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PHASE 2, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL OF TOPIRAMATE FOR THE TREATMENT OF METHAMPHETAMINE DEPENDENCE

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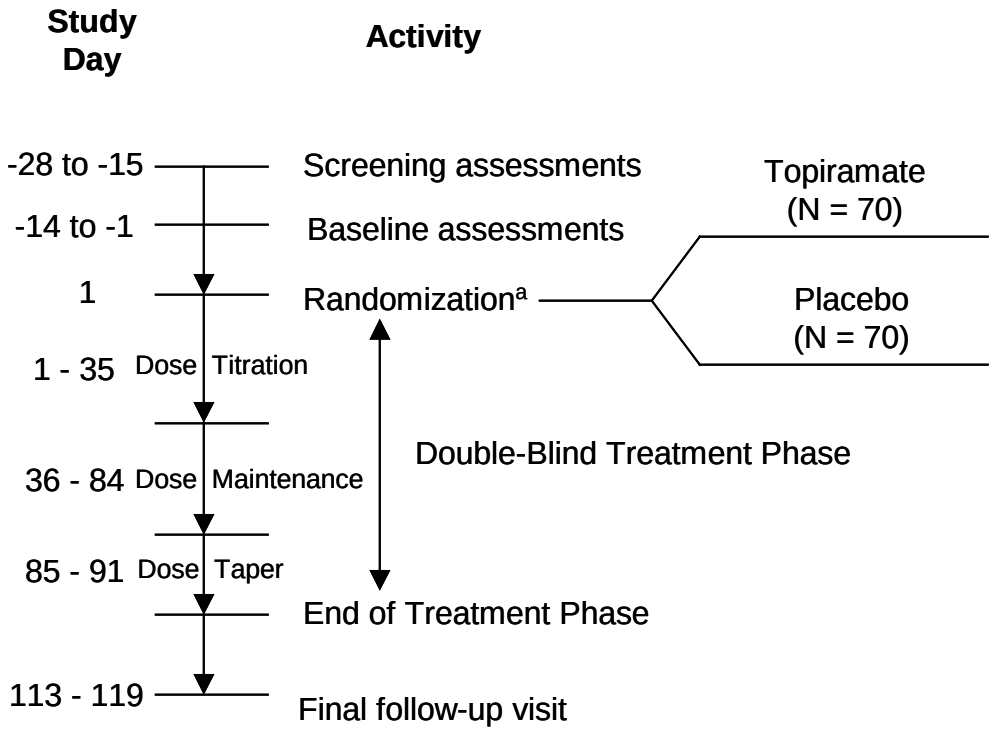
1 ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
ACE	angiotensin-converting enzyme
AE	adverse event
AGT	angiotensinogen gene
ALP	alkaline phosphatase
ALT/SGPT	alanine aminotransferase/serum glutamic pyruvic transaminase
AMPA	alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid
ASI-Lite	Addiction Severity Index-Lite
AST/SGOT	aspartate aminotransferase/serum glutamic oxaloacetic transaminse
ADHD/ADD	attention deficit (hyperactivity) disorder
BBCET	Brief Behavioral Compliance Enhancement Treatment
BMI	Body mass index
BSCS	Brief Substance Craving Scale
BUN	blood urea nitrogen
CAP	College of American Pathologists
CBT	Cognitive Behavioral Therapy
CGI-O/CGI-S	Clinical Global Impression Scale – Observer and – Self
CLIA	Clinical Laboratory Improvement Amendment of 1988
CNS	central nervous system
CRF	Case Report Form
CYP2D6	cytochrome P450 2D6 isoform
DA	dopamine
DAT	dopamine transporter
DRD2	dopamine receptor D2 gene
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	electoencephalograph
FDA	Food and Drug Administration
GABA	gamma-aminobutyric acid
HIV	human immunodeficiency virus
HRBS	HIV Risk-taking Behavior Scale
5-HTT	serotonin transporter
ITT	intention-to-treat
IRB	Institutional Review Board
ITTRS	Inter-active Touch Tone Randomization System
LDH	lactate dehydrogenase
MAO	monoamine oxidase
MADRS	Montgomery-Asberg Depression Rating Scale
MTD	maximum tolerated dose
NIDA	National Institute on Drug Abuse

Abbreviation	Definition
OTC	over-the-counter
PET	positron-emission tomography
PPD	purified protein derivative (test for tuberculosis)
PT	prothrombin time
RPR	rapid plasma reagin (test for syphilis)
SAE	serious adverse event
SCID	structured clinical interview for DSM-IV
SNP	single nucleotide polymorphisms
SSRI	selective serotonin reuptake inhibitor
SUR	substance use report
TLFB	timeline followback
VAS	visual analog scale

Term	Definition
Trial Subject:	An individual who participates in a clinical trial, either as a recipient of the investigational product(s) or as a control. Anyone who signs the informed consent form is considered a trial subject.
Investigational Product(s):	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use. Specifically in this study, topiramate and matched placebo.
Study Treatment:	Topiramate or matched placebo.
Treatment Period:	The 91 days of the trial during which topiramate or matched placebo is administered. Only assessments performed during the first 84 days of treatment during dose escalation and maintenance will be included in the efficacy analysis. The safety analysis will include the entire study period starting on the day that the subject signs the consent form until their last follow-up contact (in-clinic or by telephone).

2 STUDY SCHEMA



[a]Adaptive randomization will be used to balance treatment groups with respect to prognostic variables, i.e., site and methamphetamine use within the 7 days before randomization (using – anyone with a self report of methamphetamine use or a methamphetamine positive urine sample versus abstinent – anyone reporting no use and all urine samples negative for methamphetamine).

Treatment consists of oral topiramate or matched placebo for 91 Days. Topiramate will be escalated over the first 35 days of the study starting with a 25 mg/day dose until a daily dose of 200 mg/day or the subject's maximum tolerated dose is achieved. Topiramate will be tapered over the last week of treatment to 100 mg/day for 3 days, 50 mg/day for 2 days, then 25 mg/day for 2 days. Brief Behavioral Compliance Enhancement Treatment (BBCET) will be administered once during baseline and weekly during treatment.

3 ABSTRACT

STUDY OBJECTIVES: The objectives of this study are to assess the efficacy and safety of topiramate as compared to placebo in reducing methamphetamine use in subjects with methamphetamine dependence. It is hypothesized that topiramate, as compared to placebo, will be well tolerated and associated with a decrease in methamphetamine use as measured by quantitative urinalysis for methamphetamine as well as a decrease in the severity of methamphetamine dependence based on psychological measures.

STUDY DESIGN: This is a double-blind, multi-center, placebo-controlled, randomized, parallel group design study in methamphetamine dependent outpatients. Subjects meeting the eligibility criteria after a screening period not to exceed 14 days and a 14-day baseline assessment period will be randomized in a 1:1 ratio to daily dosing with the investigational products, topiramate or matched placebo. Randomization variables include investigational site and methamphetamine use within 7 days before randomization (using – anyone with self report of methamphetamine use or a methamphetamine positive urine sample versus abstinent – anyone reporting no use and all urine samples negative for methamphetamine). Once during baseline and once per week during the treatment phase, all subjects will receive Brief Behavioral Compliance Enhancement Treatment (BBCET), a manual-driven, low-intensity supportive program to foster, maintain, and promote compliance with investigational product use and to promote continuation in the study. A final follow-up assessment will be conducted approximately 28 days after completion of treatment.

STUDY POPULATION: One hundred forty (140) subjects with Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV) criteria for methamphetamine dependence, determined by structured clinical interview (SCID), will be randomized into one of two treatment groups (70 subjects per group). Subjects, at least 18 years-of-age, who meet all eligibility criteria, provide at least one methamphetamine positive urine specimen (>500 ng/mL) during the 14-day screening period and 14 consecutive days of other baseline measures, and provide written informed consent will be randomized into the study. Screening and baseline measures must be completed within 28 days prior to randomization.

TREATMENTS: After randomization, subjects will receive either topiramate, up to 200 mg/day, or matched placebo orally for 91 days. During the dose titration phase (Days 1 to 35), the daily dosage of topiramate will be escalated using a flexible dosing schedule targeting the following daily doses: Days 1 to 7 - 25 mg/day, Days 8 to 14 - 50 mg/day, Days 15 to 21 - 100 mg/day, Days 22 to 28 -150 mg/day, and Days 29 to 35 – 200 mg/day. During the maintenance phase (Days 36 to 84), the daily dose will be the maximum tolerated dose (MTD) determined during the titration period, but will not exceed 200 mg/day. However, to continue in the study, the subject must be able to tolerate at least 50 mg/day. During the taper phase (Days 85 to 91), the dose will be reduced over the last week of treatment to 100 mg/day for 3 days, 50 mg/day for 2 days, then to 25 mg/day for 2 days. With the exception of the 25 mg dose, the rest of the doses should be taken by splitting the total daily dose as evenly as possible twice per day, once in the morning and once in the evening. When a dose cannot be split into two equal amounts, the amount over half the dose will be taken with the rest of the evening dose. In instances where splitting the dose as such causes side effects, such as drowsiness, that interfere with the subject's

ability to carry out his/her daily routine, the site investigator, after communicating with the Medical Monitor, may instruct the subject to take the study drug once per day, usually in the evening. BBCET will be administered once at the beginning of the baseline period and at each clinic visit when investigational products are dispensed (once per week) during the treatment phase of the study. At the investigator's discretion, the escalation rate and the maximum dose may be adjusted to the MTD, but may not exceed more than an increase of > 100 mg/day and a maximum daily dose of 200 mg/day. Dose adjustments are permitted throughout the titration period (Days 1 – 35) at a rate not to exceed that which is tolerated; however, after titrations occurring on Days 8 to 14, subjects must take at least 50 mg/day throughout the remainder of the titration and dose maintenance periods (Days 15 – 84). At the end of the titration period, subjects should maintain their MTD for the duration of the dose maintenance period (Days 36 – 84). A single dose reduction during the maintenance period to the next lower previously tolerated dose will be permitted to manage tolerability (provided subjects maintain a minimum daily dose of 50 mg).

SAFETY ASSESSMENTS: All candidates for study enrollment will have a structured clinical interview (SCID) for Axis I disorders according to the criteria in the Diagnostic and Statistical Manual of Mental Disorders - Fourth Edition (DSM-IV), a Montgomery-Asberg Depression Rating Scale (MADRS) assessment, physical examination, a 12-lead electrocardiogram (ECG), clinical laboratory studies [blood chemistries, hematology, medical urinalysis and urine pregnancy test, if female], and a tuberculin skin test (PPD) or chest X-ray completed during screening. Prior and concomitant medication use and a urine drug screen for substances of abuse will be assessed during screening and treatment periods. Vital signs will be assessed once during screening and once weekly during baseline and the treatment periods (preferably at the first visit of each week), at termination, and at the follow-up visit. A urine pregnancy test, if female, will be performed during screening, on Study Day 1 before the first dose of investigational product, every 4 weeks during treatment, and at the final follow-up visit during week 17. Blood chemistries will be assessed every four weeks during treatment. Adverse events (AEs) will be assessed at each visit and evaluated by a physician weekly. At treatment Day 84 or at the time of premature study discontinuation, subjects will be evaluated for AEs, vital signs, physical examination, ECG, and clinical laboratory studies (including urine pregnancy test, if female). AEs will be assessed at the end of dose taper and at the final follow-up visit (approximately Day 119).

EFFICACY ASSESSMENTS: The primary outcome response measure will be negative methamphetamine use weeks during Weeks 6 through 12 of treatment (the last week of dose taper will not be included in the analysis). Efficacy will be evaluated during this part of the treatment period when subjects are taking their maintenance dose of investigational products. A secondary analysis will be performed on negative methamphetamine use weeks during the entire Week 1 through 12-treatment period. Use weeks are defined as each 7-day period starting with the first day of investigational product administration. A positive use week is any week in which at least one of the urine drug screens for methamphetamine was positive (≥ 300 ng/mL). A negative use week is any week in which all of the urine drug screens for methamphetamine were negative (< 300 ng/mL). If no drug screening results are available, the data for that week is considered as missing. Quantitative analysis results from the central laboratory will be used for this outcome measure. Secondary assessments include analyses of other measures of success in the reduction of methamphetamine use including, for example, the proportion of subjects with 21

consecutive days of abstinence as shown by methamphetamine-negative urine samples, quantitative urinalysis results, proportion of methamphetamine non-use days by self report, the largest number of consecutive methamphetamine non-use days, and reductions in use as compared to baseline. A subset analysis will be performed on those subjects who were abstinent at the start of treatment (abstinent is defined in accordance with the randomization variable for using and abstinent). Additional measures of treatment effect will include treatment retention, Addiction Severity Index (ASI)-Lite scores, Brief Substance Craving Scale (BSCS) score, and Clinical Global Impression scores as assessed by the subjects (CGI-S) and an observer (CGI-O).

ANALYSIS: Each primary and secondary outcome variable will be analyzed using appropriate statistical methods for the intention-to-treat (ITT) population and the evaluable population. The ITT population is defined as the subjects who are randomized to treatment and who receive the first dose of investigational product. The evaluable population is defined as the subjects who are randomized and properly qualified to participate in the study in accordance with the eligibility criteria and who contributed at least six (6) usable on-study urine samples and took at least 50 mg/day of topiramate (or equivalent placebo) for a period of 21 Days. The primary efficacy outcome measure, negative methamphetamine use-weeks during study Weeks 6 through 12, will be compared between groups using Generalized Estimating Equations (GEE). It is hypothesized that the group treated with topiramate will have an increase in the proportion of subjects with methamphetamine-negative use weeks compared to the placebo group during this 7-week maintenance-dosing period (study Weeks 6 through 12). As a secondary analysis, baseline abstinence or use, age, race, gender, and clinical site will also be included in the model, as appropriate. Statistical tests will be two-sided at a 5% Type I error rate. Confidence intervals will be two-sided with a 95% confidence level. Summaries of the demographic characteristics and baseline methamphetamine use of the subject population in each treatment group will be prepared for the ITT and the evaluable populations. Weekly treatment retention will be summarized. All AEs will be reported in tabular form indicating the frequency and severity of each type of event.

4 INTRODUCTION

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, epinephrine, and norepinephrine. It also inhibits monoamine oxidase (MAO), an action that would increase its cathecholaminergic activity. Amphetamines affect serotonergic systems as well. Thus, *d*-amphetamine releases serotonin and may act as a direct agonist of serotonin receptors (Weiner, 1985; Kuczenski, 1983); 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 dopamine 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 *et al.,* 2001a). This low level of D2 dopamine 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 *et al.,* 2001a).

Methamphetamine readily enters the central nervous system, and has a marked stimulant effect on mood (Johnson *et al.,* 1999a; 2005a) and alertness (Johnson *et al.,* 2000; 2005b). Methamphetamine is neurotoxic to dopamine terminals when administered to laboratory animals, including monkeys (Wrona *et al.,* 1995; Cadet *et al.,* 2003; Kita *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 *et al.,* 2001b). 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 *et al.*, 2001b; Wang *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 *et al.,* 2001b). 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 *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 *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 *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 *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 *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 Pharmacokinetics

Pharmacokinetics of methamphetamine is similar to those of ephedrine: it has high bioavailability, a long duration of action, and a significant fraction of methamphetamine is excreted unchanged in the urine. Following intravenous 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 (Lin *et al.,* 1997) and by hydroxylation to 4-OH methamphetamine (Lin *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 *et al.,* 1995). Methamphetamine and amphetamine also inhibit CYP2D6 with an apparent ki of 25 μM and 26.5 μM, respectively (Wu *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 *et al.*, 1999b). 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 regulate 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 *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 *et al.*, 2003), increased blood pressure (Johnson *et al*., 2000), and irreversible, stroke-producing damage to small blood vessels in the brain (McGhee *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 (Klee, 1992; 1997a), Japan (Suwaki, 1991), Australia (Hando and Hall, 1997; Makai and McAllister, 1993), and in many other countries (Klee, 1997b). 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, as well (NIDA Research Report on Methamphetamine, 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 (King and Ellinwood, 1995; 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 *et al*., 1990; Johnson *et al*., 1998; Peltier *et al*., 1996). 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.

Traditionally, the attempts to develop new medications to treat addiction were focused on the brain's "all-purpose" dopaminergic mesocorticolimbic reward area. However, recent reports indicate that the reward function operates independently from craving for a drug. This has been confirmed in a study by Vorel *et al*. (2001) that anatomically located the relapse circuitry in the brain (i.e., ventral subiculum of hippocampus) and showed that the main chemical implicated is not dopamine but glutamate. Inhibition of prefrontal glutamatergic neurons blocks cocaine-induced reinstatement of drug seeking behavior in rats (Cornish and Kalivas, 2000; McFarland *et al*., 2003). Preclinical studies have also suggested that medications that foster GABAergic neurotransmission reduce the dopamine response to both cocaine administration and to conditioned cues of prior cocaine use (Dewey et *al*., 1992, 1997; Gerasimov *et al*., 1999). Also, increases in GABAergic activity induced by gamma-vinyl-GABA, an irreversible GABA transaminase inhibitor, have an attenuating effect on reward system and block cocaine self-administration in rats (Roberts *et al.*, 1996; Kushner *et al.*, 1999). Conceptually, medications that inhibit glutamatergic activity and promote GABAergic activity may have a therapeutic potential for the treatment of cocaine and methamphetamine abuse. Topiramate, an

anticonvulsant that antagonizes glutamatergic activity through effect at kainate/AMPA receptors (Severt *et al*., 1995) and enhances GABA activity at GABA-A receptors (Kuzniecky *et al*., 1998; Petroff *et al*., 1999; White *et al*., 1997) may have a potential in the pharmacotherapy of relapse to methamphetamine use.

