CLINICAL PROTOCOL

PROTOCOL SUMMARY

TITLE:	KETAMINE-ASSISTED THERAPY OF ALCOHOLISM
STUDY OBJECTIVES:	To replicate data from a previous study showing significant clinical improvement of alcoholic patients after treatment with Ketamine-Assisted Therapy (KAT).
STUDY POPULATION:	Males and females, 18 - 60 years old, meeting DSM-IV criteria for alcohol dependence.
STUDY DESIGN:	Prospective, single-dose, double-blind, placebo-controlled, randomized, parallel group clinical trial.
STUDY MEDICATION:	Ketamine Hydrochloride.
DOSAGE:	2 mg/kg.
ROUTE OF ADMINISTRATION:	Intramuscular.
DURATION OF TREATMENT:	Single session with Ketamine or placebo during the middle stage of standard six week outpatient treatment of alcohol dependence.
DURATION OF SUBJECT PARTICIPATION:	18 weeks.
NUMBER OF SUBJECTS REQUIRED:	60 (30 per treatment group).
ANTICIPATED MAXIMUM NUMBER OF SUBJECTS:	90 (45 per treatment group).

PROTOCOL

THE KETAMINE ASSISTED THERAPY OF ALCOHOLISM

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I. ABSTRACT:

This is a prospective single-site, double-blind, placebo-controlled, randomized, short-term outcome, parallel group clinical trial of the efficacy of single administration of Ketamine as an enhancement to standard treatment of Alcohol Dependence. Following patient selection and consent procedures, patients will receive a single dose of Ketamine during the middle stage of standard treatment in a six weeks substance abuse program. Short-term outcome will be measured for three months following discharge.

General Description Study Flow

Consecutive admissions to a substance abuse treatment program will be examined for possible participation in the study. Patients meeting inclusion and exclusion criteria will be solicited for participation in the study. Patients who consent to participate will be randomly assigned to either the Ketamine-assisted or placebo treatment groups. Baseline data will be collected prior to administration of the treatment (see schedule of evaluations in Study Activities and Observations).

The Ketamine-assisted treatment and the treatment with placebo (normal saline) will be administered by the principal investigator or co-investigator. No other aspects of the patient's treatment program will be affected or altered as part of the study.

Standard treatment is based on a psychoeducational model of treatment and is approximately six weeks in duration from the date of admission to the treatment program. The Ketamine (in the dose of 2 mg/kg IM), or normal saline, will be administered during the middle stage of standard treatment.

Patients will be followed for a period of three months after discharge. Two follow-up contacts (within one month and three months) will require an outpatient appointment during which the patient will complete a substance use interview, an alcohol and drug screen, and a set of psychological measures.

II. STUDY OBJECTIVES:

The goal of this study is to replicate the data from previous studies showing the relationship between the treatment of alcoholic patients with the Ketamine assisted therapy and clinical improvement as reflected in objective measures of therapeutic outcome. This outcome would be demonstrated by statistically greater and more sustained improvement in the patients who received Ketamine assisted therapy. At the end of the therapy and throughout the follow-up period of three months the patients who were treated with Ketamine would demonstrate less alcohol abuse, report fewer psychiatric symptoms, demonstrate less psychopathology, exhibit more stable personality characteristics, greater positive value orientation and superior social adjustment, as compared to the control group treated with standard anti-alcohol therapies.

The design of the proposed study will not allow rejection of alternative explanations for improvement in the active treatment group: specifically of possible experimenter bias in administration of the placebo and experimental treatments. The proposed study is, in fact, designed to reveal any potential positive effects of Ketamine-assisted therapy. Failure to find positive effects under this set of conditions would therefore strongly argue against further exploration of Ketamine-assisted therapy in the treatment of substance abuse.

The finding of positive effects in the proposed study would therefore primarily provide only a more substantive foundation for conducting a scientifically more rigorous, and substantially more expensive study. This subsequent study would require at minimum three groups of subjects: standard treatment, Ketamine-assisted therapy, and standard treatment plus psychoactive placebo.

