4-1-2019

Psilocybin-Assisted Therapy: A Double-Blind Randomized Controlled Trial

Katherine Gruppo
Yale Physician Associate Program, k.gruppo@gmail.com

PSILOCYBIN-ASSISTED THERAPY:
A DOUBLE-BLIND RANDOMIZED CONTROLLED TRIAL

A Thesis Presented to
The Faculty of the School of Medicine
Yale University

In Candidacy for the Degree of
Master of Medical Science

April 2019

Katherine Gruppo, PA-SII
Class of 2019
Yale Physician Associate Program

John Krystal, MD
Robert L. McNeil, Jr. Professor of Translational Research and Professor of Psychiatry, Neuroscience; Chair, Department of Psychiatry; Chief of Psychiatry, Yale-New Haven Hospital; Director: NIAAA Center for the Translational Neuroscience of Alcoholism; Director, Clinical Neuroscience Division, VA National Center for PTSD

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Abstract

Alcohol use disorder is one of the most prevalent mental health disorders worldwide, treatment options are limited, and relapse rates are high. There remains an urgent need for effective treatments. Research involving the therapeutic potential of classic hallucinogens has reemerged in recent decades and the hallucinogen psilocybin has shown some promise in early studies. **We aim to assess the efficacy of psilocybin in treating alcohol use disorder with a 10-week double blind randomized double dummy crossover control trial comparing psilocybin-assisted psychotherapy to ketamine-assisted psychotherapy in individuals with alcohol use disorder.** Our primary outcome will be the mean percent heavy drinking days in the four-week periods following drug administration sessions among participants in both treatment groups. We hope that our results will provide further evidence for the therapeutic role of psilocybin in addiction and that our study design may serve as a model for future randomized controlled trials of psychedelics.

Chapter 1 – Introduction

1.1 Background Information and Rationale

Alcohol use disorder (AUD) is one of the most prevalent mental health disorders worldwide and the third leading preventable cause of death in the United States.[1] The National Institute on Alcohol Abuse and Alcoholism (NIAAA) defines AUD as a chronic relapsing brain disease characterized by an impaired ability to stop or control alcohol use despite adverse social, occupational, or health consequences.[2] In the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-V), AUD comprises both alcohol abuse and alcohol dependence disorders; it is further subclassified into mild, moderate, or severe.[3]

AUD exacts a heavy social, economic, and medical burden in the United States and globally. The World Health Organization (WHO) estimates that in 2012 the 12-month and lifetime prevalence of AUD ranged from 13.9 to 29.1% of the global population.[4] In the U.S., an estimated 16 million people had AUD in 2015.[5] AUD is a significant contributor to global morbidity and mortality. In 2012, an estimated 3.3 million deaths, or 5.9% of all global deaths, were attributable to alcohol consumption. The WHO ranks alcohol use as the eighth leading risk factor for death worldwide; in the U.S., alcohol misuse is the third leading cause of death. AUD also has severe negative effects on one's productivity, interpersonal and psychological functioning, as well as one's short- and long-term health.[4] Chronic excessive alcohol use can damage every organ in the body and contributes to over 200 diseases and injury-related health conditions, including liver cirrhosis, cancers, and dementia.[1] These consequences come at an economic cost including lost productivity and increased health care dollars. In 2006, it is estimated that the economic cost of excessive drinking in the U.S. was $223.5 billion[6].

Despite a high societal cost of AUD, treatment options are few and relapse rates are high, even when treatment methods are combined.[7,8] Common treatment options for AUD are pharmacological interventions, behavioral therapy, and mutual support groups. The FDA has approved only three drugs for AUD: Naltrexone, Acamprosate, and Disulfiram, and these medications display poor efficacy, low adherence rates, or adverse effects at a population level.[5] Empirically-validated behavioral interventions include cognitive behavioral therapy, motivational interviewing, and marital and family counseling. Mutual support treatment groups include Alcoholics Anonymous and other 12-step programs. Due in part to the low efficacy rates of available treatments (and other factors such as the stigma attached to this disease), the majority of people with AUD in the U.S. go untreated. According to the NIAAA, based on data from 2001-2002, only 14.6% of people with AUD ever receive treatment.[9] There remains substantial room for the development of effective treatment alternatives and classic hallucinogens, particularly psilocybin, have shown promise in early studies.