4.1.9 Pharmacogenomics of Drug Treatment and Genetics of Methamphetamine Dependence

Pharmacogenomics has the potential to identify sources of inter-individual variability in drug response (both efficacy and toxicity) in order to help individualize therapy with the intent of maximizing effectiveness and minimizing risk. The FDA is encouraging drug developers to conduct pharmacogenomic testing during drug development as a step toward this goal. There are no known valid biomarkers for drug response associated with the treatment of methamphetamine dependence or any other diseases or disorders with topiramate; thus, this study will explore a broad range of genetic variants and gene expression profiles during treatment to attempt to establish a relationship with clinical response.

The rationale for screening for genetic variants stems from family and twin studies suggesting that substance abuse and addiction traits are inherited. Support for this concept is provided from a large study of twins, where the concordance rates of DSM-III-R-defined drug abuse or dependence for monozygotic twins were almost double the rates for dizygotic twins (Tsuang *et al*., 1996). There are a number of plausible candidate genes for methamphetamine dependence — that is, genes likely to affect an individual's vulnerability to methamphetamine dependence. Among the candidate genes operative in addiction disorders are serotonin, norepinephrine, human γ-aminobutyric acid (GABA), glutamate, and opioid receptors, all of which modify dopamine metabolism and dopamine neurons. It has been proposed that defects in various combinations of the genes for these neurotransmitters result in a reward deficiency syndrome and that such individuals are at risk for abuse of the "unnatural rewards" (Comings and Blum, 2000).

Because of its importance in substance abuse, the gene for the dopamine receptor D2 (DRD2) has been a major candidate gene for study; however, thus far, no association with methamphetamine dependence has been reported. These studies focused on the association between methamphetamine dependence and the TaqI A polymorphism of the DRD2 in unrelated methamphetamine-dependent subjects. In one study by Sery *et al*. (2001), no association was shown between DRD2 polymorphisms and methamphetamine dependence in Czechoslovakian males. Additionally, no association was found with two other candidate genes, angiotensin-converting enzyme (ACE) and angiotensinogen gene (AGT). However, a significant difference in allele I frequency was found between male and female control groups for the ACE polymorphism. Studies in Chinese males with methamphetamine dependence failed to demonstrate any association between polymorphisms in the dopamine transporter (DAT) 3'-variable number tandem repeat, the serotonin transporter (5-HTT) gene promoter, and a 5-HTT variable number tandem repeat, suggesting that these polymorphisms do not play a major role in methamphetamine dependence in the Chinese male population (Hong *et al*., 2003).

Evidence has been provided suggesting that the GABA receptor γ2 subunit gene (GABRG2) has an association with methamphetamine use disorder (Nishiyama, 2005). After genotyping

subjects with methamphetamine use disorder, two representative single nucleotide polymorphisms (SNPs) in GABRG2 were found to be in moderate linkage disequilibrium. The genotypic and allelic frequencies of the two SNPs in the methamphetamine population did not differ significantly, whereas the distributions of haplotypic frequencies were found to be significantly different between methamphetamine use disorder and control subjects. Furthermore, data were provided suggesting that the irreversible GABA-transaminase inhibitor, γ-vinyl GABA, attenuates the increase in dopamine release following the acute administration of amphetamine. With a limited amount of support thus far, further investigations of the genetic basis of methamphetamine use disorder predisposition and response to medication appear to be warranted. Thus, in this study, we plan to investigate the potential association of genetic variants of a number of genes with methamphetamine dependence. The first set of genes that will be studied includes genes in the dopaminergic reward system, such as the genes encoding tyrosine hydroxylase, dopamine transporters, dopamine receptors, and monoamine oxidase A and B. Additional genes of interest include those encoding serotonin transporters, opioid receptors, and cannabinoid receptors.

Additionally, we plan to study gene expression profiles of subjects in response to topiramate treatment over different time points. Methods to define the patterns of gene expression have been applied to a wide range of biological systems. One approach to understanding physiological mechanisms is to identify gene expression patterns associated with varying physiological states. For example, investigators have been interested in examining differentially expressed genes in different cell types, in cells during different stages of differentiation and under various growth conditions, and during drug treatment versus controls. Various methods to compare patterns of gene expression have been reported, including differential hybridization screening (Tedder *et al.*, 1988), differential display (Liang and Pardee, 1992), series analysis of gene expression (Velculescu *et al*., 1995; Zhang *et al*., 1997), and cDNA microarray (DeRisi *et al*., 1996, 1997).

The techniques of differential display and the generation of ESTs were first used for the identification of genes exhibiting marked differential expression across tissues, developmental stages, or normal versus pathological conditions. The analysis of gene expression patterns derived from normal and pathological situations is a valuable tool in the discovery of therapeutic targets and diagnostic markers. The recognition of coordinated expression profiles between characterized or anonymous genes also enables inferences about biological pathways and gene functions. Microarray technology, which facilitates the measurement of the relative gene expression levels through a massively parallel approach, has begun to revolutionize biomedical research. The technology behind microarray was developed over the last several years once it became apparent that new, more powerful analytical approaches were needed to utilize the flood of genomic data and resources being acquired through the various genomic projects. At the moment, the measurement of gene expression using microarray appears to be the sole approach to gene characterization capable of matching the speed of sequencing and the scale required for functional genomics.

Array technologies have made it straightforward to simultaneously monitor the expression patterns of thousands of genes during different experimental conditions. Protocols have become more refined, so good quality of microarray data can now be obtained. The greatest challenge

that researchers face is to make sense of such massive data sets. Many mathematical techniques have been developed for identifying the underlying patterns in a complex data set. Currently, the most popular way to identify interesting genes and their function is to perform cluster analysis on the relative expression pattern changes obtained from a typical microarray experiment. However, it is not clear which clustering technique(s) is likely to be most useful for interpreting gene expression data. Hierarchical clustering is the most commonly used method (Eisen *et al*., 1998; Spellman *et al*., 1998; Wen *et al.*, 1998), in which data points are forced into a strict hierarchy of nested subsets with branch lengths reflecting the degree of similarity in expression. Several other clustering techniques also have been applied to the analysis of gene expression patterns, which include k-means clustering (Herwig *et al*., 1999), self-organizing maps (Tamayo *et al.*, 1999), and quality clustering (Heyer *et al*., 1999).

There is no doubt that cluster analysis contributes significantly to our understanding of the underlying biological phenomena in differential gene expression. Primarily, cluster analysis has been used for data reduction and visualization and can be used to generalize or predict the categorization of new samples (for a review, see Slonim, 2002). Further, clues to unknown gene function may be inferred from clusters of genes similarly expressed across many samples (Eisen *et al.*, 1998). Clustering samples over the expression levels of multiple genes also has been proposed as a way of defining new disease subclasses (Golub *et al.*, 1999; Alizadeh *et al*., 2000). However, most of these methods have some restrictions, one of which is their inability to determine accurately the number of clusters. The difficulty may be related to the fact that, in many methods, there is no clear definition of what constitutes a cluster in the first place. Furthermore, the clustering results from these methods may not be stable (Zhang and Zhao, 2000; Kerr and Churchill, 2001). An important clustering technique that improves and provides alternative solutions to these issues is the model-based clustering approach (McLachlan and Basford, 1988), which has been applied to cluster gene-expression patterns (Holmes and Bruno, 2000; Yeung *et al.*, 2001). Another concern in microarray data clustering is related to the assumptions made when interpreting the results obtained using these methods. The fundamental premise of the clustering approach is that genes having similar expression profiles across a set of experimental conditions also may share similar functions. As we know, this assumption may not be true in all cases. Genes, the products of which may have the same function, do not necessarily share similar transcriptional patterns. Conversely, genes having different functions can have a similar expression profile simply by chance. To overcome this limitation, a novel approach, called shortest path analysis, recently has been proposed to group genes involved in the same biological process, even without showing significant expression similarity (Zhou *et al.*, 2002).

In addition to the expression pattern discovery, identification of genes that are differentially expressed under varying experimental conditions is equally important to molecular biologists who are using the microarray technique to address the biological questions of their interest. In earlier microarray studies, a fixed fold-change cut-off (generally two-fold) was used to identify the genes exhibiting the most significant variation. This set value is arbitrary and sometimes unreliable since it does not take individual variability into account. Recently, more sophisticated statistical methods have been proposed to overcome this shortcoming, including analysis of variance (Kerr *et al.*, 2000; Wolfinger *et al.*, 2001; Churchill, 2002), maximum likelihood analysis (Ideker e*t al.*, 2000), a regression modeling approach (Thomas *et al.*, 2001), an

empirical Bayes method (Efron and Tibshirani, 2002), and a Significance Analysis of Microarray method (Tusher *et al*., 2001).

Since its development, the microarray technique has revolutionized almost all fields of biomedical research by enabling high-throughput gene expression profiling. Using cDNA or oligonucleotide microarrays, thousands of genes from various organisms have been examined with respect to differentiation/development, disease diagnosis, and drug discovery. Nevertheless, research on drug addiction using the microarray approach has been rather limited. Therefore, the current study provides a unique opportunity for us to determine which sets of genes are significantly modulated by topiramate and how their expression levels are changed over different time points of treatment. Such information may shed light on the understanding of molecular mechanisms underlying the pharmacological effects of topiramate in individuals with methamphetamine dependence.

4.2 **Topiramate**

4.2.1 Rationale for Studying Topiramate

This study will investigate the anticonvulsant drug, topiramate, as a possible medication for treatment of methamphetamine dependence. Anticonvulsants are becoming an adjunctive therapy for the treatment of craving for various substances (Johnson *et al*., 2004), including alcohol (Myrick *et al.,* 1998) and cocaine (Brown *et al*., 2003; Myrick *et al*., 2001a, b). Topiramate is a anticonvulsant drug with several mechanisms of action that encompasses GABAergic and antiglutamatergic properties and also activity against voltage-sensitive sodium and calcium excitatory currents (Langtry *et al*., 1997). Johnson (2005a) published a comprehensive review discussing the proposed mechanism of action of topiramate for treating substance abuse disorders as well as the clinical experience. Topiramate is currently undergoing investigation for the treatment of alcohol, cocaine, and opiate dependence, smoking cessation, pathological gambling, and binge-eating disorder.

It is hypothesized that topiramate may treat methamphetamine dependence through two potential mechanisms of action. It can antagonize glutamatergic activity through effect at kainate/AMPA receptors (Severt *et al*., 1995) and can enhance GABA activity at GABA-A receptors and thus raise cerebral GABA levels (Kuzniecky *et al*., 1998; Petroff *et al*., 1999; White *et al*., 1997). Facilitation of GABAergic function through a non-benzodiazepine site on GABA-A receptor will decrease mesocorticolimbic dopaminergic activity, and increases in GABAergic activity (i.e., induced by gamma-vinyl-GABA, an irreversible GABA transaminase inhibitor) are reported to have an attenuating effect on reward system and block cocaine self-administration in rats (Roberts *et al.,* 1996; Kushner *et al.,* 1999). Available data indicate that withdrawal can be mediated through kainate-activated (AMPA) receptors in locus coeruleus (Rasmussen, 1995). Preclinical studies of withdrawal from opioids indicate that while AMPA receptor antagonists may not be able to prevent the development of tolerance or dependence, they may ameliorate both the physical and emotional consequences of withdrawal. Therefore, AMPA receptor antagonists, like topiramate, may represent a new approach for treating the consequences of drug abuse and a promising alternative to clonidine or opiate tapering as treatment for opiate withdrawal. The ability of topiramate to inhibit glutamatergic transmission through effect at kainate/AMPA receptors may reduce both craving for methamphetamine and reinstatement of

methamphetamine-seeking behavior since preclinical data indicate that glutamate transmission in the nucleus accumbens mediates relapse to cocaine and cocaine-induced reinstatement of drug-seeking behavior (Cornish and Kalivas, 2000; McFarland *et al.,* 2003).

4.2.2 Previous Human Experience with Topiramate

Topiramate (TOPAMAX®) is approved by FDA for initial monotherapy in patients 10 years of age and older with partial onset or primary generalized tonic-clonic seizures, as adjunctive therapy for adults and pediatric patients ages 2-16 years with partial onset seizures, or primary generalized tonic-clonic seizures, and in patients 2 years of age and older with seizures associated with Lennox-Gastaut syndrome, and is indicated for adults for the prophylaxis of migraine headache (TOPAMAX® – Package Insert). Topiramate has been investigated for efficacy in treating other addictions that have direct clinical relevance to methamphetamine-dependence, such as cocaine addiction, and opiate and alcohol dependence, and published reports suggest its efficacy.

Phase 1 interaction study of topiramate and methamphetamine. Johnson *et al.* (2005b) conducted a double-blind, placebo-controlled, cross over study in the inpatient setting of 10 non-treatment seeking methamphetamine-dependent individuals (7 males and 3 females). A 3 x 3 factorial design was used in which subjects were exposed to placebo, 100 or 200 mg of topiramate, and intravenous methamphetamine (15 and 30 mg infusions). Methamphetamine infusions were conducted at one-to-two day intervals between infusions. Hemodynamic responses (blood pressure, heart rate, mean arterial pressure, and pulse pressure) were continuously monitored during infusions. Methamphetamine significantly increased ($p < 0.0001$) all hemodynamic responses (**Table 1**). When methamphetamine was infused in subjects taking topiramate, there were no consistent additional effects on the hemodynamic response. There were no serious or significant adverse events in any subject throughout treatment (**Table 2**). Three subjects reported having adverse events. For subject # 1 there were three episodes: 1) at a dose of 30 mg of methamphetamine with the 100 mg daily dose of topiramate, there was one isolated atrial premature contraction, slight S-T Changes, elevated blood pressure, and described having palpitations; 2) at a dose of 200 mg of topiramate and 30 mg of methamphetamine, there was a slight change in p waves and associated change in the R-R interval; and, 3) at a dose of 0 mg of topiramate and 15 mg of methamphetamine, there was an isolated premature atrial contraction. For subject # 2, there was an episode of mild sinus arrhythmia. For subject # 3, there was a report of skin discomfort with the precordial leads. The recorded arrhythmias all followed methamphetamine infusion. No arrhythmia required specialized intervention or medication. All resolved spontaneously. None of these adverse events were considered of significant clinical importance.

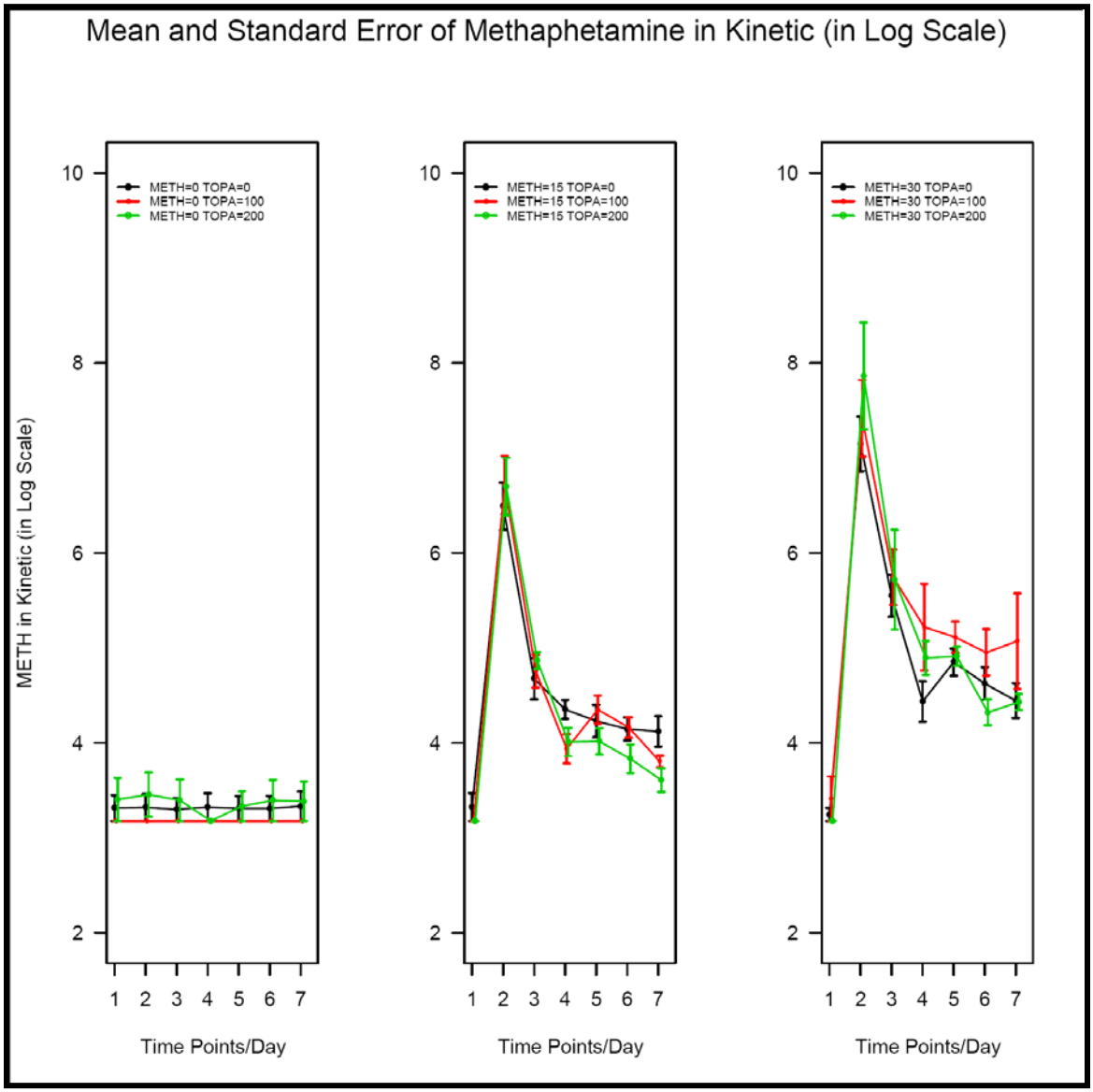
Subjective effects and reinforcement of methamphetamine were also examined using visual analog scales and several questionnaires along with the effects of topiramate on methamphetamine-induced changes in performance, attention, and concentration. Methamphetamine administration was associated with significant increased mood and reinforcement; topiramate had a trend toward decreasing this methamphetamine effect. Topiramate appeared to enhance methamphetamine positive effects and reinforcement; however, this was probably the result of greater "appreciation" of mood after pre-dosing with

methamphetamine. Acute administration of topiramate appears to act as a "partial anti-reinforcing" agent – thus stimulating greater drive to overcome effects. It would, however, be reasonable to expect that chronic topiramate administration would result in sustained antagonism of methamphetamine's reinforcing effects. Methamphetamine enhanced performance, attention, and concentration. Topiramate's effects on cognitive processing were mixed: concentration was enhanced but perceptual motor function was decreased as compared to methamphetamine alone. Improved concentration may be a result of mood stabilization.