III. INTRODUCTION

Alcohol is the number one drug of abuse in the U.S.A. Close to 113,000,000 of Americans are using alcohol on a regular basis. 10% of the U.S.A. population are either alcoholic or have serious alcohol related problems. Alcohol use is also associated with liver disease, cancer, cardiovascular disease, fetal alcohol syndrome, highway fatalities, accidents and suicide. NIAAA estimates the costs to U.S.A. society from Alcoholism and alcohol related problems at approximately $116 billion in 1990.

Recent extensive investigation (Walker, at al., 1994) of all (539,557) inpatients treated in V.A. medical centers in fiscal year 1991 found that nearly one-quarter (127,762) of all male veterans treated in the study year had Substance Use Disorders. 87.7% (112,943) of all veterans with Substance Use Disorder had Alcohol Dependence.

Efforts to treat Alcohol Dependence are costly and have low rate of recovery. Previous meta-analysis of outcomes of treatment for Alcoholism (Nathan, 1986) showed that different treatment methods do not appear to be associated with significantly different long-term outcomes. Treatment factors, including theoretical orientation, content, locus, and intensity of treatment reveal little or no difference in treatment outcome, despite great differences in costs. Although abstinence rates one year after treatment may reach 50% for good treatment prospects (well motivated, employed, subchronic alcoholics with substantial personal resources treated at private treatment facilities), typical abstinence rates for poorly

motivated, unemployed, chronic alcoholics with few personal resources seen at public treatment facilities are 25% or lower. Rates of abstinence at and beyond the three-year mark are half or less of one-year rates.

The recent controlled study in Russia (Krupitsky et al., 1992) of Ketamine assisted therapy of Alcoholism has demonstrated a significant clinical effect of this treatment: 69.8% of patients were sober for more than one year, while in the control group only 24% remained abstinent during one year follow-up period.

Ketamine Hydrochloride is a rapid-acting, non-narcotic, non-barbiturate agent, which has been termed "dissociative" anesthetic (as it appears to selectively interrupt association pathways to the brain before producing somesthetic sensory blockade). The drug produced extremely effective analgesia and was the most widely used battlefield anesthetic in Viet Nam. Since 1970 Ketamine has been widely used in clinics and hospitals due to its rapid onset, short duration of action and large margin of safety (White, et al., 1982). Previous clinical studies have failed to detect any long term impairment of behavior or personality functioning as the consequences of continued use of Ketamine (Siegel, 1978).

The Ketamine dissociative reactions, while producing analgesia, also produce specific reactions, which has been labeled as "emergence phenomena". Descriptions of this phenomena include feelings of floating in space, vivid dreams of past memories, transcendental and religious experiences. Although the "emergence phenomena" has been documented by multiple studies, the experience of this phenomena does not present psychological problems for the patients. A number of psychiatric investigators have utilized treatment with Ketamine to create abreactive effects in psychotherapy. One previous study showed that Ketamine narcopsychotherapy was very effective in treatment of various psychiatric disorders (Khorramzadeh et al., 1973).

Because of such remarkable clinical success of Ketamine assisted therapy, it is important to replicate these results in controlled study in the U.S.A.

IV. STUDY DESIGN

A. DESIGN

This will be a prospective single-site, double-blind, placebo-controlled, randomized, short-term outcome, parallel group outpatient clinical trial. Subjects will be randomly assigned to one of two treatment groups:

1. Psychoeducational model treatment program and single administration of Ketamine 2 mg/kg, IM.

2. Psychoeducational model treatment program and single administration of placebo (normal saline), IM.

The Ketamine or placebo treatment will be administered in addition to any and all treatment components as part of the routine six week outpatient substance abuse treatment program.

Evaluations will be conducted on admission, following signed consent and prior to administration of the Ketamine, just prior to discharge, and twice following discharge for a period of three months (within one month and three months). No other alterations will be made to the patients' treatment program as a result of participation in the study.