Classic hallucinogens exert their primary effects through agonist activity at serotonin 2A (5-HT_{2A}) receptors, and include lysergic acid diethylamide (LSD), dimethyltryptamine (DMT), psilocybin, and mescaline. [10-12] These hallucinogens have significant perceptual, cognitive, affective, and somatosensory changes, such as visual and auditory hallucinations, difficulty thinking, mood disturbances and dissociative phenomena.[13] Interest in the therapeutic use of classic hallucinogens to treat addiction and other mental health diseases originated in the 1950s, shortly after Albert Hoffman discovered the psychoactive effects of LSD and recognized its therapeutic potential.[14]

Over the subsequent 20 years until their scheduling by the US government as controlled substances, psychedelic research expanded rapidly.

The earliest investigations began with Humphry Osmond and Abram Hoffer's work in Saskatchewan in the early 1950s, which emerged from clinical observations suggesting that some alcohol dependent patients who had experienced delirium tremens (a severe form of alcohol withdrawal that involves sudden and severe mental or nervous system changes) subsequently decreased their drinking.[15] They hypothesized that this hallucinatory state was therapeutic and, therefore, LSD might reduce drinking by inducing a delirium tremens-like state. At the conclusion of their work Osmund and Hoffer ended up parting from their original hypothesis instead proposing that the observed efficacy of LSD in their subjects was attributed to the drug's ability to induce deep introspection and insight, which made subjects more amenable to psychotherapy.[14,16,17]

This led to numerous hypothesis-generating studies exploring the ideas put forth by Humphry and Osmund. Researchers observed that relatively high doses of psychedelics induce a "peak-psychedelic" or mystical experience of ego loss (characterized by profound alterations in perception, mood, volition, cognition, and self-experience), which impacts long-term behavior, personality and cognition.[18,19] Furthermore, researchers found that when combined with psychotherapy, hallucinogens facilitated the psychotherapeutic process and strengthened the therapeutic relationship.[14,20] Several studies on alcohol dependence found improvements in self-acceptance and interpersonal relationships, as well as reductions in craving and alcohol use, among subjects treated with LSD.[18,21,22]

1.2 Problem Statement

While the work done during the 1950s to early 1970s generated substantial support for the therapeutic role of psychedelics in addiction, much of the research done during that time period had significant methodological limitations; most notably, a lack of randomized, double-blind, placebo-controlled trials.[16,18] Further, the randomized clinical trials that did exist did not preserve the blind (i.e. the hallucinogen under investigation was compared to an inactive substance or a non-hallucinogen such as amphetamine). Thus, the patients in the studies always knew when they were getting hallucinogen or the presumed inactive comparator. When psychedelic research resumed in the 1990s, researchers expanded upon the earlier work of their colleagues, refining treatment models of psychedelic therapy and establishing specific guidelines for the adequate study of treatment effectiveness of psychedelics.[16,23] By the beginning of the 21st century, psychedelic research was again undergoing rapid growth.

In this new era of psychedelic research, major advances have been made towards understanding the acute effects of psychedelics on physiology, cognition, emotion, and brain function.[24] Numerous studies have demonstrated the safety of these drugs when administered in a controlled clinical setting. [24-26] Recent addiction research has shifted its focus from LSD to psilocybin as a potential adjunct for treatment because psilocybin works through the same mechanism of action, but is shorter-acting and overall, better tolerated.[27] Several lines of evidence suggest that psilocybin has clinically relevant effects in the treatment of addiction. Recently completed proof-of-concept studies of psilocybin in conjunction with psychotherapy for nicotine and alcohol dependence demonstrated that the intervention led to substantial decreases in use of the target substance[28,29] This proof-of-concept study of psilocybin for AUD was the first to ever test

this relationship[28]. Currently, Phase 2 randomized-controlled trials (RCTs) are underway to test the efficacy of psilocybin-assisted treatment of tobacco, alcohol, and cocaine use disorders. Given the current plethora of evidence in support of psilocybin as a useful pharmacological tool for treatment of AUD and the dearth of RCTs investigating this hypothesis, further investigation is warranted.