Table 1. Hemodynamic Effects of Methamphetamine and Topiramate – Phase I Interaction Study of Johnson *et al.* (2005)										
	Study Agent Dose									**ANOVA**
Methamphetamine Infusion dose (mg)	0	0	0	15	15	15	30	30	30	**Main effect of meth**[a]
Topiramate Daily Dose (mg)	0	100	200	0	100	200	0	100	200	**Main effect of topiramate**[b]
Measurement	**Least Squares Means (95% Confidence Intervals)**									**p-value**
Systolic Blood Pressure	134 (125-143)	137 (128-147)	132 (123-142)	147 (137-156)	146 (137-155)	147 (138-156)	153 (144-163)	158 (148-167)	154 (145-163)	0.0001[a]
										0.45[b]
Diastolic Blood Pressure	95 (88-103)	99 (92-106)	101 (94-108)	101 (94-108)	99 (91-106)	99 (91-106)	102 (95-109)	101 (94-109)	99 (92-107)	0.53[a]
										0.99[b]
Pulse Pressure	58 (52-64)	60 (54-66)	57 (52-63)	62 (57-68)	61 (56-67)	63 (57-69)	66 (60-71)	69 (63-75)	63 (58-69)	0.0015[a]
										0.46[b]
Mean Arterial Pressure	105 (97-112)	108 (101-116)	108 (100-115)	111 (104-119)	112 (104-119)	111 (103-119)	115 (108-123)	117 (110-125)	115 (106-123)	0.0009[a]
										0.66[b]
Heart Rate	106 (97-116)	98 (89-108)	98 (88-107)	106 (97-116)	112 (103-122)	108 (99-118)	110 (101-120)	117 (107-127)	119 (110-129)	0.0004[a]
										0.86[b]

Table 2. Adverse Events Reported in Phase I Interaction Study of Johnson *et al.* (2005)									
	Study Agent Dose								
Methamphetamine Infusion dose (mg)	0	0	0	15	15	15	30	30	30
Topiramate Daily Dose (mg)	0	100	200	0	100	200	0	100	200
Adverse Event	**Number of Subjects**								
Blood Pressure	0	0	0	0	0	0	0	0	1
Heart Rate	0	0	0	0	0	0	0	0	0
S-T Change	0	0	0	0	0	0	0	1	0
Arrhythmia	0	0	0	1	0	0	0	1	2
Palpitations	0	0	0	0	0	0	0	1	0
Skin discomfort around ECG leads	0	0	0	0	0	0	0	0	1
Total	**0**	**0**	**0**	**1**	**0**	**0**	**0**	**3**	**4**

The pharmacokinetics of topiramate (100 mg and 200 mg orally) and methamphetamine (15 mg and 30 mg intravenously), both alone and in combination, was also evaluated in this study. Blood draws occurred at 7 time points (pre methamphetamine -15 minutes, and post methamphetamine 30, 60, 120, 180, 240, and 300 minutes). Statistical analyses were conducted using PROC MIXED in SAS. For both area under curve and peak estimates, both topiramate and methamphetamine levels increased as a function of dose ($p < 0.0001$), and there was no statistically significant kinetic interaction between topiramate and methamphetamine. As can be seen below, there was a non significant trend for topiramate to increase methamphetamine levels which was most noticeable for the combination of methamphetamine 30 mg intravenously and topiramate 100 mg orally. Lack of statistical significance for this interaction might be attributable to the small subject numbers, and therefore, relatively low statistical power to detect such a difference. Notably, there was no evidence of a kinetic interaction that would preclude formal clinical testing of topiramate for the treatment of methamphetamine dependence.



Experience in cocaine-dependent subjects. Johnson and colleagues (2003, unpublished) also conduced a preliminary trial of topiramate (up to 300 mg/day) in a six-week open-label study of six (4 males, 2 females; mean age = 37.6 years) DSM-IV–diagnosed cocaine-dependent subjects with an average drinking level of 15.2 standard drinks/week at baseline. All subjects received weekly cognitive behavioral therapy. Since there was no placebo group, no firm conclusions could be drawn about efficacy. Nevertheless, it is quite promising that the benzoylecgonine/ creatinine ratio showed practically complete cessation of cocaine use across the study weeks. No subject was reported to be drinking on the last study day, and there was a reduction in alcohol craving from baseline to study end in the 24 hour period prior to each of these two clinic visits (from 61% to 23%, respectively). Frequency rates for the five most common adverse events were as follows: fatigue - 23%; paresthesia - 17%; weight loss - 8.6%; taste abnormality - 8.2%, and dizziness - 5.7%. No serious adverse events occurred. Two subjects were lost to follow-up.

The efficacy of topiramate for cocaine dependence was tested in a recently completed 13-week, double-blind, placebo-controlled pilot (n=40) trial (Kampman *et al*., 2004). Topiramate was titrated gradually over 8 weeks to a dose of 200 mg daily. The primary outcome measure was cocaine abstinence verified by twice weekly urine BE tests. The results of this study indicated that topiramate may be an effective treatment of cocaine dependence because topiramate-treated subjects were more likely to be abstinent from cocaine than placebo-treated subjects (p=0.01) and were also more likely to achieve 3 weeks of continuous abstinence from cocaine than placebo-treated subjects (p=0.05). Importantly, 82% of subjects completed the trial. These effects of topiramate were observed after week 8, when topiramate dose titration was complete. Topiramate-treated subjects also showed improvement both in drug use and employment problems measured by ASI composite scores. With a slow dose titration, topiramate appeared to be safe and well tolerated. The AEs were mainly mild and the most commonly reported ones included headache (n=6), fatigue (n=6), diarrhea (n=6), constipation (n=4) and nausea (n=4). One of the topiramate-treated subjects developed symptoms of kidney stones and was referred to an urologist for treatment.

Taken together, these studies provide preliminary evidence that topiramate is a promising medication for the treatment of individuals who are dependent on cocaine alone or those with co-morbid cocaine dependence and alcohol abuse.

Experience in subjects with alcohol dependence. A prospective, open-label, single-centre study was conducted to evaluate effectiveness of topiramate in control of alcohol craving for a 10-week period (Rubio *et al*., 2002). All subjects (N=24) had at least one other psychiatric comorbidity, and 21 were concomitantly treated with psychoactive drugs (mainly antipsychotics, lithium and/or SSRIs). Topiramate was used as adjunctive therapy at an initial dose of 50 mg/day and titrated upward by 25 mg every 3 days to a maximum dose of 400 mg/day. Topiramate reduced craving for alcohol (based on VAS scores) and alcohol use (i.e., total amount of drinks per day); it was well tolerated and no serious safety issues were reported.

More recently, topiramate was also found to be more effective than placebo in reducing alcohol use in a randomized placebo-controlled, double-blind trial involving alcohol-dependent subjects (Johnson *et al.,* 2003). In that trial, 75 subjects were assigned to topiramate (escalating dose of 25-300 mg/day) and 75 had placebo for 12 weeks. BBCET was applied in both groups to

promote medication compliance. The results of this study indicate that topiramate is more effective than placebo at reducing drinking and promoting abstinence in alcohol-dependent subjects who are seeking treatment (based on self-reported drinking and plasma levels of gamma-glutamyl transferase) as well as in reducing craving for alcohol (Johnson *et al.*, 2003). No serious adverse events were reported in this study. The following adverse events were reported more frequently in the topiramate group than the placebo group: dizziness (28.0% versus 10.7%), paresthesias (57.3% versus 18.7%), psychomotor slowing (26.7% versus 12.0%), memory or concentration impairment (18.7% versus 5.3%), and weight loss (54.7% versus 26.7%). Twelve of the 75 subjects treated with topiramate also tested positive by urine drug screen for marijuana (6 subjects), cocaine (3 subjects), opiates (1 subject), phencyclidine (1 subject), and amphetamine (1 subject).

Experience in subjects with opioid dependence. Topiramate was found to be effective for the treatment of opiate withdrawal in 3 patients undergoing an inpatient opiate detoxification program (Zullino *et al.*, 2002). All patients had a long history of opiate abuse and had been in outpatient and inpatient detoxification programs before. One of the patients received 100 mg of topiramate the first day, 500 mg the second day, 300 mg the third and fourth days and, finally, 100 mg the fifth day of withdrawal. Besides slight muscle aches, no withdrawal symptoms were experienced during the 10 days of hospitalization. The only observed AE was a slight fatigue on the second day of treatment. Another subject received 500 mg of topiramate the first 2 days of treatment with a subsequent taper off until day 8, in addition to methadone at 10 mg/day. Under this drug regime, no withdrawal signs were assessed during the whole 14 days of hospitalization. In the third subject, topiramate was introduced at a dose of 500 mg/day and rapidly tapered off until day 5 of treatment. This subject reported having experienced the most comfortable withdrawal until now and was discharged after 9 days of inpatient treatment. Overall, based on these three case reports, topiramate seems to be associated with less adverse events than clonidine and is more efficacious in reducing manifestations of withdrawal symptoms. Also, compared to the methadone-tapering method, topiramate does not produce opioid-like tolerance or physical dependence and it avoids the post-methadone rebound of withdrawal symptoms, which makes it possible for subjects completing a course of topiramate-assisted withdrawal to be immediately treated with opioid antagonist (i.e., naltrexone), if indicated. A further advantage may be topiramate's mood stabilizing properties. These data indicate that topiramate may be a promising alternative to clonidine or opiate tapering as treatment for opiate withdrawal.

4.2.3 Pharmacokinetics of Topiramate

Absorption of topiramate is rapid, with peak plasma concentrations occurring at approximately 2 hours following 400 mg of oral dose (TOPAMAX® – Package Insert). The relative bioavailablility of tablet formulation of topiramate is about 80%; the bioavailablility of topiramate is not affected by food. The pharmacokinetics (PK) of topiramate are linear with dose proportional increases in plasma concentration over the dose range studied (200 to 800 mg/day). The mean plasma elimination half-life of topiramate is 21 hours after single or multiple doses; the steady state is reached in about 4 days in subjects with normal renal function.

Topiramate is not extensively metabolized and is primarily eliminated unchanged in the urine (approximately 70% of the administered dose). Six metabolites have been identified in humans,

none of which constitutes more than 5% of an administered dose. The metabolites are formed via hydroxylation, hydrolysis and glucuronidation. Overall, oral plasma clearance (CL/F) is approximately 20 to 30 mL/min in humans following oral administration. The clearance of topiramate was reduced by 42% in moderately renally impaired (creatinine clearance 30-69 mL/min/1.73m^2) and by 54% in severely renally impaired (creatinine clearance <30 mL/min/1.73m^2) compared to subjects with normal renal function (creatinine clearance >70 mL/min/1.73m^2). Since topiramate is presumed to undergo significant renal reabsorption, it is unclear whether this experience can be generalized to all situations of renal impairment. In hepatically impaired subjects, the clearance of topiramate may be decreased; the mechanism of that is not well understood.

4.2.4 Topiramate Dose Justification

The current study will test a daily target dose of topiramate of 200 mg/day, which is known to be safe when slowly titrated. This dose did not show significant interactions with methamphetamine in a clinical pharmacology study and was efficacious for the treatment of cocaine dependence. The recommended total daily dose of topiramate as adjunctive therapy for epilepsy is 400 mg/day in two divided doses (TOPAMAX® – Package Insert).

4.2.5 Safety of Topiramate

Topiramate is a marketed product with which there is extensive experience and has been shown to be well tolerated. AEs most often associated with use of topiramate in adult populations are central nervous system-related. The most significant of these can be classified into three general categories: 1) cognitive-related dysfunction (e.g., confusion, psychomotor slowing, difficulty with concentration/attention, difficulty with memory, and speech and language problems, in particular, word-finding difficulties; 2) psychiatric/behavioral disturbances (e.g., depression or mood problems, and 3) somnolence or fatigue. Although in some cases these were mild to moderate, they at times led to withdrawal from treatment. Of the 1,135 patients exposed to topiramate in placebo controlled trials, 25% discontinued due to adverse events compared to the 10% of the 445 placebo patients. AEs associated with discontinuation of therapy included paresthesia (7%), fatigue (4%), nausea (4%), difficulty with concentration/attention (3%), insomnia (3%), anorexia (2%), and dizziness (2%). In the double-blind phases of clinical trials in approved and investigational indications, suicide attempts occurred at a rate of 3/1000 patient years (13 events/3999 patient years) on topiramate versus 0 (0 events/1430 patient years) on placebo. One completed suicide was reported in a bipolar patient on topiramate. The incidence of psychomotor slowing is only marginally dose-related, but both language problems and difficulty with concentration or attention clearly increased in frequency with increasing dosage in five double-blind trials (TOPAMAX® – Package Insert).

In the order of frequency, the most commonly observed AEs associated with the use of topiramate are: somnolence, dizziness, nervousness, ataxia, fatigue, speech disorders, abnormal vision, paresthesia, psychomotor slowing, difficulty with memory, nystagmus, confusion, nausea, diplopia and tremor (TOPAMAX® – Package Insert). In the Phase 1 topiramate interaction study of Johnson *et al.* (2005), dose of topiramate up to 200 mg daily did not increase

the hemodynamic effects of methamphetamine nor result in any clinically significant adverse effects.

Acute myopia with secondary angle closure glaucoma has also been reported in subjects receiving topiramate. Symptoms include acute onset of decrease visual acuity and/or ocular pain. Oligohidrosis (decreased sweating) and hyperthermia, infrequently resulting in hospitalization, has also been reported in association with topiramate.

As topiramate is a weak carbonic anhydrase inhibitor, it may cause lowering of blood bicarbonate levels causing metabolic acidosis. A Question and Answer sheet on this condition has been prepared by Ortho-McNeil Neurologics, Inc., and is provided in **Appendix I**. The post marketing reporting rate of serious adverse events in which metabolic acidosis was observed is 2.2 per 100,000 patient-years of exposure. A total of 32/2,086 (1.5%) of adults exposed to topiramate during its development reported the occurrence of kidney stones, an incidence about 2-4 times that expected in a similar untreated population. Carbonic anhydrase inhibitors are associated with promoting kidney stone formation by reducing urinary citrate excretion and by increasing urinary pH. Paresthesia, another AE associated with the use of other carbonic anhydrase inhibitors, is frequently reported by topiramate-treated patients as well. Certain agents including carbonic anhydrase inhibitors such as Diamox® (acetazolamide) or Zonegran® (zonisamide) may increase the risk of metabolic acidosis and should be used with caution. Blood electrolytes will be measured during study Weeks 4, 8 and 12 to monitor changes in blood bicarbonate levels and the risk of developing metabolic acidosis. Metabolic acidosis has been reported in patients receiving as low a dose as 50 mg/day and generally occurs early in the course of treatment.

4.3 **Brief Behavioral Compliance Enhancement Treatment (BBCET)**

BBCET was chosen as an adjunct to topiramate to foster, maintain, and promote compliance with the investigational product regimen using an easily disseminated strategy delivered by a research nurse. The primary goals of the sessions are to help subjects overcome the ambivalence that may be keeping them from making desired changes, thereby increasing motivation to change and increasing actual behavioral change. The BBCET method to be used in this study was modeled on that used in the National Institutes on Mental Health depression trial and the placebo controlled topiramate study of alcohol dependent subjects of Johnson *et al.* (2003). Treatment retention is a key element in the successful treatment of drug dependence and not easy to achieve. Johnson *et al.* (2003) reported that 73% of alcohol dependent subjects completed the full 12 weeks of treatment with topiramate when BBCET was used to promote compliance.

Ortho-McNeil Neurologics, Inc., is monitoring drug use compliance in another clinical trial designed to assess the efficacy of topiramate for the treatment of alcohol dependence. In this ongoing study, topiramate is escalated over a 5-week period using a flexible dosing schedule to a maximum dose of 300 mg/day. BBCET is being used in this study to promote compliance and treatment retention. Of the 157 subjects enrolled and randomized to topiramate treatment to date, 92% of these subjects were taking the 200 mg/day dose of topiramate by Week 5. Medication compliance was measured by counting the number of tablets dispensed and then returned at each study visit as well as with a diary card completed by the subject documenting tablet

consumption. Approximately 86% of the subjects reported taking at least 80% of the prescribed dose over the course of treatment.

5. STUDY OBJECTIVES

5.1 Primary Efficacy Objective

The primary efficacy objective of this study is to determine if topiramate relative to placebo reduces methamphetamine use in subjects with methamphetamine dependence as measured by quantitative urinalysis for methamphetamine. The primary efficacy outcome measure is negative methamphetamine use weeks during study Weeks 6 through 12. Data collected during this phase of treatment will be the focus of the primary outcome measure as this is the time period in which the subject will be treated with the maintenance dose of topiramate. However, secondary analyses will include the evaluation over the entire 12-week treatment period (excluding dose taper during Week 13). Use weeks are defined as each 7-day period staring with the first day of investigational product administration. A positive use week is any week in which at least one of the urine drug screens for methamphetamine was positive (≥ 300 ng/mL). A negative use week is any week in which all of the urine drug screens for methamphetamine were negative (< 300 ng/mL). If no drug screening results are available, the data for that week are considered as missing.

