorded on an AE CRF and will be reviewed at least weekly by a study physician.

3. Report the severity of the event following the guidance in section B below.

4. Report the relatedness of the event to the investigational product administration according to the guidance in section C.

B. DEFINITIONS – SEVERITY OF EVENTS

Mild:	Awareness of symptom, but easily tolerated.
Moderate:	Discomfort enough to cause interference with usual activity.
Severe:	Incapacitating with inability to work or do usual activity.

C. DEFINITIONS – RELATEDNESS OF EVENTS

The study physician is responsible for defining, in his/her best judgment, the relationship of the AE/SAE to the investigational product. The degree of certainty for which the AE/SAE is attributed to the investigational product or alternative causes (e.g. natural history of the underlying disease, concomitant therapies, etc.) should be determined by how well the experience can be understood in terms of one or more of the following:

- ***Exposure:*** Is there evidence that the subject was actually exposed to the investigational product?

- ***Timing of the administration of investigational product:*** Did the AE/SAE follow in a reasonable temporal sequence from administration of the investigational product?

- ***Consistency with investigational product safety profile:*** Known pharmacology and toxicology of the investigational product in animals and man; reaction of similar nature having been previously described with the investigational product.

- ***Alternative explanations*** for the adverse event such as concomitant medications, concurrent illness, non-medicinal therapies, diagnostic tests, procedures or other confounding findings.

- ***Response to discontinuation*** of the investigational product.

Terms and definitions to be used in assessing the investigational product relationship to the AE/SAE are:

- ***Unknown:***
  Use this category only if the cause of the AE/SAE is not possible to determine

- ***Definitely Not Related:***
  The subject did not receive investigational product, the temporal sequence of the AE/SAE onset relative to administration of the investigational product is not reasonable, or there is another obvious cause of the AE/SAE.

- ***Remotely Related:***
  There is evidence of exposure to the investigational product or there is another more likely cause of the AE/SAE.

- ***Possibly Related:***
  There is evidence of exposure to the investigational product, the temporal sequence of the AE/SAE onset relative to administration of the investigational product is reasonable, but the AE/SAE could have been due to another equally likely cause.

- ***Probably Related:***
  There is evidence of exposure to the investigational product, the temporal sequence of the AE/SAE onset relative to administration of the investigational productis reasonable, and the AE/SAE is more likely explained by the investigational product than by any other cause.

- ***Definitely Related:***
  There is evidence of exposure to the investigational product, the temporal sequence of the AE/SAE onset relative to administration of the investigational product is reasonable, the AE/SAE is more likely explained by the investigational product than by any other cause, and the AE/SAE shows a pattern consistent with previous knowledge of the investigational product or investigational product class.

D. SPECIFIC INSTRUCTIONS – LABORATORY/ECG ADVERSE EVENT

A laboratory or ECG AE is any clinically significant worsening in a test variable that occurs during the course of the study, whether or not considered to be investigational product related. For each such change, provide the information requested on date of test, severity, likelihood of a relationship to investigational product, change in investigational product dosage due to the AE, and treatment required.

All laboratory AEs should be specified as an increased or decreased test result (e.g. “increased glucose”, “decreased potassium”) or as a term that implies an abnormality (e.g., hypercalcemia, azotemia, hypokalemia, or bradycardia). Any abnormal laboratory value that is considered not

clinically significant will be recorded as such on the clinical laboratory report CRF along with a comment providing justification for that determination.

E. SERIOUS ADVERSE EVENT AND UNEXPECTED ADVERSE EVENT REPORTING

24 hour Reporting Requirements

Any serious adverse event, including death due to any cause, which occurs to any subject from the time of admission through discharge whether or not related to the investigational product, must be reported ***within 24 hours*** to the NIDA Medical Monitor, the NIDA Project Officer, the NIDA Project Manager, and the Sponsor-Investigator.