B. RANDOMIZATION AND BLINDING PROCEDURES

Subjects will be assigned to the treatment condition according to a computer-generated randomization schedule at the time of completion of informed consent. Treatment will be administered by the principal investigator or co-investigator. The principal investigator or co-investigator will not be aware of the subject's treatment condition (i.e., they will be blind to the treatment conditions).

Blinding of the study medication will be accomplished by making all study medication look alike. Ketamine and normal saline will be dispensed into the syringes by a pharmacist. Only the pharmacist will be aware of the subjects' treatment condition. The syringes will be delivered to the treatment room by the pharmacist, who will not be blind to the treatment conditions. Injections will be administered the principal investigator or co-investigator who will not be aware of the subject's treatment condition (i.e., they will be blind to the treatment conditions).

C. PROCEDURES TO BREAK BLIND

Both the principal investigator and the treating physician (in some cases the treating physician will be the principal investigator) will not know the subject's treatment condition. In case of emergency, the blinded study medication for a specific subject can be identified by Jorge Forte, Pharm.D., who will not be blind to the treatment condition.

V. SUBJECT SELECTION

A. INCLUSION AND EXCLUSION CRITERIA

Inclusion Criteria:

Subjects must:

1. Be willing to participate voluntarily as described in the written Informed Consent.

2. Be between the ages of 18 and 60, inclusive.

3. Identify alcohol as the drug of choice and satisfy the DSM-IV criteria for Alcohol Dependence (303.90).

4. Be approved for participation by their treating physician.

5. Be non-childbearing potential or taking adequate precautions.

Exclusion Criteria:

1. Clinically unstable disease, including cardiovascular, hepatic, renal, gastrointestinal, pulmonary, metabolic, endocrine, or other systemic disease.

2. Treatment with any drugs that might interact adversely with or obscure the action of the study medication (Benzodiazapines, Barbiturates and Opioids).

3. Clinically unstable psychiatric disorder characterized by psychotic symptoms.

4. The presence of suicide precautions.

5. The presence of Post-Traumatic Stress Disorder (PTSD).

6. History of Phencyclidine and Hallucinogenic drug use.

Items 3, 4, 5 and 6 will be determined by a structured clinical interview based on DSM-IV criteria (MINI 5.0; Sheehan et al., 1998)

B. INFORMED CONSENT

Before a subject participates in the study, his or her written informed consent will be obtained. The subject will be asked to read a consent form and sign it to indicate consent to participate in the study. Informed consent will be obtained before any procedures necessary for conducting the study are performed. See the INFORMED CONSENT for additional information about the informed consent process.

C. SCREENING PROCEDURES

1. Pre-study evaluation

As part of the normal admission process to the substance abuse treatment program, the following information is collected on all patients:

a. Medical history and physical exam.
b. Psychiatric evaluation including substance abuse history.
c. Laboratory evaluations, including CBC, blood chemistry panel, urine analysis, UDS, breathalyzer.

2. Screening/Baseline Evaluation

Subjects meeting the inclusion criteria and not excluded per exclusion criteria 1-3 will be solicited for participation. Subjects who consent to participate, as indicated by a signed informed consent form, will be administered a screening/baseline evaluation that consists of the revised NEO Personality Inventory, the Beck Depression Inventory, the Beck Anxiety Inventory, and the MINI. Subjects who are not excluded per exclusion criteria will be admitted to the study.

D. SUBJECT ENROLLMENT

A minimum of 90 subjects, 45 in each of the Ketamine and placebo groups, will be enrolled in the study. Because of random assignment, the number of subjects in either group may exceed the minimum slightly. These subject requirements are based on the minimal number of subjects for statistical analyses (30 per group) and take into account a very liberal attrition rate during the three-month follow-up period.

On average, the substance abuse treatment program discharges 15 patients per month who satisfy inclusion criteria 1 and 2. Assuming that only 40% of similarly defined admissions met other selection criteria and consent to participate, enrollment of 90 patients will take about 15 months.