5.2 Secondary Efficacy Objectives

Secondary objectives include determining topiramate's effect as compared to placebo on:

1. The maximum consecutive number of methamphetamine non-use days for each subject according to self-report during study Days 36 through 84 and separately during study Days 1 to 84.
2. The proportion of subjects who achieved at least 21 consecutive days of methamphetamine non-use days during study Days 36 through 84 and separately during study Days 1 to 84 by self report and confirmed by negative urine tests for methamphetamine during the same period. All urine specimens collected and tested during the 21-day period of self-report must be negative. Specimens can be missing.
3. The weekly proportion of methamphetamine non-use days determined by subject's self-report during study Weeks 6 through 12 and separately during study Weeks 1 through 12.
4. The proportion of subjects who reduce their overall proportion of methamphetamine use days during study Days 36 through 84 and separately during study Days 1 to 84 by 25% or 50% or more of that assessed during the 14-Day baseline period or during the entire screening and baseline period.
5. The weekly median of the $\log_{10}$ of quantitative urine d-methamphetamine level during study Weeks 6 through 12 and separately during study Weeks 1 through 12.
6. The length of continued abstinence in the subset of subjects who were abstinent within the 7-day baseline period before randomization as defined in the randomization variables.
7. The severity of methamphetamine dependence, as assessed by changes from baseline in ASI-Lite and ASI-Lite Follow-up scores and Self and Observer scored CGI, and craving, as assessed by changes in BSCS scores.
8. HIV risk-taking behaviors (assessed by HRBS).

5.3 Safety Objectives

The safety profile of topiramate in methamphetamine dependent subjects will be determined by assessing AEs, MADRS assessments, clinical laboratory analyte levels, vital signs, weight, and ECG changes.

6 STUDY SPONSOR

This study will be conducted under an investigator-sponsored Investigational New Drug Application (IND) held by Dr. Bankole Johnson, IND # 68,400.

7 STUDY SITES

The will be a multi-center study conducted at 8 clinical sites under the direction of the investigator-sponsor who is the IND holder, Dr. Bankole Johnson, with two Study Co-Chairmen, Drs. Elmer Yu and Ahmed Elkashef.

8 STUDY DESIGN

This is a double-blind, multi-center, placebo-controlled, randomized, parallel group design study in methamphetamine-dependent outpatients. Subjects meeting the eligibility criteria after a screening period not to exceed 14-days and a 14-day baseline assessment period will be randomized in a 1:1 ratio to daily treatment with topiramate or matched placebo. Randomization variables include investigational site and methamphetamine use within 7 days before randomization (using – anyone with a self report of methamphetamine use or a methamphetamine positive urine sample versus abstinent – anyone reporting no use and all urine samples negative for methamphetamine). Once during baseline and at each weekly visit when investigational products are dispensed during the treatment phase, all subjects will receive BBCET, a manual-driven, low-intensity supportive program to foster, maintain, and promote compliance with the dosing regimen and to promote continuation in the study. A final follow-up assessment will be conducted approximately 28 days after completion of treatment.

9 SUBJECT SELECTION

Target enrollment includes one hundred forty (140) males and females with methamphetamine dependence (approximately 70 subjects per treatment group). Entry into this study is open to both men and women and to all racial and ethnic subgroups. An attempt will be made to randomize at least 30% females. Potential study subjects will be recruited from a variety of sources. The primary source will be individuals seeking treatment for methamphetamine dependence via referrals from local treatment providers and word of mouth from subjects already participating in the trial. Additional individuals will be recruited from the community by means of advertising in local media. Recruitment advertisements will be approved by each site's Institutional Review Board (IRB) and by NIDA.

9.1 Inclusion Criteria

Potential subjects must:

1. Be at least 18 years-of-age.

2. Have a DSM-IV diagnosis of current methamphetamine dependence as determined by SCID.

3. Be seeking treatment for methamphetamine dependence but not currently in a "formal" treatment program (see exclusion criteria #17 for the definition of formal treatment program).

4. Be able to provide written informed consent.

5. Be willing and able to comply with study procedures.

6. Have a BMI >18 kg/m^2 (due to potential anorexic effects of topiramate).

7. Have at least 1 methamphetamine or amphetamine positive urine specimen (> 500 ng/mL) within the 14-day screening period.

8. Have provided at least four urine specimens including one urine specimen within 7 days prior to randomization, and the accompanying other baseline repeated measures within the required 14-day baseline measurements period.

9. If female, have a negative pregnancy test and agree to use of one of the following methods of birth control:

    a. prescription oral contraceptives*
    b. contraceptive 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 and agree to use another method should sexual activity commence
    h. hormonal vaginal contraceptive ring
    i. contraceptive sponge
    j. surgical sterilization
    k. partner is surgically sterile
    l. be post menopausal for one year

    *Note: Since topiramate may compromise the effectiveness of oral contraceptives, subjects taking oral contraceptives will be encouraged to use a barrier method too and should be asked to report any change in their bleeding patterns and agree to use a barrier method should a change in bleeding patterns occur. This problem has only been reported for oral contraceptive use.

9.2 Exclusion Criteria

Potential subjects must not:

1. Have current dependence, defined by DSM-IV criteria, on any psychoactive substance (i.e., opioids) other than methamphetamine, nicotine, or marijuana or have physiological dependence on alcohol or a sedative-hypnotic (e.g. a benzodiazepine) that requires medical detoxification.

2. Have clinically significant depression defined by a total MADRS score of >24 during screening or current (within the past 30 days) suicidal ideation/plan (MADRS item 10 ≥ 4).

3. Have a urine drug screen positive for benzodiazepines (within 7 days prior to starting treatment) or barbiturates (within 14 days prior to starting treatment) per compliance with the washout period for prohibited drugs listed in **Appendix II.**

4. Have psychiatric disorders, such as current major depression, psychosis, bipolar illness, organic brain disorder, or dementia as assessed by the SCID interview, which require ongoing medication treatment or which would make medication compliance difficult. Have had electroconvulsive therapy within the past 90 days before screening, or have a history of Bipolar I Disorder or diagnosis of attention deficit (hyperactivity) disorder (ADHD or ADD) by history or SCID (see Notes).

5. Have a current diagnosis of anorexia nervosa or bulimia disorder.

6. Have serious medical illnesses or neurological disorders including, but not limited to, uncontrolled hypertension, significant heart disease (including myocardial infarction within one year of enrollment), angina, hepatic or renal disorders, Parkinson's disease, epilepsy, active syphilis that has not been treated or refuse treatment for syphilis (see note), or have had therapy with any opioid-substitutes (methadone, buprenorphine) within 2 months prior to enrollment, or have any gastrointestinal disorder that could result in a clinically significant alteration of metabolism or excretion of topiramate, or any serious, potentially life-threatening or progressive medical illness other than addiction that may compromise subject safety or study conduct. Any ECG/cardiovascular abnormality (e.g., QTc interval prolongation > 450 milliseconds in men or > 470 milliseconds in women), which in the judgment of the investigator is clinically significant.

7. Clinically significant renal disease and/or impaired renal function defined as an estimated serum creatinine clearance of ≤60 mL/min.

8. Have Hemoglobin A1c > 7%.

9. Have diabetes with unstable control of blood glucose in the past year before screening (controlled diabetic subjects should be monitored more closely during the study).

10. Have glaucoma or have a known family history of glaucoma. (Family is defined as the immediate biological relatives including mother, father and/or siblings).

11. Have a history of nephrolithiasis.

12. In the opinion of the investigator, be expected to fail to complete the study protocol due to probable incarceration or relocation from the clinic area.

13. Be pregnant or lactating (topiramate is a pregnancy category C drug).

14. Have clinically significant laboratory values, in the judgment of the investigator.

15. Have AST or ALT > 3 x upper limit of normal or bilirubin > 2 x upper limit of normal.

16. Have active tuberculosis (positive tuberculin test and confirmatory diagnostic chest x-ray).

17. Have participated in any behavioral and/or pharmacological intervention study or received "formal" psychosocial treatments within 2 months preceding the beginning of screening with "formal" defined as any treatment provided by a healthcare provider for which they could be reimbursed by an insurance company.

18. Be suspect for adult obstructive airways disease, but without formal diagnosis, for example: 1) have a history of wheezing and/or chronic coughing, 2) have a history of adult obstructive airways and/or treatment for this condition more than two years before the current application for the study, 3) have a history of other respiratory illness, e.g., complications of pulmonary disease (exclude if on beta-agonists), 4) use over-the-counter agonist or allergy medication for respiratory problems (e.g., Primatene Mist). If suspect, a detailed history and physical exam should be performed, and possibly pulmonary consult and/or pulmonary function tests, prior to including or excluding from the study.

19. Have a diagnosis of adult (i.e., 21 years or older) asthma, or chronic obstructive pulmonary disease (COPD), including those with a history of acute asthma within the past two years, and those with current or recent (past 3 months) treatment with inhaled or oral beta-agonist therapy (because of potential serious adverse interactions with methamphetamine), or have an FEV_1 <70 %.

20. Have received a drug with known potential for toxicity to a major organ system within 30 days prior to screening (e.g., isoniazid, methotrexate).

21. Be undergoing medication treatment for HIV with antiviral and/or non-antiviral therapy.

22. Be taking a medication that could interact adversely with topiramate unless the medication is discontinued and the washout criteria specified in **Appendix II** is met.

23. Be mandated by the court to obtain treatment for methamphetamine-dependence where such mandate required the results of urine toxicology tests to be reported to the court.

24. Have previously been treated with topiramate for any reason including research protocols and discontinued treatment due to an adverse event or due to a hypersensitivity reaction to topiramate or are currently taking topiramate for any reason (the 7 Day washout period as shown in Appendix II applies in this case).

Notes on inclusion/exclusion criterion: All potential subjects will be offered optional HIV testing. This test is offered as a courtesy to the prospective subject along with HIV education. A positive test for HIV is not an exclusion criterion.

Potential subjects who are positive for syphilis by the RPR test will have a microhemagglutination for *Treponema pallidum* (MHA-TP) confirmatory test performed and will be referred for appropriate follow-up and/or treatment, if required. If treatment is required, it must be completed within the 14-day screening window. Documentation of appropriate follow-up and/or treatment is required prior to randomization. Subjects may continue to be screened while the evaluation process is ongoing.

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. However, if liver function tests (e.g., ALT and AST) are over three times normal it is presumptive evidence that the subject has active hepatitis and should be excluded from the study. A tuberculin test (PPD) is performed on all subjects unless they report having a positive PPD in the past, in which case a chest X-ray is required. A positive 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 tests are positive, the subject will be notified of the test results and referred to treatment.

Potential subjects with respiratory disease who consent to discontinue beta-agonist use, with their prescribing physician's approval, may be considered for inclusion.

Any subjects taking a prohibited medication (Appendix II) can be considered for inclusion if the subject or clinic staff contact the prescribing physician and document that discontinuation meets with his/her approval, the subject agrees to discontinue the medication, and the washout period is met before randomization.

A history of methamphetamine-induced psychosis does not exclude a candidate from the study; however, the presence of current psychotic symptoms will exclude a candidate from the study until clinically stabilized.

10 INVESTIGATIONAL PRODUCTS

Topiramate: Topiramate is a sulphamate-substituted monosaccharide. The chemical name is 2, 3, 4, 5-Di-*0*-isopropylidene-beta-D-fructopyranose sulphamate. Topiramate has the molecular formula of $C_{12}H_{21}NO_8S$ and a molecular weight of 339.37. It is a white crystalline powder. It is freely soluble in acetone, chloroform, dimethylsulfoxide, and ethanol; it is also soluble in alkaline sodium carbonate or sodium phosphate solutions (pH of 9-10).

Topiramate will be supplied by NIDA, in 25 mg (round, white) and 100 mg (round, yellow) film coated tablets for oral administration.

Placebo: Identically appearing matched placebo tablets will also be supplied by NIDA.

10.1 Dispensing Investigational Products

Investigational products will be dispensed to subjects once per week at the first clinic visit of the week; however, as a flexible dosing schedule will be used, the dose may be adjusted at each clinic visit. Investigational products will be distributed directly to the subject by an investigative staff member authorized to distribute investigational products by a study physician, or study staff member legally authorized to prescribe medications and authorized by the site PI to perform this function for the study.

Because a flexible dosing schedule will be used in this trial, subjects' doses may be adjusted at each clinic visit. Subjects will be given an investigational product instruction card and will be instructed to take investigational products precisely as indicated on the card. The card details specific information relating to the investigational product, either topiramate or placebo. For example, tablets should not be broken and can be taken without regard to meals. Subjects will be asked to return their investigational product instruction card and tablet bottles for reconciliation and compliance assessments at the first visit of the week, during the BBCET visit.

10.2 Packaging

Topiramate will be provided in bottles containing 30 tablets per bottle of either the 25 mg or the 100 mg tablet. The following is a breakdown of the estimated number of tablets taken during each study period by a subject, if the schedule shown in Table 3 (section 11.1) is followed.

Study Days	Total # 25 mg tablets estimated to be taken	Total # 100 mg tablet estimated to be taken
1 - 7	7	
8 - 14	14	
15 - 21	28	
22 - 28	42	
29 - 84		112
85 - 91	18	
Total 91 Days	**109**	**112**

10.3 Labeling

The bottle of investigational product with 30 tablets per bottle will have a 2-part, tear-off label with directions for use and other information on each part. The tear-off section of the label will be removed and attached to the progress note when the investigational product is dispensed. The

second part of the label will remain affixed to the bottle. The Subject ID number and date dispensed (where applicable) must be added to all labels.

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 investigator or designated study personnel will maintain a log of all investigational products dispensed and returned. Bottles of investigational product dispensed will be inventoried and accounted for throughout the trial for each subject. Compliance with investigational product will be assessed by tablet count and by subject self-report. Subjects will be instructed to bring their bottle of investigational product back to the clinic at the first visit of each study week. During the BBCET session, which occurs at this visit, the BBCET administrator, a staff member who is qualified to dispense medication, will perform a pill count (number of tablets dispensed versus the number of tablets returned) and will complete the Weekly Dosing Record.

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 Investigator-Sponsor at the end of the study.

11 TREATMENT PLAN

11.1 Investigational Products

Blinded supplies of topiramate and/or matched placebo tablets will be distributed by authorized investigative staff weekly for daily self-administration by subjects. Subjects will be administered their first dose of investigational product at the first clinic visit after randomization. For the remainder of the trial, subjects will b e instructed to take investigational products once or twice daily according to the recommended dosing schedule in **Table 3**. During the first week of titration, subjects will receive investigational product, either topiramate or matched placebo, orally once a day. Subjects will receive investigational product orally twice a day from day 8 through day 89 and once a day on days 90 and 91. The dose will be titrated to the maximum dose of 200 mg/day or to the subject's maximum tolerated dose (MTD) over a 35-Day period. An investigational product instruction card will be provided at each visit with instructions for daily dosing until the next visit.

At the investigator's discretion, the titration rate may be adjusted and the maximum dose may be adjusted to the MTD, but may not exceed more than an increase of > 100 mg/day and a maximum daily dose of 200 mg/day. All dosing will occur as a twice-daily regimen except for the first week of the study, which will be a single evening dose of 25 mg. With the exception of the 25 mg dose, the rest of the doses will be taken by splitting the total daily dose as evenly as

possible twice per day, once in the morning and once in the evening. When a dose cannot be split into two equal amounts, the amount over half the dose will be taken with the rest of the evening dose. In instances where splitting the dose causes side effects, such as drowsiness, that interfere with the subject's ability to carry out his/her daily routine, the site investigator, after communicating with the Medical Monitor, may instruct the subject to take the study drug once per day, usually in the evening. Tablets should not be broken. After the second week of titration, subjects must take at least 50 mg/day of topiramate or matching placebo for the duration of the treatment phase. If the subject experiences significant drug related adverse events during the titration period, the dosage may be adjusted as necessary; however, the subject must maintain a minimum dose of 50 mg/day. Downward dose adjustments should revert to the previously tolerated dose. During the maintenance period, subjects should remain at the dose attained during the titration period. A single dose reduction will be permitted during the maintenance period to manage tolerability. Upon completion of the maintenance period, subjects will taper their study investigational product by decreasing the dose over a 7-day period until they are no longer taking investigational products. The dose will be reduced in a step-wise manner as follows: 100 mg/day for 3 days, 50 mg/day for 2 days, 25 mg/day for 2 days, then discontinuation.

Table 3. Double-Blind Topiramate/Placebo Recommended Dosing Schedule

Days	Investigational Products		Total Daily Dose	
	25 mg Tablets or Matching Tablet(s)	**100 mg Tablets or Matching Tablet(s)**	**Topiramate**	**Placebo**
Dose Titration				
1-7	1 tablet (PM)		25 mg	Matching tablet(s)
8-14	1 tablet bid (AM/PM)		50 mg	
15-21	2 tablets bid (AM/PM)		100 mg	
22-28	3 tablets bid (AM/PM)		150 mg	
29 - 35		1 tablet bid (AM/PM)	200 mg	
Maintenance Dose				
36-84		1 tablet bid (AM/PM)	200 mg	Matching tablets
Dose Taper				
85 –87	2 tablets bid (AM/PM)		100 mg	Matching tablets
88-89	1 tablet bid (AM/PM)		50 mg	
90-91	1 tablet (PM)		25 mg	

Dose Adjustments/Missed Doses. Every attempt will be made to maintain subjects at the investigational product dose specified in this protocol. However, subjects who are unable to tolerate the specified dose will be allowed to continue in the study at a reduced dose (the MTD as determined by the research physician). However, each subject must tolerate at least a 50 mg dose to continue in the study. When topiramate reduction is warranted due to adverse events, the site principal investigator (PI) or site physician will decrease the number of tablets of investigational

product from the maximum to the amount that is clinically reasonable. As dose reductions are permissible in both groups, this will not break the blind for a subject.