NIDA Medical Monitor (Dr. Roberta Kahn): 301-443-2281

NIDA Project Officer/Project Manager (Jurij Mojsiak): 301-443-9804

Sponsor-Investigator (Dr. Eugene Somoza): 513-487-7800

The following information must be provided with the initial report of an SAE or unexpected AE:

- Name of person reporting the SAE/unexpected AE
- Subject's I.D. number
- Name of the principal investigator and institution
- Date the subject signed informed consent
- Date(s) of administration of investigational products
- Description of the SAE/unexpected AE
- Date and time of onset
- Date/time of administration of last dose of investigational product prior to the SAE/unexpected AE
- Severity of the SAE/unexpected AE
- Investigator's assessment of the relationship of the SAE/unexpected AE to investigational product (related, possibly related, probably related, unlikely related, not related)
- Any action taken with the investigational product, alteration to protocol defined schedule, diagnostics, and treatments secondary to the SAE/unexpected AE.

3-day Supporting Documentation Requirements

Written documentation for all SAEs/unexpected AEs must be received by the NIDA Medical Monitor/Alternate, the NIDA Project Officer and Project Manager, and the Sponsor-Investigator within 3 days of reporting the event. Required documents that must be submitted include the following:

- SAE Form
- Concomitant Medication CRF pages
- Adverse Events CRF pages

- Copies of source documents pertinent to the event (lab reports, ECG tracings, medical chart notes, etc.)
- Any other relevant information necessary to facilitate the investigator's judgment regarding the SAE's relatedness to the severity OR by request of the Medical Monitor/Alternate

These documents may be submitted by facsimile, as email attachments, or via overnight courier.

Follow-Up of All Adverse Events/Serious Adverse Events

All adverse medical events must be followed until they are resolved, or until all attempts to determine the resolution of the AE/SAE are exhausted. This may require an extended hospitalization period or a change in status from outpatient to inpatient. All treatments, outcomes and information regarding whether or not the subject was referred to their Primary Care Provider for additional follow-up must be recorded in the source document. All serious and unexpected AEs occurring 30 days after administration of the last dose of investigational product must be reported. All follow-up Day 24 AEs will be recorded and followed to resolution only if they are serious, or if the study physician assesses them to be clinically significant.

The investigator is required to provide the Medical Monitor/Alternate and the IND Sponsor with all relevant follow-up information necessary to facilitate a thorough understanding of the event and judgment regarding the relationship to the investigational product.

Reporting to the FDA

The IND Sponsor is required to report SAEs to the FDA:

- in 7 days if the SAE is unexpected (or, if expected, unusually serious or rarely seen), life-threatening or lethal, and at least possibly related to the investigational product, with a follow-up written report in 8 days;
- in 15 days if the SAE is unexpected (or, if expected, unusually serious or rarely seen), but not immediately life-threatening; and
- in an annual report in all other cases.

Reporting to Health Canada

During a clinical trial, the Sponsor is required to inform Health Canada of any serious, unexpected adverse drug reaction that has occurred inside or outside Canada:

- where it is neither fatal nor life-threatening, within 15 days after becoming aware of the information;
- where it is fatal or life-threatening, immediately where possible and, in any event, within 7 days after becoming aware of the information; and
- within 8 days after having informed Health Canada of the adverse drug reaction, submit as complete a report as possible which includes an assessment of the importance and implication of any findings.

APPENDIX III: Certificate of Confidentiality

The only people who will know the identity of the subjects are members of the research team and, if appropriate, the physicians and nurses. No information about the subjects, or provided by the subjects during the research, will be disclosed to others without the subjects' written permission, except:

- if necessary to protect subjects' rights or welfare

When the results of the research are published or discussed in conferences, no information will be included that would reveal subjects' identity. Authorized representatives of the FDA and NIDA study monitors may need to review records of individual subjects. As a result, they may know subjects' names, but they are bound by rules of confidentiality not to reveal their identity to others. The results of this study including laboratory results and clinical information collected during this study will be submitted to the FDA and may be used for research purposes. The results of this study may be published but will not personally identify any subjects. All records will be kept in locked storage locations that will be accessible only to authorized study personnel.