VI. TREATMENT

The treatment program is a structured psychoeducational model. Patients receive six hours per week of lectures, films, group therapy and counseling, all tailored to meet their individual needs. Each patient is assigned to a psychiatrist/counselor team, which performs an individualized treatment plan during the first three days, which is reviewed and updated with other members of multidisciplinary treatment team. The program is structured to last six weeks, but length of stay for individual patients can vary as a function of their medical care needs. See Appendix B for a full schedule of intensive out-patient program at James A. Haley Veterans Hospital.

The treatment with Ketamine or placebo will be scheduled during the middle stage of standard psychoeducational model program. There will be one treatment session with Ketamine or placebo. The length of the session will be two hours. A physician and a trained therapist will be present throughout the session.

The patient will be recommended to have a light dinner on the night immediately preceding the session and only liquids (fruit juice, milk, etc.) for breakfast. The patient will be asked to abstain from any intake of food or liquids during the eight hours prior to the session. The patient will be instructed to

have light, casual and comfortable clothes; any restricting garments or potentially dangerous belongings (belts, tight bras, watches, artificial dentures, pieces of jewelry, contact lenses, glasses, etc.) should be removed from the body.

An injection of Ketamine (2 mg/kg) or normal saline will be given by the principal investigator or co-investigator and the patient will be instructed to recline on a comfortable couch/bed and put on eyeshades. From that point the patient will be in a reclining position until the effect of Ketamine will be discontinued. The patient will receive stereophonic headphones and will listen to specially preselected evocative music with little concrete content ("Music to be born by", by Mickey Hart). The instruction will be given "to let go and surrender to the experience". Verbal exchange between the therapist and the patient will be kept at minimum.

If the patient becomes excessively anxious, non-specific support and reassurance will be given. In case of extreme complications (psychomotor agitation, panic attack) the patient might be given (on discretion of the physician) an injection of Lorazepam, 1 - 2 mg. IM, to terminate the session.

When the pharmacological effect of Ketamine will be wearing off (45 - 60 minutes after injection), the patient will be given opportunity to share the experience. The therapist will be giving interpretations of the experience as it relates to the patient's problems with alcoholism. After the patient returns to the usual state of consciousness (2 hours after injection) the patient will leave accompanied and driven by an informed friend or family member. The patient will be instructed to maintain a quiet, meditative mood throughout the rest of the day. A physician will be on-call in case any difficulties arise.

During the next day the patient will be asked to write a detailed account of the Ketamine experience. Later that day a session with the patient will be scheduled to facilitate the integration of the Ketamine induced experience in order to change the patient's attitude toward alcohol abuse. During the last week of treatment one group session will be conducted for all patients undertaking Ketamine sessions. Group size will be limited to four or five patients. The session will last two hours. The goals of the group session will be to further validate the material of Ketamine assisted psychotherapy, to help patient's to terminate the alcoholic's lifestyle and to provide the basis for continuing sobriety.

Previous study (Krupitsky et al, 1992) established that the descriptions of Ketamine experience by the patients with alcohol dependence had much in common. All patients described the loss of self control, the persistent guilt, the suffering resulting from one's own isolation and loss of significant relationships, the horror of approaching catastrophe, the feeling of the loss of identity, the fear of death. It is significant that the patients did not attribute their symbolic experience to the action of the medication. They attributed the negative character of the Ketamine experience to the destructive effect of their alcoholism. It seemed that their denial was breached during the procedure and that they were able to identify the destructive nature of their alcohol dependence. This interpretation had a paramount effect on the patient's awareness of the need to maintain abstinence as a necessary condition for sober living.

VII. PLACEBO CONTROL

Subjects in the placebo group will receive an injection of normal saline instead of an injection of Ketamine. No other aspects of the patients' treatment program will be affected or altered as part of the study.

VIII. STUDY ACTIVITIES AND OBSERVATIONS

A. ADMISSION PERIOD (Week 1)

As part of the routine admission procedure for all patients, the following evaluations will be completed:

1. Medical history and physical examination.
2. Psychiatric evaluation including substance abuse history.
3. Laboratory evaluations, including CBC, blood chemistry panel, urine analysis, UDS, Breathalyzer.