1.3 Goal and Objectives

This study aims to further clarify whether psychedelic-assisted treatment with psilocybin of AUD is clinically useful. Specifically, this study aims to: (1) characterize the acute effects of psilocybin in alcoholic patients (2) evaluate the effect of psilocybin treatment on drinking outcomes relative to a ketamine control.

1.4 Hypothesis

Psilocybin administered in conjunction with targeted psychotherapy will lead to a greater clinically significant reduction in the mean percent heavy drinking days compared to active placebo ketamine among individuals with alcohol use disorder.

1.5 Definitions

Mean percent heavy drinking days: mean days during which participants consume five or more standard drinks (14 g of alcohol per drink) if male, or four or more standard drinks if female.

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Chapter 2 – Review of the Literature

2.1 Introduction – Literature Search Criteria

A thorough review of the literature was conducted from December, 2018 to April, 2019 using Ovid (Medline), PubMed, Embase, and Cochrane Medical Library using a concept table (Appendix A). Searches included clinical trials, randomized control trials, systematic reviews, and meta-analyses. All publications that used hallucinogens as a therapy for addiction were selected for further review. Additional publications relevant to this study were obtained through forward searches and hand searches, and included in the review.

2.2 Overview of Current Treatments for AUD

AUD is a heterogenous disease with a wide range of phenotypes, and individual response to treatments varies greatly. Accordingly, current interventions for AUD integrate pharmacological treatment with psychosocial therapy to target the genetic, psychological and environmental factors that are believed to interact to cause this disorder. Goals of treatment include: achieving abstinence; reducing the frequency and severity of relapse, and improving both health and psychosocial functioning.

2.2.1 Approved Medications for AUD

Disulfiram was the first medication to become approved by the FDA for the treatment of AUD. It is prescribed as an anti-craving medication to abstinent individuals with a high motivation to stay sober, since it works by inhibiting the metabolism of alcohol which induces severe adverse reactions if alcohol is ingested. While disulfiram has been found to act as a deterrent to alcohol ingestion in a controlled environment, its efficacy drops significantly in an unsupervised environment.[1] As a result, in "real world" RCTs, adherence rates were low and disulfiram did not show efficacy.[2] A meta-analysis

of open-label trials and RCTs of disulfiram use in alcoholics found that overall, compared to controls, disulfiram showed a higher success rate, with Hedge's g = 0.58 (95% CI = 0.35-0.82). However, only open-label trials showed significant superiority over controls (g = 0.70, 95% CI = 0.46-0.93). Disulfiram was also found to be more effective than the control condition when compared to naltrexone (g = 0.77, 95% CI = 0.52-1.02) and to acamprosate (g = 0.76, 95% CI = 0.4-1.48)[3]. While the rate of disulfiram prescription continues to climb in some parts of the world, overall disulfiram prescription rates are dropping as its role in treatment is generally displaced by more recently introduced medications.[4]

Naltrexone is a non-selective opiate antagonist that targets and blocks the rewarding neurobiological effect of alcohol.[1,5,6] It is prescribed as an adjunct to psychosocial intervention for reducing heavy drinking in alcohol dependent individuals and prolonging abstinence.[1,7] Trajectory-based studies of naltrexone suggest that it is most effective in patients who have a high likelihood of drinking heavily on a regular basis during treatment and that it is ineffective in patients who drink sporadically during treatment.[8,9] A 2013 meta-analysis of RCTs of naltrexone for alcohol dependence found a small but significant effect of Naltrexone compared to placebo on the outcome of heavy drinking (g = 0.189, CI 0.123-0.255, $p < 0.001$).[10]