A Certificate of Confidentiality, or equivalent coverage in Canada, will be sought for each participating site.

This Certificate of Confidentiality helps researchers protect the privacy of subjects in health research projects against compulsory legal demands (e.g., court orders and subpoenas) that seek the names or other identifying characteristics of research subjects. The certificate was developed to protect against the involuntary release of personally identified research information of a sensitive nature sought through any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. This authority was granted under the Comprehensive Drug Abuse Prevention and Control Act of 1970, Public Law No. 91-513, Section 3(a).

This certificate is necessary for investigators to avoid being required to involuntarily disclose personally identifiable research information about individual study subjects. Under this statute:

"The Secretary [of the Department of Health and Human Services] may authorize persons engaged in biomedical, behavioral, clinical, or other research (including research on mental health, and on the use and effect of alcohol and other psychoactive drugs) to protect the privacy of individuals who are the subject of such research by withholding from all persons not connected with the conduct of such research the names or other identifying characteristics of such individuals. Persons so authorized to protect the privacy of such individuals may not be compelled in any Federal, State, or local civil, criminal, administrative, legislative, or other proceedings to identify such individuals" (Public Health Service Act 301 (d), 42 U. S. C. 241 (d), as amended by Public Law No. 100-607, Section 163 (November 4, 1988)).”

Accordingly, this special privacy protection can be granted only to research (i.e., a systematic investigation, designed to develop or contribute to generalizable knowledge). It is granted only

when the research is of a sensitive nature where the protection is judged necessary to achieve the research objectives.

The study subjects should be informed that a Certificate is in effect, and be given a fair and clear explanation of the protection it affords, including the limitations and exceptions. This information will be included in the informed consent. Please see below some suggested wording:

"We have received a Certificate of Confidentiality from the National Institute on Drug Abuse, which will help us protect your privacy. The Certificate protects against the involuntary release of information about your participation in this study. The researchers involved in this project cannot be forced to disclose your identity or your participation in this study in any legal proceedings at the federal, state, or local level, regardless of whether they are criminal, administrative, or legislative proceedings. However, you or the researcher may choose to voluntarily disclose the protected information under certain circumstances. For example, if you or your guardian requests disclosure of your participation, the researchers will provide research data. The Certificate does not protect against that voluntary disclosure.

Furthermore, federal agencies may review our records under limited circumstances, such as a DHHS request for information for an audit or program evaluation or a Food and Drug Administration request under the Food, Drug and Cosmetics Act."

or

"A Certificate of Confidentiality has been obtained from the Federal Government for this study to help insure your privacy. This Certificate means that the researchers cannot be forced to tell people who are not connected with the study, including courts, about your participation, without your written consent. If we see [learn] something that would immediately endanger you, your child, or others, we may discuss it with you, if possible, or seek help."

Study subjects will be notified that a Certificate has expired if they are recruited to the study after the expiration date of the Certificate and an extension of the Certificate's coverage has not been granted.

If the research scope of a project covered by a Certificate should change substantially, the PI will request an amendment to the Certificate; however, the NIDA Certificate Coordinator may require a new Certificate depending on the extent of the change in scope. An extension of coverage must be requested if the research extends beyond the expiration date of the original Certificate, as research information collected after the expiration of a Certificate is not protected from compelled release.