In the case of drug related adverse events, discontinuation of the investigational product altogether may be necessary. In such a situation, the research physician will evaluate the subject to determine whether the investigational product should be discontinued immediately, or should be tapered prior to discontinuation. If a woman becomes pregnant, she will be instructed to immediately stop taking investigational products without any dose tapering. All pregnancies reported during the study starting with the day in which informed consent was given until the final study visit will be reported as serious adverse events to NIDA in accordance with the reporting requirements in **Appendix IV**. Subjects who discontinue taking investigational agents prematurely will be discontinued from the study except that all adverse events must be followed until resolution or the event has stabilized.

If a subject misses a dose, s/he will be instructed to start taking the investigational product at the last dose that s/he was taking before stopping.

11.2 Brief Behavioral Compliance Enhancement Treatment (BBCET)

11.2.1 BBCET Overview

An initial BBCET session will be conducted with each subject during his/her first baseline visit. This initial session is intended to be informational about consequences of methamphetamine abuse. The negative aspects of methamphetamine use will be discussed fully with subjects, including health risks, decreased cognitive function, psychosis, and risks associated with needle sharing. Educational materials will be provided to subjects. During treatment, subjects will participate in BBCET sessions once per week with the BBCET administrator (see qualifications for this person below). Each session will last approximately 15-30 minutes. These sessions have been modeled after the National Institute of Mental Health (NIMH) Treatment of Depression Collaborative Research Program (Fawcett *et al.*, 1987). The BBCET manual to be utilized in this trial is provided in Appendix VI. The primary goal of these sessions is to help subjects overcome the ambivalence that may be keeping them from making desired changes, thereby increasing motivation to change and increasing actual behavioral change. The techniques of achieving the primary goal include proven strategies from the motivational and behavioral change literature, such as helping subjects to understand the consequences of their substance use, emphasizing that it is a disease rather than a problem of poor willpower; providing a rationale for medication testing; providing support for and belief in behavioral change; praising positive change; and reinforcing subjects' desires to get better and their desire and ability to become more involved in improving their condition.

In each session, the subject is encouraged to continue the use of investigational product and participate in the study. The BBCET administrator will be responsive to the subject's complaints and needs while also maintaining control of the session. In order to engage the subject in a positive relationship, the BBCET administrator will create an atmosphere of warmth and trust based on sharing all the information with regard to the research nature of the trial and the choice of the medication.

In each session, the BBCET administrator will communicate and discuss investigational product effects, if any, subjects' concerns about any adverse events and compliance barriers with the subject in understandable terms, and will clearly convey her/his knowledge and expertise in the treatment of methamphetamine dependence. If there are minor adverse events, especially in subjects who are apprehensive about taking investigational products, further educative efforts regarding the 'hows' and 'whys' of investigational product use will be employed.

When given the investigational product for the first time, subjects will instructed to seek immediate medical attention if they experience blurred vision or periorbital pain at any time throughout the trial. Additionally, subjects will be encouraged to maintain adequate fluid intake to minimize the risk of renal stone formation. Subjects will be warned about the potential for somnolence, dizziness, confusion, and difficulty concentrating and subjects will be advised not to drive or operate machinery until they have gained sufficient experience to determine if there are effects on their motor performance. If the subject experiences weight loss, he/she will be instructed to consider additional food intake.

Subjects will neither be encouraged nor discouraged from seeking other behavioral modification treatments such as self-help or 12-step programs during their participation in the study. Participation in self-help or 12-step programs and attendance at scheduled BBCET sessions will be documented.

11.2.2 BBCET Administrator Training, Qualification, and Quality Control

Several methods will be used to ensure that the BBCET is administered with expertise and uniformity across study sites. Selection and training of the BBCET administrator, as well as ongoing monitoring and supervision, will be used as quality control procedures. To monitor and prevent deviation from the protocol, all BBCET sessions will be audiotaped, tapes will be sent to the University of Virginia, Center for Addiction Research and Education, and a random sample of at least 10% of tapes from a single administrator will be selected by a study statistician for review by the Investigator-Sponsor's designee for quality and adherence to manual guidelines. The Investigator-Sponsor will approve selection of the BBCET administrator at each site. A BBCET administrator must be someone trained to identify drug related AEs, such as a research nurse. Training will be provided to all the BBCET administrators and training tapes or CDs will be provided to all the sites for the training of new staff. Each BBCET administrator will be certified to conduct the sessions. For this purpose the audiotapes of the first two sessions conducted by any new administrators will be reviewed by the University of Virginia for conformance to the manual. Each study site will appoint a BBCET supervisor as well as a BBCET administrator. The BBCET supervisor must be a physician licensed to prescribe medications. The BBCET supervisor will monitor BBCET sessions and provide training and guidance to the BBCET administrator as needed.

12 Study Procedures

12.1 Subject Recruitment

Interested candidates who are seeking treatment and are available to come to the clinic for 133-to-147 days will meet with the investigator or designated investigational staff and will 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. A separate consent form will be used for potential subjects who agree to participate in the genetics analysis part of the study. Recruitment strategies vary across each site based on their local population, however standard tactics will be used (i.e., flyers, newspaper ads, radio ads). Local IRBs and NIDA will approve all advertising materials used for subject recruitment.

12.2 Screening/Baseline Assessments

Screening and baseline assessments will be conducted as shown in Table 4. Once a methamphetamine-positive urine is provided and other screening measures have been completed, the subject may proceed to baseline assessments.

During screening, all potential subjects who provided separate consent to participate in the pharmacogenetics part of this study will submit 3 blood samples for analysis. A single blood draw for genetic samples will be performed at screening. This one draw will result in the collection of one tube of blood for genomic DNA analysis and two tubes of blood for RNA analysis. These subjects will also provide data to be used in conjunction with the genomic analyses, even if they are ultimately found ineligible to participate in the main study. Data that will be used in the genomic analyses include: demographic data, medical and substance use history, family history, and diagnostic information obtained by the SCID. Detailed information about what data will be used in the pharmacogenetic part of the study is enumerated in a separate Pharmacogenetics Informed Consent Form. Note: Subjects who do not consent to the genetics analysis part of the study will not have a Family History taken.

Baseline assessments will occur over a consecutive 14-day period. A potential subject must complete the minimum set of baseline measures over this consecutive 14-day period to be eligible for the study. If a subject fails to satisfy eligibility criteria during the screening and baseline periods, s/he may not be re-screened. Baseline measures over the consecutive 14-day period include collection of at least four urine specimens with one of these being collected in the 7-day period prior to randomization and the accompanying other baseline repeated measures. Demographic data and the reason that any subject did not meet eligibility criteria must be recorded for anyone who consented to screening even if the individual is a screening failure.

12.3 Subject Randomization and Enrollment

Adaptive random allocation of subjects to study groups will be used to balance groups with respect to baseline prognostic variables. The procedure allocates treatment assignment based on the assignments and prognostic variable levels for all previously enrolled subjects. A new subject will be randomized with a "biased coin" procedure that uses randomization probabilities, favoring the treatment with the deficit enrollment, to improve the balance on group assignment (Efron, 1971).

The VA Cooperative Studies Program Coordinating Center (CSPCC) in Perry Point, MD will act as the Data Management Center for this trial. Information pertinent to the randomization variables for treatment assignment will be obtained from site personnel through the CSPCC's

Interactive Touch Tone Randomization System (ITTRS). The ITTRS is an automated phone system which is able to provide random treatment assignments 24 hours/day, 7 days/week.

Subjects meeting all study eligibility criteria throughout the screening and baseline periods will be scheduled to come to the clinic for a final eligibility determination. Subjects must be randomized by the seventh day after the last urine sample collected in baseline, and within the period of 15-18 days after the first day of baseline. If the subject is determined to still be eligible, site personnel who are authorized to randomize subjects and who have completed training for the ITTRS will call the system and provide the site number, unique Subject ID and Alpha Code, and the assessment of whether the individual used methamphetamine or was abstinent during the 7-day period prior to the randomization request. Anyone with a self-report of methamphetamine use or a methamphetamine-positive urine sample in this 7-day period is defined as having used. Any individual who reports no methamphetamine use and provides urine samples that are all negative for methamphetamine in this 7-day period is considered abstinent. The ITTRS will provide a random treatment kit number, which assigns the subject to one of the two treatment groups. After successful randomization, the subject will be administered the first dose of investigational product in the clinic.

For subjects who meet eligibility requirements and who have provided separate informed consent to participate in the pharmacogenetics portion of the study, enrollment in the pharmacogenetics portion of the study will take place during the ITTRS randomization call for the main topiramate study. For subjects who do not meet eligibility requirements to participate in the topiramate study, a separate ITTRS call is required to enroll them in the pharmacogenetics portion of the study. This call, or portion of the call, will be brief and will serve to identify subjects who have consented to the pharmacogenetics arm of the study and who have provided blood samples at screening for genetic analyses by a unique barcode number. This barcode number will be placed on all genetic blood samples and will allow all potentially identifying information, including Subject ID Number, Site Number and Alpha Code to be omitted from blood samples sent to the lab for genetic analysis. This also maintains the link between genetic samples and Subject ID directly in the dataset, rather than by site personnel.

12.4 Treatment Phase

Subjects will be scheduled for assessments three times per week usually on a Monday, Wednesday, and Friday for 91 days. Treatment may start any day of the week. Two consecutive days may be scheduled around holidays or other schedule conflicts. All subjects will be offered an opportunity for HIV testing and counseling and HIV/AIDS education (**Appendix III**). Subjects will be given investigational products once per week and instructions on taking the investigational products during BBCET sessions. Clinical evaluations are described in detail in section 13.0.

12.5 Early Termination

Subjects who terminate from participation in the study before the completion of the treatment phase, will be asked to come to the clinic for a final assessment, unless they have formally withdrawn and have asked not to be contacted. These assessments include all those to be conducted during study Week 12 (Table 4). Staff will attempt to contact those subjects who have

not specifically requested otherwise to establish their reason for early termination and to determine whether or not they experienced any untoward effects from study participation.

12.6 17-Week Follow-up

Subjects will be asked to come to the clinic for a final follow-up visit during week 17 (Study Days 113 to 119). The subject will be asked to provide a urine specimen for methamphetamine/creatinine and a urine drug screen, provide self-report for methamphetamine, alcohol, marijuana, nicotine, cocaine, opiates, benzodiazepines and barbiturates use, and report any AEs. Vital signs will be checked and a pregnancy test will be performed on all female subjects. The ASI-Lite Follow-up, BSCS, CGI-S and CGI-O will be administered at the Week 17 follow-up visit. In addition, subjects will be administered the HRBS assessment at the final follow-up interview. The subject will be asked to report any current treatments for drug or alcohol abuse and to give an overall impression of the investigational product. If it is not possible to arrange for the subject to return to the clinic, the subject will be telephoned and asked to provide a current self-report of methamphetamine and other drug use, current treatment for drug or alcohol abuse, and an impression of the investigational product. If a subject cannot be contacted directly, attempts will be made to reach the individual(s) previously identified by the subject as a contact source.

12.7 Maintaining and Breaking the Study Blind

The decision to break the study blind for an individual subject lies with the site principal investigator, the Investigator-Sponsor, and/or with the NIDA medical monitor or NIDA designee, but should be resorted to only in cases of life-threatening emergency when knowledge of the investigational product will influence clinical management. See the study Operations Manual for a detailed list of contact numbers and the procedure for unblinding.

12.8 Subject Compensation

Subjects will be compensated for travel expenses and for time contributed to this research study in the form of vouchers or retail scrip. Upon each clinic visit during the screening/baseline period as well as during the treatment phase, subjects will be compensated $10 per visit (maximum of $160 during screening and baseline and $380 during treatment). In addition, subjects will be compensated $25 at treatment completion and $10 at the follow-up visit. The total maximum earning for compensation is $575 in vouchers or retail scrip. Travel expenses (bus or cab fares) may be paid with an acceptable form of compensation. Subjects will be compensated regardless of whether they continue to receive the investigational product. This compensation is for time and expenses incurred for study participation (e.g., gasoline, public transportation).

12.9 Study Termination

12.9.1 Subject Discontinuation

An investigator will discontinue a subject's participation in the study if s/he deems it clinically appropriate or for any of the following reasons:

1. Significant AEs associated with the investigational products,
2. Subject cannot tolerate a 50 mg/day dose of investigational product,
3. Serious or unexpected AEs that would make further study participation not in the subject's best interest,
4. Total MADRS overall score is > 24, and/or question item 10 (suicidal thoughts) is ≥ 4 at any visit during the study,
5. Pregnancy (see Section 11.1),
6. Inability to comply with the study protocol (see below),
7. Subject engages in cognitive behavioral therapy or psychotherapy,
8. Serious or chronic protocol violations,
9. Serious intercurrent illness, or
10. Administrative reasons such as presenting a danger to staff or other subjects.

Incarceration. No study procedures will be performed on, nor assessments obtained from, any individual during the time he or she may be considered a prisoner through the course of the trial. A prisoner is defined as any individual involuntarily confined or detained in a penal institution. The term is intended to encompass individuals sentenced to such an institution under a criminal or civil statute, individuals detained in other facilities by virtue of statutes or commitment procedures that provide alternatives to criminal prosecution or incarceration in a penal institution, and individuals detained pending arraignment, trial, or sentencing (45CFR46.303, October 1, 2004).

Failure to comply with protocol. A subject will no longer be eligible for study participation, if s/he misses 7 consecutive study visits. If a subject is to be discontinued, s/he will be contacted to schedule all final termination assessments scheduled during study Week 12.

Voluntary withdrawal. A subject may withdraw from the study anytime s/he wishes. If a subject withdraws, s/he will be contacted to schedule all treatment termination assessments scheduled during study Week 12, unless he/she has requested not to be contacted.

Study subjects withdrawn from the trial secondary to a medical or psychiatric concern will be referred for appropriate treatment. Subjects will be asked to sign a general consent for the release of information to the referred health care. Study staff may request transportation for emergency treatment of a subject if medically appropriate (e.g., for acutely psychotic or suicidal subjects).

Every study subject will be encouraged to carry a wallet card that identifies him or her as a subject in a clinical research study. The card will provide the name and phone number of the investigator (physician) at the site who can be contacted in the event of an emergency. The card will also instruct the non-study physician rendering emergency care to provide information to the study physician with regards to that care.

12.9.2 Trial Discontinuation

The study Investigator-Sponsor (Dr. Bankole Johnson) and NIDA have the right to discontinue the trial at any time.

12.10 Concomitant Medications

Any medications (including prescription, over-the-counter, herbal supplements and health store products) to be taken during the study must be approved by a study physician. A list of prohibited medications is provided in **Appendix II.** If a subject is taking any of these medications during screening, he/she must consent to stop taking the medication for the trial and the washout period for the medication must be within the allowed screening and baseline limitations (28-days) in order for him/her to be considered eligible for the study. Before any changes are made to a subject's prescription medications, the prescribing physician should be consulted by the site investigator or study physician, if the subject agrees, or by the subject him/herself. Subjects who are on medications that need to be tapered or discontinued will be given instructions for tapering/discontinuing.

13 Clinical Evaluations

Study assessments should be completed according to the schedule provided in **Table 4.**

Notes on the Schedule of Assessments

Screening Assessments. Prior to enrollment in the study, subjects will be screened to determine if they meet eligibility requirements. During screening, each urine specimen will be tested using an onsite test device for amphetamine, methamphetamine, cocaine, opiates, benzodiazepines, tetrahydrocannabinol, and barbiturates. Once one methamphetamine-positive urine is provided and other screening measures have been completed, the subject may proceed to baseline assessments. During screening, all potential subjects who provided separate consent to participate in the pharmacogenetics portion of the study will submit 3 blood samples for analysis. A single blood draw for genetic samples will be performed at screening. This one draw will result in the collection of one tube of blood for genomic DNA analysis and two tubes of blood for RNA analysis. These subjects will also provide data to be used in conjunction with the genomic analyses, even if they are ultimately found ineligible to participate in the main study. Data that will be used in the genomic analyses include: demographic data, medical and substance use history, family history, and diagnostic information obtained by the SCID.

Table 4. Table Time and Events Schedule																	
Assessment	**Screen-ing[a]**	**Base-line**	**Treatment**														**Follow-up**
			Dose Titration					**Dose Maintenance**							**Dose Taper**		
Study Week	-4 to -2	-2 to -1	1	2	3	4	5	6	7	8	9	10	11	12/ Term	13		17
Study Days	-28 to -15	-14 to -1	1-7	8-14	15-21	22-28	29-35	36-42	43-49	50-56	57-63	64-70	71-77	78-84	85-91		113-119
Screening																	
Informed consent	X																
SCID/Psych evaluation[b]	X																
Demographics[b]	X																
Medical and Family History[b]	X																
Breathalyzer test (if indicated)	X	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		-
Prior medications	X																
Infectious disease panel	X																
HIV test (optional)	X																
Eligibility checklist			X														
Randomization			**X**														
Safety																	
Physical exam	X													X			
Vital signs + weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Hematology[d]	X													X			
Hemoglobin A1c	X																
Blood Chemistry[e]	X					X				X				X			
Medical urinalysis	X													X			
Urine pregnancy test	X		X[c]			X				X				X			X
ECG	X													X			
Adverse events	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		X
Con. medications		X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
MADRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Efficacy																	
ASI-Lite/ASI-Lite Follow-up		X				X				X				X			X
HRBS		X												X			X
BSCS + CGI-S + CGI-O		1X/week	X	X	X	X	X	X	X	X	X	X	X	X			X
SUR	X	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	X		X
Urine drug screen – onsite test device	X	✓															
Urine drug screen –lab		✓[f]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓			X
Blood for DNA (optional substudy)[b]	X																
Blood for RNA (optional substudy)[g]	X									X				X			
BBCET (dosing compliance)		X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Follow-up interview																	X

Table 4. Table Time and Events Schedule

SYMBOLS: X = one time during screening, baseline, treatment study week, or follow-up week. ✓ = every visit scheduled for three times per week.