Acamprosate is an analogue of GABA and is thought to act as a functional glutamate antagonist, dampening glutaminergic hyperactivity associated with alcohol withdrawal.[11,12] Results on the efficacy of Acamprosate are mixed. A meta-analysis of RCTs comparing acamprosate to naltrexone for alcohol dependence found a small but significant effect of Acamprosate compared to placebo on the outcome of heavy drinking

that was similar to that of Naltrexone (g = 0.359, CI 0.246-0.472, $p < 0.001$).[10] However, it did not show efficacy on its primary endpoints in either of the large RCTs conducted in the U.S. including NIAAA Project COMBINE, the largest pharmacotherapy study in the history of the field.[13,14]

2.2.2 Evidence-Based Psychosocial Interventions

Psychosocial interventions are psychologically-based interventions that aim to reduce consumption behavior or alcohol-related problems.[15] The most commonly used interventions are motivational interviewing (MI), cognitive-behavioral therapy (CBT), brief interventions, and Twelve-step facilitation programs (TSF).[16] Clinical trials have found no superiority of one behavioral treatment over another.[1] These interventions have shown moderate efficacy in reducing drinking and maintaining abstinence, and not all individuals benefit from psychosocial therapy.

The psychosocial intervention proposed in this study is motivational enhancement therapy (MET), which is a type of MI, and a common intervention for the treatment of AUD; it is one of the few treatments designed specifically for abstinence initiation[17]. MET consists of a patient-centered therapy that aims to produce rapid internally-motivated changes by exploring and resolving ambivalence towards behavior.[18] A systematic review of RCTs published between 1997 and 2007 assessing the beneficial or detrimental effects of motivational techniques in the treatment of alcohol dependence found that MET was significantly more effective than a minimal intervention control at reducing heavy alcohol use when assessed at five-month follow-up (moderate effect size).[18] Additionally, MET was favored over control in individuals who drank

excessively and frequently at six-month follow-up (large effect size). The analyses showed a trend favoring MI with relapse prevention over control ($p = 0.07$).[18]

2.3 Promise of Psilocybin-Assisted Psychotherapy for AUD

2.3.1 Clinical Studies of Classic Hallucinogens in Substance Use Disorders

The main focus of research during the 1950s-1970s in the field of addiction was the use of LSD for the treatment of alcoholism. Following the success of Drs. Hoffer and Osmond, administration of LSD with psychotherapy to alcoholic patients became an accepted clinical treatment in Saskatchewan and the subject of many studies. The majority of these studies had significant methodological flaws, including an absence of adequate control groups; substantial variation in dose quantity and duration; a lack of control for confounding factors; non-standardized criteria for therapeutic outcome; and diverse theoretical approaches for assessing beneficial effects.[19,20] In a recent meta-analysis of these studies, about a dozen were reported to have some form of control group, only six were randomized trials (N = 536), and of these, five were fully double-blind.[21] All of these studies employed a single high-dose LSD session and controls that included inactive placebo, low-dose LSD (50 mcg), ephedrine, and amphetamine. At the post-treatment follow-up (which ranged from one to 12 months), the odds ratio for improvement was 1.96 (95% confidence interval [1.36-2.84], Z = 3.59, $p = 0.0003$). Among the five studies reporting dichotomous outcomes, 59% of the LSD-treated participants were significantly improved vs. 38% of the control participants (pooled benefit difference 16%, 95% confidence interval 8%-25%, $p = 0.0003$, number needed to treat = 6). All six studies demonstrated robust treatment effects, which remained significant at six months follow-up.[19,21] Despite their methodological flaws, these studies

provide persuasive preliminary evidence for the efficacy of 5-HT_{2A} receptor agonists in the treatment of alcoholism.