B. BASELINE PERIOD (Weeks 2-3)

Patients who are potential candidates on the basis of results from the admission period evaluations will be solicited for participation. Patients who consent to participate as subjects in the study will then complete the following evaluations:

1. NEO-Personality Inventory - Revised (NEO)
2. Beck Depression Inventory (BDI)
3. Beck Anxiety Inventory (BAI)
4. MINI

C. TREATMENT PERIOD (Week 4-5)

During this period subjects will be randomly assigned to treatment groups. Treatment with Ketamine or placebo will be administered during this period.

D. DISCHARGE EVALUATION (Week 6)

Subjects will complete the following evaluations on the day prior to discharge, no later than the last day of treatment in the substance abuse program.

1. Beck Depression Inventory (BDI)
2. Beck Anxiety Inventory (BAI)

E. 30 DAY FOLLOW-UP (Post-discharge days 25-35)

Subjects will complete the following evaluations as part of the 30-day follow-up:

1. Ketamine Study Follow-up Questionnaire.

2. Breathalyzer.
3. Urine drug screen.

F. 90 DAY FOLLOW-UP (Post-discharge days 75-105)

Subjects will complete the following evaluations during an outpatient appointment as part of the 90-day follow-up:

1. Ketamine Study Follow-up Questionnaire.
2. NEO - Personality Inventory - Revised (NEO).
3. Beck Depression Inventory (BDI).
4. Beck Anxiety Inventory (BAI).
5. Breathalyzer.
6. Urine drug screen.

A Study Completion Report will be completed following the 90-day follow-up evaluation or at the point when the subject leaves the study.

G. Alternative Approaches

There are no alternative approaches to the induction of the profound altered state of consciousness induced by Ketamine.

H. Precaution

Because of the medication used in the procedure, the following precautions will be used.

1. The patient will take nothing by mouth for at least 8 hours before the session.

2. The patient will be attended throughout the Ketamine session by a trained therapist and a physician;

3. The patient will be released only to family members or significant others and will not be allowed to drive home.

4. A psychiatrist will be on call for the day and night of the Ketamine session.

I. Additional Precautions

Because of the innovative application of the medication in the treatment setting, additional precautions will be implemented:

1. The advisory panel.

In order to monitor the study on a continuing basis, the advisory group will be established. This group will include David Sheehan, M.D., an internationally recognized drug treatment researcher, Patricia Ordorica, M.D., the Chief of Psychiatry, Robert F. Bedford, M.D., the Chief of Anesthesiology and Michael T. McCormick, R.Ph., M.S., The Chief of Pharmacy Service. The panel will be asked to meet prior to study of the first patient to clarify their concerns and details of their monitoring function. The advisory panel will have the power to terminate Ketamine Protocol at any time in case of any unforeseen adverse affects.

2. Pilot feasibility study.

The first ten patients in the study will be monitored closely by an anesthesiologist and will be reviewed on an individual basis by the advisory panel. John Scharf, M.D., Anesthesiologist, will attend the Ketamine session with the first ten patients in the study, monitoring heart rate, blood pressure, and blood oxygen levels as a precaution for unexpected side-effects. The experience of each of the ten subjects will be reviewed with the advisory group. The principal investigator and co-investigator will be certified by the Department of Anesthesiology to administer a conscious sedation. Once the procedure is worked out to the satisfaction of the advisory panel, the study will proceed.

IX. HUMAN SUBJECTS

A. The characteristics of the subject population have already been given under the section on method.

B. Source of research material: psychological and clinical evaluations will be obtained from each patient at the beginning, during, at the end of treatment and at follow-up points.

C. Plans for the recruitment of subjects have already been given. When the patient has received adequate information as to the nature of the experimental treatment, the therapist will ask him or her to sign a consent form (see example of approved consent form) and will be given ample opportunity to ask questions related to the information included in the consent form. All subjects will be completely voluntary. No form of coercion will be employed and all subjects will be free to withdraw from the study at any time without jeopardy or prejudice.