[a]Once one methamphetamine-positive urine is provided and other screening measures have been completed, subjects may proceed to baseline assessments.

[b]These screening assessments will be performed on each individual who consented to genetic analysis. For those not eligible for study participation, if the data has been collected, it will be transcribed onto CRFs. Two DNA tubes will be collected during screening. Family history will only be collected on those subjects agreeing to the genetics study.

[c]The urine pregnancy test must be negative on the first day that investigational products are given and repeated monthly.

[d]Hematology analytes include hemoglobin, hematocrit, red blood cells, platelets, total white blood cells, and percentage of neutrophils, lymphocytes, monocytes, eosinophils, and basophils.

[e]Blood chemistries include: blood urea nitrogen (BUN), creatinine, glucose, alanine aminotransferase (ALT/SGPT), aspartate aminotransferase (AST/SGOT), gamma glutamyltranspeptidase (GGT), direct and total bilirubin, alkaline phosphatase (ALP), sodium, potassium, chloride, and bicarbonate.

[f]Only urine samples collected during from subjects who were randomized will be sent to NWT to analysis.

[g]Blood for RNA analysis should be collected at the same time of day at every collection time point to control for circadian rhythm effects on expression. One RNA tube will be collected during screening and at all other time points during treatment.

Baseline Assessments. Baseline assessments to be completed over a single 14-day period include the following:

1. Three times a week for 14 consecutive days:
   a. Alcohol breathalyzer test (if indicated)
   b. Urine drug screen using an onsite testing device.
      Subjects must provide at least 4 urine specimens in a consecutive 14-day period. No more than 3 of the specimens may be obtained in one 7-Day period of the 14-day baseline and no more than two specimens can be collected on consecutive days.
   c. Substance Use Report (SUR).
   d. Urine methamphetamine plus creatinine measurements.
      Note: Quantitative methamphetamine assay will be performed at the central laboratory only for the urine samples collected for the subjects who were randomized into the study.
2. The following must be obtained weekly for 14 consecutive days:
   a. BSCS
   b. CGI-S
   c. CGI-O
   d. Vital Signs and weight
   e. MADRS

Assessments During Treatment. Some assessments will be collected three times per week (typically on a Monday, Wednesday, and Friday) and some will be collected once per week per the schedule in Table 4. Assessments collected one time every 7-day period during the treatment phase are ideally collected at the first visit of the week with the exception of those collected during Week 12. The once weekly assessments to be collected during Week 12 should be collected at the end of the week. If any of these measures were not collected during Week 12, they can be collected during Week 13. In addition, the assessments listed for collection during study Week 12 will be collected on any subject who discontinues the study early, as soon after discontinuation as possible. Assessments to be collected during the dose taper include treatment compliance and safety assessments. No efficacy measures are collected during Week 13. The

final visit during Week 13 should include an assessment of concomitant medication use. Clinical laboratory studies may be repeated at any time, if clinically significant values are observed.

14 ASSESSMENT METHODS

NOTE: Study personnel can assist any subject to self-administer any assessments for which a subject is unable to self-administer (e.g. physical handicap, poor reading skills) by reading the questions out loud to the subject and/or marking the subject's response on the source document or CRF. However, study personnel are not to offer interpretations of the questions.

14.1 Adverse Events (AEs)

A research nurse, physician, or medically trained staff will assess AEs at all study visits. If an AE is reported that requires medical attention, it should be reported to a study physician immediately. The study physician will meet with the study staff once a week to review AEs recorded by the research nurse on all subjects, and the study physician may then meet any subjects for whom additional follow-up or AE assessment is indicated. The study physician will also assess the subjects for any medical or psychiatric adverse event. Both the nurse and physician will assess AEs by asking the subject "How have you been feeling since I last saw you?" The type of AE, severity of the AE and the relationship of the AE to the study treatments will be recorded on an AE CRF, according to the procedures described in Section 15.6.

14.2 ASI-Lite CF Version and ASI-Lite Follow-up

The ASI-Lite CF will be administered at screening/baseline by a research staff member having at least a bachelor's degree in the social sciences or equivalent training. The ASI-Lite assesses the severity of the subject's status in seven areas (medical, employment, drug use, alcohol use, legal, family/social, and psychological). Composite scores will be calculated according to the procedures described by McGahan *et al*. (1982) and Carroll *et al*. (1994). The Lite version is a shorter version of the ASI that still retains all questions used to calculate the ASI composite scores. ASI-Lite Follow-up will be administered during weeks 4, 8 and 12; it eliminates demographic and other questions that do not change over time.

14.3 Blood Chemistry

Blood chemistries will be analyzed during screening to establish eligibility and will be repeated during weeks 4, 8, and 12. Quantitative analysis will be performed for the following analytes: blood urea nitrogen (BUN), creatinine, glucose, alanine aminotransferase (ALT/SGPT), aspartate aminotransferase (AST/SGOT), gamma glutamyltranspeptidase (GGT), direct and total bilirubin, alkaline phosphatase (ALP), albumin, sodium, potassium, chloride, and bicarbonate.

The laboratory performing these assessments should be either directly regulated by the College of American Pathologist (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.

14.4 Breathalyzer Test

If the subject appears to be intoxicated at clinic visits, the breathalyzer or breath alcohol test will be administered to assess recent alcohol intoxication and local institutional and state laws will be followed with respect to treatment of intoxicated subjects.

14.5 Brief Substance Craving Scale (BSCS)

The BSCS is a self-administered assessment that asks the subject to rate his or her craving for methamphetamine. The tool also asks the subject to assess the craving for a second and third substance, if any. The BSCS used for this study is a modification of the State of Feelings and Cravings Questionnaire (Mezinskis, *et al*., 1998).

14.6 Calculated Creatinine Clearance

The Cockroft-Gault (1976) formula will be used to calculate creatinine clearance as follows:

If serum creatinine is provided in mg/dL then use the following:

Males $\quad CrCl\ (mL/min) = \dfrac{(140 - age\ (years) \times body\ weight\ (kg))}{(72) \times (serum\ creatinine\ [mg/dL])}$

Females $\quad CrCl\ (mL/min) = \dfrac{0.85 \times (140 - age\ (years) \times body\ weight\ (kg))}{(72) \times (serum\ creatinine\ [mg/dL])}$

If serum creatinine is provided in μmole/L then use the following:

Males $\quad CrCl\ (mL/min) = \dfrac{(140 - age\ (years) \times body\ weight\ (kg))}{(0.81) \times (serum\ creatinine\ [\mu mole/L])}$

Females $\quad CrCl\ (mL/min) = \dfrac{0.85 \times (140 - age\ (years) \times body\ weight\ (kg))}{(0.81) \times (serum\ creatinine\ [\mu mole/L])}$

14.7 Clinical Global Impression-Observer (CGI-O)

The CGI-O requires a trained observer to rate the global severity of the subject's methamphetamine dependence symptoms and to rate the improvement of the subject's methamphetamine dependence since baseline. The severity of the subject's methamphetamine dependence is rated first according to eight specific problem areas often associated with methamphetamine dependence. Then the global severity is rated, followed by the global improvement.

14.8 Clinical Global Impression-Self (CGI-S)

The CGI-Self is a self-administered assessment that asks the subject to rate the global severity of his or her methamphetamine dependence symptoms and to rate the improvement of his or her methamphetamine dependence symptoms since the beginning of the study.

14.9 Prior and Concomitant Medications

All medications (prescribed and over the counter medications plus herbal remedies) taken by the subject 30 days prior to the start of screening, during the screening/baseline period, while taking investigational products, and during the follow-up period will be recorded. Medications taken after the start of screening must be pre-approved by the study physician whenever possible to avoid interactions with the investigational products. If a subject reports taking a prohibited medication (Appendix II) during screening and the subject or clinic staff has contacted the prescribing physician to document that discontinuation meets with his/her approval and the subject agrees to discontinue the medication, the dates that prohibited medications were stopped should be entered onto the prior medications case report form. All concomitant medications reported by the subject or prescribed by the study physician will be recorded. See **Appendix II** for a list of prohibited medications.

14.10 Demographics

Age, gender, ethnicity, years of education, usual employment pattern in the past 30 days, and marital status data will be collected. Demographic data will be collected on all subjects who sign a consent form.

14.11 ECG

Twelve-lead electrocardiograms will be performed according to standard procedures. Ventricular rate (bpm), PR (ms), QRS (ms) and QTc (ms) will be reported on the ECG readouts. The results will be reviewed by a study physician who will consult a board-certified cardiologist, if needed.

14.12 Follow-up Questionnaire

The Follow-up Questionnaire will document the information collected at the follow-up interview during week 17, including if contact was made with the subject, or documenting the subject's death. In addition, the form asks questions regarding the subject's drug use, and current treatment for drug and alcohol abuse.

14.13 Genetic Analysis

Microarray technology from Affymetrix will be used to perform genotyping (DNA samples) and expression analysis (RNA samples). In addition, genotyping performed at the University of Virginia will be performed on an ABI 7900 system. The GeneChip® Mapping 100K array set will be used for genotyping and the Human Genome U-133 Plus 2.0 array will be used for expression analysis. Blood samples for genetic analysis will be collected using standard phlebotomy techniques into Vacutainer™ tubes containing special preservatives for subsequent

isolation of RNA and DNA. Blood for RNA isolation will be collected at approximately the same time of day for each individual for all three collection time points to control for circadian rhythm effects on expression.

Two blood samples will be collected from every individual who consented to genetics analysis for genotyping (PAXgene™ Blood DNA). Blood samples for expression analysis will be collected into PAXgene™ Blood RNA Tubes. All of these samples will be sent to Expression Analysis for processing. After DNA extraction, Expression Analysis will send DNA to Dr. Johnson's laboratory at the University of Virginia for genotyping studies in his laboratory. Detailed procedures for the proper collection of blood for genotyping and expression analysis and shipping to Expression Analysis and the University of Virginia are provided in the study's Operations Manual. Blood must be shipped the same day that it was collected and only should be collected on Mondays through Wednesday to assure delivery to the laboratory during the work-week.

Gene expression and SNP profile data produced at Expression Analysis will be submitted to Information Management Consultants (IMC) for data warehousing and analysis using IMC's TeraGenomics® genomics data warehouse solution. The TeraGenomics application takes advantage of the detail-rich, probe-level feature information in Affymetrix GeneChip® .CEL files to calculate gene expression levels, calls, and associated statistics. The application computes pair-wise comparisons among thousands of chips through a rapid point-and-click interface, and stores the comparison results in the warehouse for reuse. It also supports Robust Multichip Analysis with no limits on the number of microarray chips included in the analyzed sample set. TeraGenomics will be adapted to support SNP analysis including SNP allele calling and SNP cluster analysis. Genes of interest that emerge from the data will be investigated through links to gene curation data at NetAffx, NCBI, and other public sources.

14.14 Hematology and Hemoglobin A1c

Blood will be collected in anticoagulant containing evacuated venous blood collection tubes (e.g., Vacutainer™) for hematologic assessments. Complete blood counts (CBC) with differentials and platelet count will be performed. Quantitative analyses for hemoglobin, hematocrit, red blood cells, platelets, total white blood cells, and percentage of neutrophils, lymphocytes, monocytes, eosinophils, and basophils will be performed. A hemoglobin A1c analysis will also be performed, at screening only, for eligibility determination. The laboratory performing these assessments should be either directly regulated by the College of American Pathologist (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.

14.15 HIV Risk-Taking Behavior Scale (HRBS)

The HRBS is a brief 11-item interviewer-administered scale (Darke *et al.*, 1991), to which the 12th item ("Have you had an HIV test come back positive?") was added by NIDA. It measures two distinct HIV risk factors in the behavior of intravenous drug users: one related to injecting behaviors and the other to sexual behaviors.

14.16 HIV Test

All subjects will be offered the opportunity to have an HIV test performed. This test is not requisite for study participation. A separate HIV test informed consent must be obtained before collecting blood for this test. An antibody test will be performed on a serum sample collected from the subject after the HIV informed consent form is signed. The clinic will use its own HIV consent form. The results of the HIV test will not be reported in the study database.

14.17 Infectious Disease Panel and Syphilis Tests

Blood will be collected in a serum separation evacuated venous blood collection tube (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 on all subjects and, if positive, a chest x-ray is required to assess active tuberculosis. If the subject reports that s/he has been previously positive for the PPD test, the PPD test will not be performed and only a chest x-ray will be required. A rapid plasma reagin (RPR) test for syphilis will be performed. If positive, a MHA-TP confirmatory test will be performed. If positive, subjects must be referred for appropriate follow-up and/or treatment. If treatment is required, it must be completed within the 14-day screening window. Documentation of appropriate follow-up and/or treatment is required prior to randomization. Subjects may continue to be screened while the evaluation process is ongoing. The laboratory performing these assessments should be either directly regulated by the College of American Pathologist (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.

14.18 Medical and Family History

A medical history will be taken on all potential study subjects to assure medical fitness. A family history (parents and siblings) of substance use and dependence will also be taken for those subjects who consent to participate in the pharmacogenomics analyses.

14.19 Methamphetamine Use by Time Line Followback (TLFB)

Methamphetamine use assessed using the TLFB method will be performed twice: 1) during screening for the 30-days prior to the day that the subject signed consent and 2) at study Week # 17 for the period between the visit at Week 13 and that at Week 17. Data will be collected on any of the following drugs if these drugs are identified during the SCID as having been used by the individual: methamphetamine, alcohol, marijuana, nicotine, cocaine, opiates, benzodiazepines and barbiturates. The data will be recorded on the SUR CRF. The TLFB method was described and validated by Sobell *et al.,* (1986) for reporting alcohol use. It has also been found to be a reliable method for assessing the history of psychoactive substance use in drug-abusing populations (Fals-Stewart *et al.,* 2000).

14.20 Montgomery-Asberg Depression Rating Scale (MADRS)

The MADRS is an observer rating scale that has proven to be an efficient and practical measure of depression (Montgomery and Asberg, 1979). The scale was constructed to be sensitive to changes in treatment effects. Its capacity to differentiate between responders and non-responders to antidepressant treatment has been shown to be comparable to the Hamilton Rating Scale for Depression, another established measure of depressive symptomatology, but the MADRS has greater sensitivity to change during the course of a depressive phase. It has exhibited high inter-rater reliability and appears to be oriented more towards psychic as opposed to somatic aspects of depression. The MADRS is a 10-item checklist where items are rated on a scale of 0 to 6 with anchors at 2-point intervals. Scores range from 0 to 60. In a study by Kearns *et al.* (1982), the following mean scores correlated with global severity measures: very severe, 44; severe, 31; moderate, 25; mild, 15; and recovered, 7. The MADRS takes approximately 15 minutes to administer.

14.21 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 should be performed. Height and weight should be recorded. Weight should be recorded weekly to monitor for possible weight loss.

14.22 SCID

A SCID (Spitzer *et al*., 1995) will be conducted during screening to assess the subject's methamphetamine dependence and any other drug dependence, severity of depression, and other Axis-I disorders, according to DSM-IV criteria.

14.23 Substance Use Report (SUR)

The SUR includes the subject's report of use of methamphetamine, alcohol, marijuana, nicotine, cocaine, opiates, benzodiazepines and barbiturates for each day of the week. The subject is asked to report any use during days since the last clinic visit. The day that the subject is reporting use is not scored until the subsequent visit as use may occur later in the day.

14.24 Treatment Compliance

Treatment compliance will account for and record the amount of investigational products taken by each subject. Treatment compliance with pharmacotherapy during the 91 days of dosing will be monitored by tablet count at each week.. The amount dispensed and returned will be reconciled and recorded each week. Attendance at BBCET sessions will also be recorded at each session. Attendance at any other therapy sessions (i.e., 12-step or self-help programs) outside the clinical study will also be recorded.

14.25 Urine Collection and Analyses

Urine will be collected for five types of analyses as follows:

1. Qualitative screening for methamphetamine, creatinine, amphetamine, tetrahydrocannabinol, cocaine, barbiturates, opiates, and benzodiazepines performed at a central laboratory.
2. Quantitative analysis of methamphetamine and amphetamine performed at a central laboratory.
3. Urine drug screen performed with a qualitative onsite test device for methamphetamine, cocaine, tetrahydrocannabinol, amphetamines, barbiturates, opiates, and benzodiazepines to be used only during screening and baseline.
4. Medical Urinalysis.
5. Urine pregnancy test.

Depending upon the assessment schedule, urine samples will be collected and aliquoted into the appropriate number of specimens. One specimen will be held frozen at the clinical site as a back-up. The others will be tested immediately or will be frozen as appropriate. Specimens will be collected and tested as follows:

Methamphetamine, Creatinine, Tetrahydrocannabinol, Cocaine, Amphetamines, Barbiturates, Opiates, and Benzodiazepines Analysis. During the screening period, urine samples will be collected until a positive result is obtained as determined by qualitative analysis using the onsite testing device. Screening urine samples will not be retained further and should be discarded according to local clinic/lab guidelines. Subjects qualifying for entry into the 14-day baseline period will be scheduled to provide urine samples 3 times/week (generally Monday, Wednesday, and Friday, barring holidays and schedule conflicts).

To be eligible for randomization, subjects will be required to provide at least 4 samples within the 14-day baseline period, with at least 1 sample in the 7 DAYS IMMEDIATELY PRECEDING randomization. All urine samples collected during the 14-day baseline period will be evaluated qualitatively using the onsite testing device and retained at the site for possible shipping to a central laboratory. Only those samples for subjects who qualify AND are randomized will be shipped to the central laboratory. *Samples on subjects not successfully completing the baseline evaluation (and who are NOT randomized) should be discarded according to local clinic/laboratory guidelines.*

The central laboratory will perform a qualitative screen on the 1st sample of the week (including the 1st sample of baseline day 1-7 and on the 1st sample of baseline day 8-14, and each week after randomization up to and including week 12) for cocaine, tetrahydrocannabinol, methamphetamine, amphetamines, barbiturates, opiates, benzodiazepines, and creatinine. The central laboratory will perform a qualitative test on the 2nd and 3rd samples collected during each week for amphetamines, methamphetamine, and creatinine and will do quantitative analysis for methamphetamine and amphetamines for all the samples that were positive by the qualitative screen for methamphetamine or amphetamines. A methamphetamine test result from assays performed at NWT $\geq$ 300 ng/mL will be considered to be positive.