Clinical research on psilocybin for the treatment of addictions is still in its early stages. To date, there are only two completed studies to explore the efficacy of psilocybin-assisted treatment for substance use disorders.[22,23] The first study, led by Matthew Johnson at Johns Hopkins University, was an open-label, dose-escalating study to determine the safety and feasibility of oral psilocybin as an adjunct to tobacco smoking cessation treatment in 15 tobacco-dependent adults[23]. Oral psilocybin was administered in a moderate (20 mg/70 kg) and then high (30 mg/70 kg) dose during two treatment sessions at five and seven weeks, with an optional third session at week 13. Prior to the first psilocybin administration, subjects attended four sessions of manualized intervention consisting of CBT for smoking cessation and preparation for the drug sessions. Results demonstrated substantial decreases in nicotine use among subjects. At the six-month follow up, 80% of subjects (12/15) showed seven-day point prevalence abstinence (p = 0.001), and 73% (11/15) were biologically confirmed to have quit smoking. This abstinence rate greatly exceeds rates commonly reported for other behavioral and/or pharmacological smoking cessation therapies, which are typically less than 35%.[23] Importantly, no significant treatment-related adverse effects were found.

The second study, led by Michael Bogenschutz, investigated the efficacy of psilocybin-assisted psychotherapy with MET in 10 alcohol dependent individuals.[24] Participants received orally administered psilocybin (0.3 mg/kg and 0.4 mg/kg) in one or two supervised sessions at four and eight weeks, with an optional dose increase at week eight along with nine total MET sessions. This study found a significant increase in

abstinence among subjects following psilocybin administration ($p < 0.05$) with gains largely maintained at follow-up to 36 weeks. Furthermore, the intensity of effects in the first psilocybin session was found to be a strong predictor of change in drinking during weeks five to eight ($r = 0.76$ to $r = 0.89$). No significant treatment-related adverse effects were found.

2.3.2 Clinical studies of Psilocybin in Other Psychiatric Diseases

Preceding the research on psilocybin as a potential treatment for addiction, psilocybin was investigated during the 1950s to 1970s by researchers seeking to characterize its pharmacological and safety profile, as well as its potential therapeutic properties. Research demonstrated that psilocybin, similar to LSD, reliably induces profound changes in sensory perception, emotion, thought, and sense of self, characterized by marked alterations in all mental functions.[25] As a result, some therapists incorporated psilocybin into their psychotherapy sessions in order to facilitate access to subconscious conflicts and memories and found that it led to the successful treatment of many previously therapy-resistant patients.[26]

In the modern era of psychedelic research, more rigorous studies have been conducted to investigate the psilocybin's therapeutic potential in a variety of mental health disorders. For example, in 2006, a dose-escalating proof-of-concept study was conducted to test the effects of varying doses of psilocybin on symptoms of obsessive-compulsive disorder (OCD)[27]. The study included nine adults with symptomatic OCD who received doses of psilocybin ranging from very low (25 μg/kg) to very high (300 μg/kg). Dosing escalation occurred sequentially, at least one week apart. Results found that all doses produced significant decreases in OCD symptomatology (measured via the

Yale-Brown Obsessive-Compulsive Scale, YBOCS) during one or more of the testing sessions. Investigators concluded that psilocybin was associated with acute reductions in core OCD symptoms in this population.[27,28]

Another dose-escalating study investigated safety and efficacy outcomes for up to six months in 20 adults with moderate to severe treatment resistant depression.[29] Oral psilocybin was administered at a low dose (1 x 10 mg) followed by a high dose (1 x 25 mg) one week later. Results revealed a significant decrease in self-reported depression scores in all participants relative to baseline, which lasted up to the last follow-up at six months (Cohen's $d = 2.2$ at week 1 and 2.3 at week 5; both $p < 0.001$). Additionally, four participants met the criteria for remission at the five-week time point through the last follow-up at six months (Cohen's $d = 1.4$, $p < 0.001$).[28,29]

Other psilocybin research has focused on evaluating its efficacy in treating anxiety and depressive symptoms related to advanced-stage cancer diagnoses.[30-32] In a 2011 randomized, double-blind, placebo-controlled crossover study, 12 adults with advanced-stage cancer and reactive anxiety were treated with either 0.2 mg/kg of oral psilocybin or oral placebo (niacin, 250 mg) in a randomized order.[30] Anxiety and depression outcomes revealed an overall decrease in scores compared to niacin placebo by almost 30% from the first treatment session to one month after the second session ($t_{11} = -2.17$, $p = 0.05$); this difference was sustained and became significant at the six-month follow-up point ($t_7 = 2.71$, $p = 0.03$). Authors observed that psilocybin produced mood-elevating effects that persisted after the acute effects of the drugs, facilitated therapeutic bonds, and ameliorated underlying psychological demoralization.