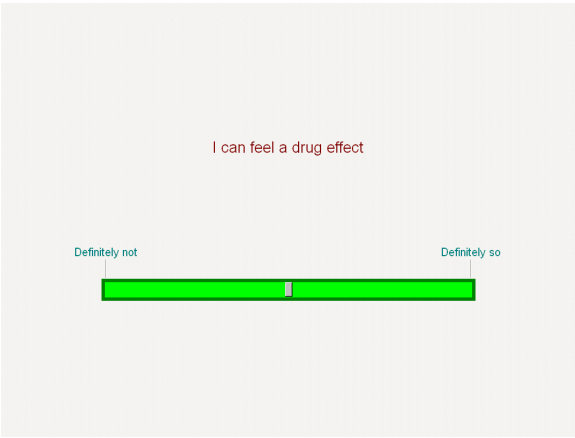
A Certificate of Confidentiality is a legal defense against a subpoena or court order, and is to be used by the researcher to resist disclosure. The researcher should seek legal counsel from his or her institution if legal action is brought to release personally identifying information protected by a certificate. The Office of General Counsel for DHHS is willing to discuss the regulations with the researcher's attorney.

APPENDIX IV: Subjective Effects Visual Analogue Scales (VASs)

The following table shows the VAS items that assess subjective drug effects. These scales have four possible interpretations: positive and negative subjective effects, the balance between positive and negative effects, and other pharmacologic effects (that is, effects that indicate an active substance, which may be perceived as either positive or negative depending on the context).

Scale interpretation	Exclude pre-dose	Scale description	Question text	Response anchors
Positive	Yes	Good effects	I can feel good drug effects	0: Definitely not
Positive		High	I am feeling high	100: Definitely so
Negative	Yes	Bad effects	I can feel bad drug effects	
Negative		Over-stimulated	I feel over-stimulated	
Negative	Yes	Anxiety re: drug effects	I feel anxious about the effects of this drug	
Other effects	Yes	Any effects	I can feel any drug effect	
Negative		Depression	I feel depressed	
Balance	Yes	Drug Liking	At this moment, my liking for this drug is	0: Strong disliking 100: Strong liking
Other effects	Yes	Like methamphetamine	My liking for methamphetamine is	0: Not at all strong 100: Very strong
Other effects	Yes	Desire for methamphetamine	My desire for methamphetamine is	

The overall appearance of all VAS items is similar to the two screen images below. The upper image shows the display for a typical question. Using the mouse, the subject must position the cursor over the small vertical box ("slider") and click on it to move it left or right (lower image). To register the response, the subject must then press the "OK" button that appears below the horizontal line. This multi-step procedure was designed to greatly reduce the possibility of either accidental or automatic responding to such scales. The questions and anchors will be modified appropriately to reflect study specific questions.



APPENDIX V: Addiction Research Center Inventory (ARCI)

The table below shows the presentation format, the questions, and the scales in which each question contributes to the total score for the 49-item ARCI (Martin, Sloan et al. 1971). Subjects indicate their responses by selecting "False" or "True" with a mouse. One point is given for each response that agrees with the scoring direction on the scale (i.e., True items receive a score of 1 if the answer is "True", False items receive a score of 1 if the answer is "False". No points are given when the answer is opposite to the scoring direction). The following 5 scales will be administered:

- Amphetamine - A
- Pentobarbital Chlorpromazine Alcohol Group – PCAG
- Morphine Benzedrine Group – MBG
- Benzedrine Group – BG
- Lysergic Acid Diethylamide – LSD

ARCI Questionnaire

	Scale				
Questions Contributing to 5 ARCI Scales	**A**	**PCAG**	**MBG**	**BG**	**LSD**
My speech is slurred		T			
I am not as active as usual		T			
I have a feeling of just dragging along rather than coasting		T			
I feel sluggish		T			
My head feels heavy		T			
I feel like avoiding people, although I usually do not feel this way		T			
I feel dizzy		T			
It seems harder than usual to move around		T			
I am moody		T			
People might say that I am a little dull today		T		F	
I feel drowsy		T			F
I am full of energy		F			
Today I say things in the easiest possible way			T		
Things around me seem more pleasing than usual			T		
I have a pleasant feeling in my stomach			T		
I feel I will lose the contentment that I have now			T		
I feel in complete harmony with the world and those about me			T		
I can completely appreciate what others are saying when I am in this mood			T		
I would be happy all the time if I felt as I feel now			T		
I feel so good that I know other people can tell it			T		
I feel as if something pleasant had just happened to me			T		
I would be happy all the time if I felt as I do now			T		F
I feel more clear headed than dreamy		F	T	T	
I feel as if I would be more popular with people today	T		T		
I feel a very pleasant emptiness	T		T		
My thoughts come more easily than usual	T		T	T	
I feel less discouraged than usual	T		T		
I am in the mood to talk about the feelings I have			T	T	
I feel more excited than dreamy	T	F			
Answering these questions is very easy today	T			T	
My memory seems sharper to me than usual	T			T	