Urine Toxicology Screen Using an Onsite Testing Device. During the screening and baseline periods, urine will be collected to test for methamphetamine use. Samples positive for methamphetamine using the onsite test device (the onsite testing device has a cutoff of ≥ 500 ng/mL) will be considered as positive for methamphetamine for inclusion criterion purposes and for randomization. This cut-off is higher than that for the assays performed at the central laboratory which is ≥ 300 ng/mL. The assay performed by the central laboratory has a lower limit of detection and greater precision than the onsite test device, hence the difference in cutoffs for a positive test.

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.

Urine Pregnancy Test. An FDA approved rapid-result urine pregnancy test will be used (i.e., dipstick test). Subjects will be asked to sign a release of information form for study personnel to access medical records to obtain information regarding the outcome of a pregnancy that occurred during the study.

14.26 Vital Signs

Vital signs to be assessed include oral temperature, sitting blood pressure, pulse rate and respiratory rate.

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 principal investigator will sign a Statement of Investigator (FDA Form 1572) prior to initiating this study and updated as needed.

15.3 IRB Approval

Prior to initiating the study, the each site's principal investigator will obtain written approval from the appropriate IRB to conduct the study. Should changes to the study protocol become necessary, protocol amendments will be submitted in writing to the IRB by the site principal investigator for IRB approval prior to implementation. In addition, once NIDA has approved advertising materials used for subject recruitment, IRBs will also approve these materials and any educational materials (e.g., HIV/AIDS Education, **Appendix III**) given to the subject. Progress reports will be submitted to the IRB annually or at a frequency requested by the IRB.

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. A separate consent will be used for the genetics sub-study within the main study. Potential study subjects may consent to the main study without consenting to the genetics sub-study.

All aspects of the study will be explained in lay language. After the subject has read the consent form, a short questionnaire will be given to the subject before signing the form. This questionnaire will review all aspects of the study discussed in the consent form. A research staff member will review the answers provided by the subject. Any subject who does not successfully complete the questionnaire will re-read the consent with a research staff member. The subject will retake the questionnaires until s/he shows complete understanding of the information discussed in the consent form before providing consent. Any subject who is unable to demonstrate understanding of the information contained in the informed consent will be excluded from study participation and assisted in finding other sources of treatment. 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/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 the Investigator-Sponsor (or responsible party) unless otherwise instructed.

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 treatment 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 Investigator –Sponsor on the severity of any SAEs, the relatedness to the study treatments, and for determining if the SAE should be reported to the FDA 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.

Clinical Monitors: All investigators will allow representatives of the Investigator-Sponsor 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 Investigator-Sponsor and NIDA with the opportunity to evaluate the progress of the study and to obtain information 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 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 good clinical practice's guidelines, confirm receipt of study supplies, and assure that acceptable facilities are available to conduct the study.

Routine monitoring visits by the Investigator-Sponsor's and NIDA's representatives will be scheduled at appropriate intervals but 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 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 Investigator-Sponsor, Ortho-McNeil Neurologics, Inc., and the FDA. Ortho-McNeil Neurologics Inc., can conduct audits during or after the trial.

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 IV**. The occurrence of AEs will be assessed starting at completion of the informed consent process and at each study 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. 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.

All AEs, 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 4 weeks following completion of, or termination from treatment. At the follow-up visit, AEs will be recorded and 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, 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. Pregnancy at any time during the study starting with completion of the informed consent process through the final study visit is considered a serious adverse event and must be reported to NIDA in accordance with the reporting requirements in **Appendix IV**.

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 IV.** There can be serious consequences including ultimately, criminal and/or civil penalties for sponsors who fail to comply with FDA regulations governing the reporting of SAEs to FDA. The investigators in this study have the responsibility of promptly reporting all SAEs to NIDA and the Investigator-Sponsor in order that the Investigator-Sponsor 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 Statistical Hypotheses

Primary Outcome: It is hypothesized that topiramate, as compared to placebo, will increase the proportion of subjects with methamphetamine negative use weeks over the maintenance treatment period (study Weeks 6 through 12).

Secondary Outcomes: It is hypothesized that topiramate as compared to placebo will increase weekly proportion of methamphetamine–free urine samples, increase the proportion of subjects with 21 consecutive days of abstinence during which time all urine drug screens must be

methamphetamine-free, increase the proportion of subjects who reduce their methamphetamine use as compared to baseline use, the weekly mean proportion of methamphetamine non-use days according to self-report alone, the proportion of methamphetamine negative urine samples, and treatment retention. It is further hypothesized that topiramate will reduce the severity of methamphetamine dependence, craving, and withdrawal as assessed by ASI-Lite, BSCS, CGI-S, and CGI-O.

16.2 Analysis Plan

There is no generally accepted definition of clinically significant improvement in the treatment of methamphetamine dependence. The primary and secondary outcome variables are intended to explore various aspects of the response to topiramate and to help define a clinically meaningful response. The primary outcome has been chosen because it is an objective measure of stopping methamphetamine use and it measures reduction in methamphetamine use over the treatment period. Some of the secondary outcome variables add a measure of clinical relevance to the reduction of use by requiring either sustained abstinence (21 Days) or a predetermined, substantial overall reduction in use days (25% or 50% of their baseline use). Other secondary outcome variables explore the effect of therapy on psychosocial aspects of methamphetamine dependency.

16.2.1 Primary Efficacy Outcome Measure

The primary efficacy outcome measure is negative methamphetamine use weeks during study Weeks 6 through 12. Use weeks are defined as each 7-day period staring with the first day of investigational product administration. A positive use week is any week in which at least one of the urine drug screens for methamphetamine was positive (≥ 300 ng/mL). A negative use week is any week in which all of the urine drug screens for methamphetamine were negative (< 300 ng/mL). If no drug screening results are available, the data for that week is considered as missing.

16.2.2 Secondary Outcome Measures

Effect on methamphetamine use

A. A secondary analysis will be conducted on the primary outcome measure, except that the treatment period will include study Weeks 1 through 12.

B. The score of the study week's urine samples for methamphetamine during the Weeks 1 through 12 and separately during Weeks 6-12. Three urine collection days are scheduled per week. The weekly methamphetamine use is scored as "0" if all urine samples in the week were negative (quantitative analysis by central laboratory <300 ng/ml). Even if only one sample is collected and is negative for methamphetamine, the proportion will be scored as "0". The weekly methamphetamine use is scored as "1" if at least one urine sample is negative and at least one sample is positive for methamphetamine during the week. The weekly methamphetamine use is scored as "2" if all urine samples collected during the week are positive. If no samples are tested during a week, the score is considered to be missing.

C. The proportion of subjects with 21 consecutive days of abstinence during study Days 1 through 84 and separately during study Days 36 through 84 during which time all urine drug screens must be methamphetamine-free (quantitative analysis <300 ng/ml). Study days between urine specimens are considered to be methamphetamine-free days. If more than three calendar days of urine specimens are missing, then this period is not considered to be abstinent.

D. The proportion of subjects with 21 consecutive days of abstinence during study Days 1 through 84 and separately during study Days 36 through 84 during which time all urine drug screens must be methamphetamine-free (quantitative <300 ng/mL) and there is no self-report of methamphetamine use. If one to seven calendar days of urine specimens are missing, self-reported methamphetamine use will be used for evaluation. If no use is reported and there are no missing self-reports during this time, this period will be considered abstinent. If more than seven calendar days of urine specimens are missing or if any self-report is missing, then this period is not considered to be abstinent.

E. The proportion of subjects who decrease the overall proportion of negative methamphetamine use days by SUR during study Days 1 through 84 and separately during study Days 36 through 84 by 25% or more of their self-reported use in the 14-Day baseline period.

F. The proportion of subjects who decrease the overall proportion of negative methamphetamine use days by SUR during study Days 1 through 84 and separately during study Days 36 through 84 by 50% or more of their self-reported use in the 14-day baseline period.

G. The proportion of subjects who decrease the median of methamphetamine quantitative urine concentration during study Days 1 through 84 and separately during study Days 36 through 84 by 25% or more of their median of methamphetamine quantitative urine concentration in the 14-day baseline period.

H. The proportion of subjects who decrease the median of methamphetamine quantitative urine concentration during study Days 1 through 84 and separately during study Days 36 through 84 to 50% or less of their median of methamphetamine quantitative urine concentration in the 14-Day baseline period.

I. Maximum number of calendar days of abstinence during which time all urine drug screens must be methamphetamine-free (quantitative <300 ng/mL) during study Days 1-84 and separately during study Days 36 through 84. Study days between urine specimens are considered to be methamphetamine-free days. If more than three calendar days of urine specimens are missing, then this period is not considered to be abstinent.

J. Maximum number of calendar days of abstinence during which time all urine drug screens must be methamphetamine-free (quantitative <300 ng/mL) and there is no self-report of methamphetamine use during study Days 1-84 and separately during study Days

36 through 84. If one to seven consecutive days of urine specimens are missing, evaluate self-reported methamphetamine use. If no use is reported and there are no missing self-reports during this time, this period will be considered abstinent. If more than seven calendar days of urine specimens are missing or if any self-report is missing, then this period is not considered to be abstinent.

K. Weekly mean proportion of methamphetamine non-use days based on subject's self report of use (SUR) during study Weeks 1 through 12 and separately during study Weeks 6-12.

L. The proportion of methamphetamine-free urines during study Weeks 1 through 12 and separately during study Weeks 6-12.

M. Weekly median $\log_{10}$ quantitative urine methamphetamine levels during study Weeks 1 through 12 and separately during study Weeks 6-12.

N. Time to relapse to methamphetamine use in the subset of subjects who were abstinent at randomization (anyone reporting no use and all urine samples negative for methamphetamine during the 7 day baseline period immediately prior to randomization).

Reduction in the severity of methamphetamine dependence, craving, and withdrawal

O. CGI-O scores (dependence).

P. CGI-S scores (dependence).

Q. ASI-Lite composite score of the drug section and methamphetamine use question individually (dependence) and composite scores of the other sections (other global measures of improvement).

R. BSCS scores (craving)

Treatment Retention

S. Time from randomization to last study visit during the treatment phase.

Safety of Topiramate

T. AEs, laboratory data, MADRS assessments, ECG, physical exams, and vital signs.

16.3 Subject Populations (Intention-to-Treat and Evaluable)

The ITT population is defined as the subjects who are randomized to treatment and who receive the first dose of investigational product. The evaluable population is defined as the subjects who are randomized and properly qualified to participate in the study in accordance with the eligibility criteria and who contribute at least six (6) usable on-study urine samples and took at least 50 mg/day of topiramate (or equivalent placebo) for a period of 21 Days.

16.4 Analysis Plan

16.4.1 Efficacy Assessments

Each primary and secondary efficacy outcome measure will be analyzed for the ITT and for the evaluable population. Major differences in the results, if any, will be further explored.

All statistical tests will be two-sided at a 5% Type I error rate. Confidence intervals will be two-sided with a 95% confidence coefficient.

Primary Efficacy Outcome

The weekly proportion of subjects with a negative methamphetamine-use week during study Weeks 6 through 12 will be compared between treatment groups using Generalized Estimating Equations (GEE) (Zeger & Liang, 1986). GEE provide a model-based regression method applicable for the analysis of the correlated data that will result from this repeated measures longitudinal study. As a secondary analysis, baseline abstinence or use, age, race, gender, and clinical site will also be included in the model, as appropriate.

Secondary Efficacy Outcomes

Unless the primary response analysis implies the need for a more elaborate model, between group comparisons of the secondary outcomes will be performed as follows:

Outcome Measure	Test
C, D, E, F, G, H, L	Fisher's Exact Test
I, J	T test or equivalent nonparametric test
A, B, K, L, M, O, P, Q, R	GEE
N	Cox Proportional Hazards Test
S	Kaplan-Meier Curves with log-rank test statistic

GEE for ordinal categorical responses (outcome measure B) will be performed according to Lipsitz *et al*., (1994). We will also consider other alternative urine methamphetamine cut-off values, ascertained empirically, to determine positive and negative methamphetamine use.

16.4.2 Safety Outcomes

The severity and frequency of adverse events, and laboratory data, physical exams, and vital signs, will be reported in tabular form. Adverse events will be coded using Medical Dictionary of Regulatory Affairs (MedDRA) preferred terms and grouped by system, organ, and class (SOC). The frequencies of adverse events by type will be compared between study arms using Chi-square analyses; however, this analysis will be considered descriptive not inferential.

16.4.3 Descriptive Statistics

Summaries of the characteristics of the subject population in each of the treatment arms at baseline will be prepared for both the ITT and evaluable subjects. A summary will be prepared to show dropouts/retention over time in each treatment group, along with the reason for early termination. The number of missing observations will be compared between treatments. Weekly treatment compliance of each group will be summarized. The types and frequency of other drugs used by self-report of use and by positive urine drug screen will also be reported for each treatment group. The proportion of subjects in each group abstinent at Week 17 (TLFB reported no use since Week 13 and negative methamphetamine drug screen result is considered abstinent).

16.4.4 Genetics Analyses

Genotyping and Association Analysis. For the genes of interest, we will select various SNPs within the gene for the association analysis based on the NCBI SNP database. If more SNPs are available for a given gene, priority will be given to those SNPs that are located in the coding or regulatory regions. Association analysis for either single or multiple SNPs (as a block) will be conducted by using the ALLELLE, CASECONTROL and HAPLOTYPE procedures of SAS/Genetics.

The ALLELE procedure of the SAS/Genetics package can calculate descriptive statistics such as the frequency and variance of alleles and genotypes, as well as estimate measures of marker informativeness, test whether genotype frequencies are consistent with HWE, and support three methods for calculation of the degree and significance of LD. Another useful procedure for the case-control design is CASECONTROL, which compares allele and genotype frequencies in topiramate-treated and placebo-treated populations using three types of chi-square tests (i.e., genotype and allele case-control tests and linear trend test) and options for controlling correlation of allele frequencies among members of the same subpopulation. Similarly, we plan to test association using haplotype information from multiple SNPs within a candidate gene/region for the case-control data. The program to be used for this purpose is the HAPLOTYPE procedure of SAS/Genetics, which uses case-control data to calculate test statistics for the hypothesis of no association between alleles comparing the haplotypes and disease or medication treatment status.

Microarray Data Analysis. All microarray data generated from the project will be subjected to a series of steps for normalization and filtering, which includes log-transformation, normalization within a slide, scaling among slides, and data filtering. To reduce individual variation, we will use expression profile of each subject at the beginning of the clinical treatment as the baseline. All expression profiles of that individual at other time points will be compared with the baseline. After appropriate normalization, various statistical approaches will be applied to select genes differentially expressed in the topiramate and placebo groups. Computer programs written in SAS, Fortran, or MatLab for the traditional *t*-test, the SAM method (a modified *t*-test), variance analysis under a mixed model, and a mixture-model approach have been implemented in our laboratory and are ready for handling the data generated from this project. Given that each method has its own features, and there is no clear standard or consensus as to which method is preferable, we plan to use all of these methods to analyze each dataset. Only those genes that can be identified repeatedly by different methods will be selected for further characterization.

After differentially expressed genes are identified, we plan to use various clustering techniques over different experimental groups to analyze the expression patterns. Expression profiles will

be grouped by: a) hierarchical cluster analysis using CLUSTER and TREEVIEW (http://rana.stanford.edu/software/), b) quality clustering (http://www.genome.org/cgi); and c) self-organizing maps (http://www-genome.wi.mit.edu/). The outputs from each program will be compared with respect to the clusters formed. These data will be used to determine relationships between the clusters, disease status, and medication treatment status and response.

16.5 Randomization Plan/Control of Bias

Adaptive random allocation of subjects to study groups will be performed by computer using site and methamphetamine use status as determined by self report or methamphetamine use and urine drug screens for methamphetamine within 7 days prior to randomization (using – anyone with self report of use or a methamphetamine positive urine sample versus abstinent – anyone reporting no use and all urine samples negative for methamphetamine).

16.6 Sample Size Calculation

No formal power analysis can be performed for this study's outcomes because there is no available information to determine the effect of topiramate on the study population. The study sample size is 70 subjects in each treatment arm. The number of 70 in each arm was selected based on other NIDA studies of substance abuse as a number that is sufficient to provide an estimate of treatment effect with 30% drop out rate, which can then be used in planning a future, pivotal trial, should it be warranted.

16.7 Post Hoc Analyses

Data will be collected in this study for scientific use and not as primary or secondary outcome measures. Additional *post hoc* analysis may be performed to evaluate other confounding factors on outcomes such as depression or patterns of methamphetamine use at baseline and after treatment.

16.8 Exploratory Analyses

We will also consider other alternative urine methamphetamine cut-off values, ascertained empirically, to determine positive and negative methamphetamine use. Study outcomes that involve methamphetamine urine drug screen data may be subjected to an exploratory analysis using a different positive cut off value.

17 DATA MANAGEMENT AND CASE REPORT FORMS (CRF)

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 onto paper 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.

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

At study completion, when 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, Investigator-Sponsor 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 <u>all</u> 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 under the Freedom of Information Act providing, in part, that proprietary information furnished to clinical investigators and Institutional Review Boards will be kept confidential by the Food and Drug Administration only if maintained in confidence by the clinical investigator and Institutional Review Board.

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 Institutional Review Board, Ethical Review Committee, 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 V**.