D. Risks to subjects in this study fall into three basic categories:

1. physical,
2. psychological, and
3. social/legal.

a. Physical Risks. The physical risks are those resulting from the administration of Ketamine. Following adverse reactions were reported: elevation of blood pressure and pulse, diplopia, nystagmus, elevation of intraocular pressure, anorexia, nausea and vomiting. The above reactions occurred after rapid intravenous administration of Ketamine or intramuscular administration of high doses of Ketamine (in a range of 9 to 13 mg/kg) used for a surgical anesthesia. The dose to be used in this study is five times (!) lower (2 mg/kg).

b. Psychological risks. The potential risks of this form of treatment are essentially those associated with any form of psychotherapy. In addition, alterations in mood, perception and cognition are expected as essential part of the Ketamine session. Also painful childhood memories or current emotional conflict may surface, which will be managed psychotherapeutically. There may be a decreased ability to concentrate the following day, along with the vivid memories of the drug experience, but without impairment of reality testing.

c. Social/legal risks. Possible sequelae to any violation of confidentially may represent social and legal risks to the patients. To guard against this possibility all date pertaining to subjects in this study shall be treated as clinical material with the attendant provisions for the maintenance of confidentiality.

E. Potential for Ketamine Abuse and Physical Dependence.

Ketamine is not subject to Schedule I-V control under the Controlled Substance Act of 1970. Available data, however, concerning the drug abuse and dependence potential of Ketamine suggest that its abuse potential is equivalent to that of Phencyclidine (PCP) and related Hallucinogen compounds.

Criteria for Substance Dependence do not apply to Phencyclidine and Hallucinogen compounds. Although craving has been reported by individuals with heavy use, neither tolerance nor withdrawal symptoms have been demonstrated in humans.

There is no consensus in medical literature regarding intensity of Ketamine Abuse. Literature search found only one study (Siegel, 1978) examining the pattern of Ketamine use in twenty-three subjects, who used Ketamine recreationally. Seven subjects were classified as experimental users (short term use of Ketamine with a maximum frequency of ten times or less in their entire drug history). Eleven subjects were classified as social- recreational users (more frequent than experimental users and was primarily motivated by individuals seeking to share with others an experience they judged to be pleasant). Two subjects were classified as circumstantial-situational users (task specific, self-limited use, motivated by desire to explore new state of consciousness and work through personal problems). Two subjects were classified as intensified
drug users (characterized by weekly use of Ketamine for several months). Only one subject was classified as a compulsive drug user (high frequency and high intensity level of relatively long duration). In all subjects the use of Ketamine was self-limited.

It is clear that there is potential for abuse of Ketamine. However, the risk for sustained "heavy" use of Ketamine is minimal.

F. Measures, which have insured the minimizing of any potential risks in the previous studies, will be employed in this study as well. These include:

1. Proper screening of patients;

2. Establishment of trust between patient and therapist prior to any Ketamine session;

3. Psychotherapist specially trained and experienced in the experimental treatment modality;

4. Continuous monitoring during Ketamine session by a trained therapist and a physician;

5. Psychiatrists on call during and in the evening and night of Ketamine session. In case of untoward reactions, the patient will be treated as an outpatient or, if necessary, admitted to an inpatient facility. The patient will be informed of this rare eventuality in the consent form.

G. The risks to the subjects in this study are minimal. Previous studies often show improvement in a large number of patients treated with the experimental treatment. There are no alternative treatments available that could give comparable benefits. Potential risks to the patients are considered minimal in relation to the potential benefits to the patients as well as to the increase in scientific knowledge.