Questions Contributing to 5 ARCI Scales	Scale				
	A	**PCAG**	**MBG**	**BG**	**LSD**
I feel as if I could do these tests for hours*	T			T	
I feel very patient	T				F
Some parts of my body are tingling	T			T	T
I have a weird feeling	T				T
My movements seem faster than usual				T	
I have better control over myself than usual				T	
My movements seem slower than usual				F	
I find it hard to keep my mind on a task or job				F	
I don't feel like reading anything right now				F	
It seems I'm spending longer than I should on each of these questions					T
My hand feels clumsy					T
I notice my hand shakes when I do these tests*					T
I have a disturbance in my stomach					T
I have an increasing awareness of bodily sensations					T
I feel anxious and upset					T
I have unusual weakness of my muscles					T
A thrill has gone through me one or more times since I started this test		F			T
My movements are free, relaxed, and pleasurable					F

T = True item
F = False item
* - item wording slightly modified for computer assessment

APPENDIX VI: Subjective Drug Value (SDV) Procedure

The task starts at the geometric mean of the range of possible values from $0.25 to $50.00, rounded up to the nearest 25 cents and asks subjects to make a choice. The screen shown in Figure a. is an example of the initial question. Figures b and c are two possible alternatives displayed, depending on the subject's initial response. If the subject chose the envelope, the drug must be subjectively worth less than $3.50, so the next question explores the range less than that value. If, on the other hand, the subject chose the capsule, the drug must be subjectively worth more than $3.50, so the next question explores the range greater than that value. The dollar value that is presented for a given question is the geometric mean of the range of uncertainty, or the square root of the product of the endpoints of that range rounded off to nearest 25 cents. At the end of the procedure (generally six questions), the procedure estimates the subjective value as the geometric mean of the last range of uncertainty.

Figure a.

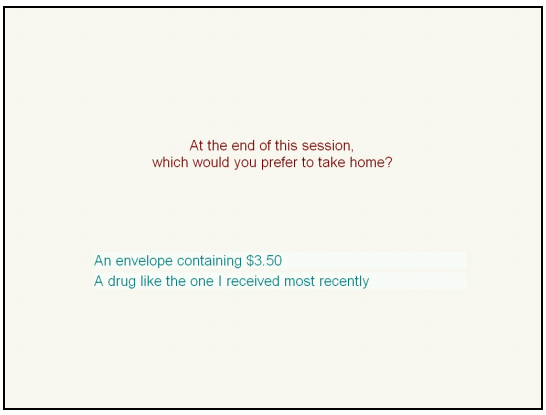


Figure b.

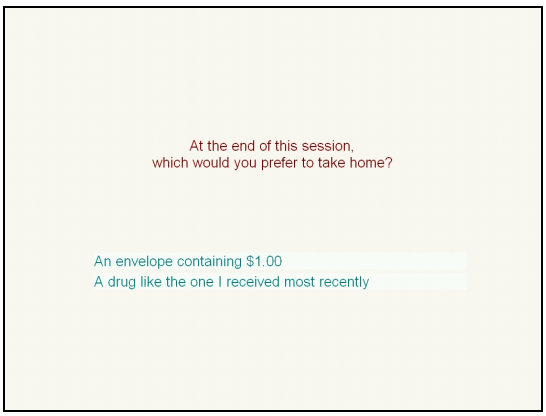


Figure c.