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 the use of topiramate for the treatment of methamphetamine dependence may not be submitted for publication until the main findings of the study have been published or 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
Erin Iturriaga, RN, CCRC Project Director	_____	_____
Liza Gorgon, M.A. Project Officer	_____	_____
Roberta Kahn, M.D. NIDA Investigator	_____	_____
Ahmed Elkashef, M.D. Co-Chairman	_____	_____
Elmer Yu, M.D., FASAM Co-Chairman	_____	_____
Ann Anderson, M.D. Medical Monitor	_____	_____

SITE 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 14.6 of this protocol.

Typed Name	Signature	Date
Bankole Johnson, M.D. Investigator-Sponsor	_____	_____
Nassima Tiouririne, M.D. Site Principal Investigator	_____	_____
Richard A. Rawson, Ph.D. Site Principal Investigator	_____	_____

Typed Name	**Signature**	**Date**
Jan Campbell, M.D. Site Principal Investigator	_____	_____
William Haning, M.D. Site Principal Investigator	_____	_____
Joseph Mawhinney, M.D. Site Principal Investigator	_____	_____
Dennis Weis, M.D. Site Principal Investigator	_____	_____
Michael McCann, M.A. Site Principal Investigator	_____	_____
Christopher J. Stock, Pharm.D. Site Principal Investigator	_____	_____

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APPENDIX I:

Q&A on Hyperchloremic, Non-Anion Gap Metabolic Acidosis Reported with TOPAMAX®

1. What is Metabolic Acidosis?
Metabolic acidosis is a condition where there is a lowering of bicarbonate levels in the blood and a resultant increase in the acidity of the blood. Under normal circumstances the fluids in our bodies are maintained at a certain pH. ***pH*** is a value, which represents the degree of acidity. The pH of our blood is maintained at a neutral value of 7.35-7.45. A pH of less than 7.35 indicates acidosis, and a pH above 7.45 indicates alkalosis. One way the body maintains the pH of the blood is by increasing or decreasing the production of bicarbonate (HCO3-). Bicarbonate is basic so that increasing bicarbonate make the blood more basic, and decreasing it makes the blood more acidic.

2. What is non-anion gap metabolic acidosis?
A ***non-anion gap*** metabolic acidosis refers to a type of acidosis in which there is loss of bicarbonate, and is typically a less severe form of acidosis.

3. What is the post-marketing *reporting rate* of metabolic acidosis in patients on topiramate?
The post marketing reporting rate of serious adverse events in which metabolic acidosis was observed is 2.2 per 100,000 patient-years of exposure. This is based on post marketing experience in more than 2.4 million patients.

4. Are there any medical conditions that may predispose patients to developing metabolic acidosis while on TOPAMAX?
Serum bicarbonate may be further decreased in patients with conditions that may predispose them to acid-base disturbances. These include renal disease, severe respiratory disorders, status epilepticus, diarrhea, surgery, ketogenic diet, or drugs, especially other carbonic anhydrase inhibitors.

5. Is routine monitoring of serum bicarbonate necessary in patients on TOPAMAX?
While the FDA did not require periodic monitoring of serum bicarbonate, it is recommended. Physicians should use their clinical judgment in deciding whether serum bicarbonate levels are necessary, especially in patients with predisposing conditions.

6. What should I do if I get an abnormal bicarbonate lab value?
Topamax has been studied for more than 11 years and in clinical trials many patients had lab values reported below 20 mEq/L. After 8 years of clinical experience in more than 2.5 million patients there has been no signal in post marketing reports linking Topamax to the theoretical consequences of long-term acidosis.

7. How does TOPAMAX cause metabolic acidosis?
TOPAMAX is a weak carbonic anhydrase inhibitor. Inhibition of carbonic anhydrase in the kidney blocks the reabsorption of bicarbonate and increases its excretion in the urine.

Carbonic anhydrase inhibition increases chloride reabsorption and reduces excretion of chloride in the urine. The loss of bicarbonate and the accumulation of chloride in the blood result in ***hyperchloremic, non-anion gap metabolic acidosis***.

8. What is the *incidence* of decreased bicarbonate reported during clinical trials of topiramate?
During controlled trials of topiramate (400 mg/day) as adjunctive therapy in epilepsy, persistent decreases of serum bicarbonate below 20 mEq/L were observed in 32% of Topamax treated adults and 1% of placebo. The incidence of markedly low serum bicarbonate, (less than 17 mEq/L and greater than 5 mEq decrease from baseline) were 3% with Topamax and 0% with placebo. In children (<16 years of age) at ~6mg/kg/day, persistent decreases of serum bicarbonate were observed in 67% of Topamax treated children* and 10% on placebo. The incidence of markedly low serum bicarbonate was 11% for Topamax and 0% for those on placebo.
*Children had POS and LGS, which may have further predisposed them to persistent decreases in serum bicarbonate

9. To what extent does topiramate decrease bicarbonate?
At doses of 400 mg/day in adults or ~6mg/kg/day in children decreases in bicarbonate were generally small, averaging 4 mEq/L.

10. Are there any medications that can increase the risk of metabolic acidosis?
Certain agents including carbonic anhydrase inhibitors such as Diamox® (acetazolamide) or Zonegran® (zonisamide) may increase the risk of metabolic acidosis.

11. How early or late in therapy can metabolic acidosis occur?
Decreased bicarbonate has generally been seen early in treatment and was mild to moderate in severity although it can occur at anytime during treatment.

12. What are the symptoms associated with metabolic acidosis?
Symptoms of metabolic acidosis may include hyperventilation, fatigue and loss of appetite. Reduction in bicarbonate reported with topiramate are usually small and typically do not result in clinical manifestations. More severe symptoms of metabolic acidosis can include, cardiac arrhythmias or impaired consciousness (lethargy, stupor). Chronic metabolic acidosis may be associated with changes in bone density. However the effect of Topamax on growth and bone related sequelae has not been established. Furthermore, carbonic anhydrase inhibitors may have a favorable direct effect that improves bone density. In children, chronic metabolic acidosis may be associated with a reduction in growth rates. However, no significant impact on growth was found in the analysis of data from clinical trials of ~500 children receiving topiramate for periods of 6-18 months.

13. Is metabolic acidosis new information not previously reported in the TOPAMAX (topiramate) package insert?
No. The label change is an update to information already included in the package insert. Acidosis continues to be listed as an infrequent adverse event in the section "Other adverse event observed in all clinical trials".

14. What is the treatment of metabolic acidosis?
If metabolic acidosis develops and persists, considerations include reducing the dose of Topamax, discontinuing Topamax, or using alkali treatment.

15. At what dose of TOPAMAX do I really need to start worrying about metabolic acidosis?
Decreases in sodium bicarbonate levels have been seen with all doses evaluated. Reduction in bicarbonate reported with topiramate are usually small and typically do not result in clinical manifestations. The post-marketing reporting rate of serious adverse events in which metabolic acidosis was observed is 2.2 per 100,000 patient-years of exposure. This is based on post-marketing experience in more than 2.4 million patients.

16. Why is this information coming out now?
As the use of Topamax extends beyond Neurology, in consultation with the FDA, Ortho-McNeil Neurologics, Inc. agreed that further details about metabolic acidosis should be included in the warning section of the Topamax label.

17. Are there particular patients that I need to be concerned about?
Renal disease, severe respiratory disorders, status epilepticus, diarrhea, surgery, ketogenic diet, or drugs especially other carbonic anhydrase inhibitors, are associated with the development of metabolic acidosis. Effects of Topamax may be additive to these conditions.

APPENDIX II:

Prohibited Medications

Subjects must not be taking any psychotropic medications or medications that could affect methamphetamine metabolism. These medications are prohibited for at least a period equal to five serum half-lives, or as specified in the protocol and the table below, prior to the start of treatment or any time during treatment. The following list specifies required washout times **for most prohibited medications.** If a medication is not listed, and the investigator deems it to have significant psychoactive properties or a new formulation is not specified, the five serum half-life rule should be employed or the medical monitor should be contacted to determine the washout for this medication. If there is any doubt about whether the concomitant medication is allowed the medical monitor should be contacted for a decision about its use.

The daily use of antacids and the use of calcium supplements greater than the recommended daily dose are also prohibited during the trial.

Subjects should not us Vick's inhalers as these contain L-methamphetamine which could result in a false positive urine drug test for D-methamphetamine.

If subjects have difficulty sleeping during the Screening Phase and during titration up to the start of the 150 mg/day dose, they may take diphenhydramine (up to 50 mg, 15 – 30 minutes before bed, no more than 3-4 times per week) as a rescue medication. This is the only medication allowed for use as a sleep aid. Diphenhydramine must not be used for any other indication.

Prohibited Medications	Washout Period
Antidepressants Selective Serotonin Reuptake Inhibitors ● fluvoxamine (Luvox®) ● paroxetine (Paxil®, Paxil CR™) ● sertraline (Zoloft®) ● escitalopram oxalate (Lexapro™) ● citalopram (Celexa™)	14 Days
● fluoxetine (Prozac®, Sarafem™)	28 Days
Serotonin Norepinephrine Reuptake Inhibitors ● venlafaxine (Effexor®)	14 Days
Serotonin$_2$ Receptor Antagonists ● trazodone (Desyrel®) ● nefazodone (Serzone®)	14 Days
Dopamine/Norepinephrine Reuptake Inhibitor ● bupropion (Wellbutrin®, Zyban®)	14 Days
D_2 antagonist ● sulpiride	14 Days

Prohibited Medications	Washout Period
Tricyclics and Tetracyclics ● amitriptyline (Elavil®) ● desipramine (Norpramine®) ● doxepin (Sinequan®, Zonalon®) ● imipramine (Tofranil®) ● imipramine pamoate (Tofranil PM®) ● trimipramine (Surmontil®) ● amoxapine (Asendin®) ● clomipramine (Anafranil®) ● nortriptyline (Pamelor®, Aventyl®) ● maprotiline (Ludiomil®)	14 Days
● protriptyline (Vivactil®)	42 Days
Drugs With Mixed Actions ● perphenazine/amitriptyline (Etrafon®) ● chlordiazepoxide/amitriptyline (Limbitrol®DS) ● mirtazapine (Remeron®)	14 Days
MAO Inhibitors ● tranylcypromine (Parnate®) ● selegiline hydrochloride (Eldepryl®)	14 Days
● isocarboxazid (Marplan®) ● phenelzine (Nardil®)	28 Days
Stimulants Monoamine-Releasing Agents ● dextroamphetamine (Adderall®,DexedrineDextroStat®) ● methamphetamine (Desoxyn®) ● methylphenidate (Concerta™, Metadate®, Methyline®,Ritalin®) ● pemoline (Cylert®)	7 Days
Norepinephrine Reuptake Inhibitors ● atomoxetine (Strattera®)	7 Days
Antianxiety Agents and Hypnotics Benzodiazepines ● alprazolam (Xanax®) ● lorazepam (Ativan®) ● oxazepam (Serax®) ● flurazepam (Dalmane®) ● temazepam (Restoril®) ● quazepam (Doral®) ● triazolam (Halcion®) ● estazolam (ProSom) ● bromazepam ● halazepam (Paxipam®)	7 Days
● clonazepam (Klonopin®) ● chlordiazepoxide (Librium®) ● clorazepate (Tranxene®, Tranxene®-SD™)	14 Days

Prohibited Medications	Washout Period
• diazepam (Valium®) • prazepam (Centrex)	21 Days
Nonbenzodiazepine hypnotics ● zolpidem (Ambien®) ● zaleplon (Sonata®) ● paraldehyde	7 Days
Barbiturates • secobarbital (Seconal®) • pentobarbital (Nembutal®) • amobarbital (Amytal®) • mephobarbital (Mebaral®) • secobarbital and amobarbital (Tuinal®)	14 Days
• butabarbital (Butisol®)	21 Days
• Phenobarbital	28 Days
Carbamate • meprobamate (Miltown®, Equanil®)	7 Days
Noradrenergic agents ● clonidine (Catapres®,Catapres-ITS,Duraclon) ● guanfacine HCl (Tenex)	7 Days
● propanolol (Inderal®, Inderal LA®) *With the exception of stable dose, chronic use for cardiovascular treatment.*	7 Days
Antihistamines ● diphenhydramine *Exception--If subjects have difficulty sleeping during the Screening/Washout Phase and during titration up to Visit 5 (Day 21), subjects may take diphenhydramine) (up to 50 mg, 15 – 30 minutes before bed, no more than 3-4 times per week) as a rescue medication. This is the only medication allowed for use as a sleep aid. Diphenhydramine must not be used for any other indication.* • Hydroxyzine hydrochloride (Atarax®) IM • Hydroxazine pamoate (Vistaril®) PO	7 Days
Neurotransmitter Receptor Agonists *5-HT$_{1A}$ partial agonists* ● buspirone (BuSpar®) ● gepirone	7 Days

Prohibited Medications	Washout Period
Herbal preparations • St. John's Wort (Hypericum Perforatum) • Kava (Piper methysticum) • Velarin (Valeriana officinalis) • Ginko (Ginkgo biloba) • Omega-3 fatty acids • S-adenosylmethionine (SAMe) • Inositol • DHEA (dehydroepiandrosterone) • L-tryptophan • Melatonin	7 Days
Other Mood Stabilizers • lithium carbonate (Eskalith®, Lithobid®, Eskalith-CR®), lithium citrate	7 Days
Antiepileptic agents • carbamazepine (Tegretol®, Tegretol®-XR, Carbatrol®, Epitol®) • divalproex sodium, divalproex, valproic acid (Depakote®, Depakote ER) • gabapentin (Neurontin®) • lamotrigine (Lamictal®) • methsuximide (Celontin®) • phenytoin sodium, phenytoin ER (Dilantin®, Phenytek™) • topiramate (Topamax®) • valproate sodium (Depacon®) • valproic acid (Depakene®) • oxycarbazepine (Trileptal®) • tiagabine (Gabitril®)	7 Days
• ethosuximide (Zarontin®)	14 Days
Antipsychotic agents • haloperidol tablet (Haldol®) • loxapine (Loxitane®) • risperidone (Risperdal®) • thioridazine (Mellaril®) • trifluoperazine (Stelazine®) • droperidol (Inapsine®) • molindone (Moban®) • quetiapine (Seroquel®) • ziprasidone (Geodon®) • clozapine (Clozaril®) • fluphenazine (Prolixin®, Permitil®) • chlorpromazine (Thorazine®) • tiapride • perphenazine (Trilafon®) • pipothiazine • prochlorperazine	7 Days

Prohibited Medications	Washout Period
● mesoridazine (Serentil®) ● olanzapine (Zyprexa®, Zydis®) ● pimozide (Orap®) ● flupenthixol PO ● thiothixene (Navane®) ● bromperidol	14 Days
● aripiprazole (Abilify™)	35 Days
● flupenthixol IM	42 Days
● haloperidol decanoate (Haldol Decanoate®)	112 Days
● fluphenazine decanoate (Prolixin Decanoate®)	140 Days
Carbonic anhydrase inhibitors ● acetazolamide (Diamox®) • zonisamide (Zonegran®)	7 Days
Potassium sparing diuretics ● triamterene, or triamterene combination product (Dyazide®, Dyrenium®, Maxzide®) • amiloride (Midamor)	7 Days 15 Days

APPENDIX III: HIV/AIDS EDUCATION

Education should be performed by trained staff and should include the following topics:

- Modes of transmission
- High risk behaviors
- Prevention behaviors
  - stop drug use
  - don't share needles
  - clean "works" before using
  - use of condoms

- HIV Testing
  - What test is for
  - Confidential *versus* anonymous
  - Optional
  - What +/- test results mean
  - Anxiety related to waiting for results

- Demonstration of:
  - Use of alcohol swipes
  - Use of bleach kits

- Subject wishes to be tested?
  - If yes, talk through the consent
  - Obtain signature
  - Offer outside referrals

APPENDIX IV:

Instructions For Evaluating and Reporting Adverse Events and Serious Adverse Events

A. GENERAL INSTRUCTIONS

1. Adverse Events (AEs) will be assessed at each visit and reviewed weekly by a study physician.

2. Record AEs as soon as the informed consent process is completed.

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 study drug/placebo. The degree of certainty for which the AE/SAE is attributed to the study drug 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 drug/placebo?

- ***Timing of the study drug/placebo:*** Did the AE/SAE follow in a reasonable temporal sequence from administration of the drug test?

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

- ***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 study drug/placebo.

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 the test drug, the temporal sequence of the AE/SAE onset relative to administration of the test drug is not reasonable, or there is another obvious cause of the AE/SAE.

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

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

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

- ***Definitely Related:***
  There is evidence of exposure to the test drug, the temporal sequence of the AE/SAE onset relative to administration of the test drug is reasonable, the AE/SAE is more likely explained by the test drug than by any other cause, and the AE/SAE shows a pattern consistent with previous knowledge of the test drug or test drug 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 completing the consent process through discharge whether or not related to the study drug/placebo, must be reported ***within 24 hours*** to the NIDA Medical Monitor, the NIDA Project Officer, and the NIDA Project Manager.

NIDA Medical Monitor: Ann Anderson, M.D., 301/443-2281

NIDA Project Officer: Liza Gorgon, M.A. 301/443-1138

NIDA Project Director: Erin Iturriaga, RN, CCRC 301-443-9807

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 of first treatment
- Description of the SAE/unexpected AE
- Date and time of Onset
- Date/time of administration of last dose of investigational agent/placebo prior to the SAE/unexpected AE
- Severity of the SAE/unexpected AE
- Investigator's assessment of the relationship of the SAE/unexpected AE to study drug (related, possibly related, probably related, unlikely related, not related)
- Any action taken with the study drug, 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 Investigator-Sponsor 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 facsimilie, 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 adverse events occurring 30 days after administration of the last dose of study drug/placebo must be reported. All follow-up week 17 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 Investigator-Sponsor with all relevant follow-up information necessary to facilitate a thorough understanding of the event and judgment regarding the relationship to the study drug/placebo.

Reporting to the FDA

The IND Investigator-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.

APPENDIX V: 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.

NIDA will apply for a Certificate of Confidentiality for all 7 participating sites.

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.