Literature Cited

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Appendix A

EVENING INTENSIVE OUTPATIENT PROGRAM

KETAMINE ASSISTED THERAPY STUDY

	Monday	Wednesday	Thursday
Week #1			
1530 hrs	Desease Concept	Medical Aspects - 1	Medical Aspects - 2
1603 hrs	Group Therapy	Group Therapy	Group Therapy
Week #2			
1530 hrs	Denial	Anger	Shame and Guilt
1630 hrs	Group Therapy	Group Therapy	Group Therapy
Week #3			
1530 hrs	Music Therapy	Communication Skills	Attitudes
1630 hrs	Group Therapy	Group Therapy	Group Therapy
Week #4			
1530 hrs	Surrender	Trust	Spirituality
1630 hrs	Group Therapy	Group Therapy	Group Therapy
Week #5			
1530 hrs	Meditation	Powerlessness	Grief
1630 hrs	Group Therapy	Group Therapy	Group Therapy
Week #6			
1530 hrs	Intimacy	Family Roles	Relapse Prevention
1630 hrs	Group Therapy	Group Therapy	Group Therapy

Appendix B

DESCRIPTION OF EVALUATION INSTRUMENTS

A. NEO Personality Inventory -- Revised

The recent revision of the NEO Personality Inventory (NEO-PI-R) is the most comprehensive and perhaps the best validated instrument to explore personality structure. It is designed to assess the basic five factors of personality titled Neuroticism, Extroversion, Openness, Agreeableness, and Conscientiousness (Costa, P.T. et al. 1955). Six different dimensions provide more detailed examination of personality within each of five domains. The NEO-PI-R is a self-report inventory comprised of 240 items, which are rated on a five point scale.

B. Beck Depression Inventory

The Beck Depression Inventory is a brief instrument designed to provide global measures of depressive mood states. It is a self-report inventory comprised of 21 items, which are based on a four point scale. The Beck Depression Inventory has long been a standard measure of depressed mood. Current reviews of the reliability and validity of this instrument is provided in Beck and Steer (1987).

C. Beck Anxiety Inventory

The Beck Anxiety Inventory is a brief self-report instrument designed to provide global measures of anxious mood state. The Beck Anxiety Inventory is a more recently developed instrument, designed with essentially the same psychometric methods as the Beck Depression Inventory. Current reviews of the reliability and validity of this test is provided in Beck and Steer (1990).

D. Mini-International Neuropsychiatric Interview.

Mini-International Neuropsychiatric Interview (M.I.N.I.) is modeled after the structured Clinical Interview for DSM-IV (SCID). It is a user friendly clinician rated questionnaire (see attachment) designed to identify symptoms of mental illnesses and addictive disorders to meet diagnostic criteria of DSM-IV. Current reviews of the reliability and validity of this instrument is provided in Sheehan, et al. (1995).

E. Ketamine Study Follow-up Questionnaire.

The Ketamine Study Follow-up Questionnaire is a brief follow-up interview about alcohol and drug use. It is a modification of a questionnaire used for previous program outcome studies (see attachment).

References

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Costa, P.T., Jr., & McCrae, R.R. (1985). The NEO Personality Inventory manual. Odessa, FL: Psychological Assessment Resources.

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Appendix C

FLOW CHART OF THE STUDY

	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 10	Week 14	Week 18
Entry / Demographic Evals:									
Informed Consent	**X**								
Psychiatric Eval	**X**								
Medical History	**X**								
Randomization	**X**								
Efficacy Evaluations:									
Primary Efficacy Measures									
Sobriety Interview	**X**						**X**	**X**	**X**
Breathalyzer	**X**						**X**	**X**	**X**
Urine Drug Screen	**X**						**X**	**X**	**X**
Secondary Efficacy Measures									
NEO-PI-R	**X**								**X**
Beck Depression Inventory	**X**								**X**
Beck Anxiety Scale	**X**								**X**
Safety Evaluations:									
MINI	**X**								
CBC	**X**								
Blood Chemistry Panel	**X**								
Urine Analysis	**X**								
Pregnancy Test	**X**								
Vital Signs	**X**								
Physical Exam	**X**								
Body Weight	**X**			**X**					
Treatment Session:									
Ketamine or Placebo				**X**					