A notable limitation of this study is that a relatively low dose of psilocybin (0.2 mg/kg) was chosen for the experimental condition. This could have accounted for the modest effects found for psilocybin on anxiety and depression outcomes. Similar studies conducted in the 1960s and 1970s, which utilized much higher doses of hallucinogens, reported that subjects experienced profound psychospiritual epiphanies, which correlated with therapeutic outcome. These results are consistent with other recent studies that have demonstrated an association between higher doses of hallucinogens and transcendent states of consciousness.[31,33,34]

Two subsequent RCTs that investigated the effects of psilocybin in this population. The first investigated the effects of psilocybin doses (high vs. low) on anxiety- or depressive-related outcomes in 56 adults with cancer.[31] This study used a double-blind crossover design to randomize subjects (N = 56) to one of two sequences involving a low dose ("placebo-like") or high dose of oral psilocybin. Primary outcome measures of depression and anxiety demonstrated sustained and statistically significant improvements following high-dose psilocybin treatment vs. placebo for up to six months.

The second study, which investigated the efficacy of a single dose of psilocybin vs. placebo in conjunction with psychotherapy in 29 individuals, found similar results.[32] In this crossover study, 29 subjects were given a single dose of 0.3 mg/kg psilocybin or 250 mg niacin, both in conjunction with psychotherapy, with crossover occurring at seven weeks. Results found that the group that received psilocybin first showed "immediate, substantial, and sustained" clinical improvements in anxiety and depression scores, which lasted through the seven-week time period between treatments and up to the six-month follow-up. The group that received niacin first showed transient reductions

that were not sustained at seven weeks. After these subjects received psilocybin, immediate and sustained reductions in anxiety and depression were observed [35]. In all, approximately 60-80% of the 29 total patients, experienced enduring and clinically significant reductions in depression or anxiety at the six-month follow-up[32].

Taken together, these studies demonstrate the safety and feasibility of psilocybin-assisted treatment when administered in a controlled clinical setting to individuals with varying mental health disorders. Furthermore, they lend substantial support for the efficacy of psilocybin in these populations.

2.3.3 Safety Considerations for Psilocybin Administration

Additional clinical studies on psilocybin in healthy volunteers further support the feasibility and safety of psilocybin-assisted psychotherapy.[19,24,27,31,32,34,36,37] Studies on the psychopharmacological properties of psilocybin have found that when psilocybin is ingested by humans it is rapidly enzymatically cleaved to produce psilocin, which exerts its primary psychoactive effects at serotonin 5-$HT_{2A/C}$ receptor sites in the brain. The bioavailability of oral psilocybin is approximately 50%, and the half-life of psilocin in blood is two to three hours. Psychoactive effects become noticeable within one hour of administration, peak around two hours, and disappear around six hours.[28,38] Accordingly, protocols for clinical trials have mandated that subjects be observed until about eight hours after psilocybin dosing.

A meta-analysis of eight double-blind placebo-controlled studies of 110 healthy volunteers who had received oral psilocybin ranging from 45-315 μg/kg in one to four sessions, demonstrated that the psychomimetic and physiologic effects of psilocybin are dose-dependent.[28,36,39,40] Common symptoms included profound changes in mood,

perception, thought, and self-experience. Importantly, most subjects described the experience as pleasurable, enriching, and non-threatening. Factors other than dose have also been reported to modulate psilocybin's overall effects, such as personality structure and setting (i.e. environment). See Section 2.4.1 for more on the effects of set and setting.

The most commonly reported adverse psychological events of psilocybin were anxiety, negative emotional states, and paranoid/delusional thinking, and the most commonly reported physical effects were increased blood pressure, heart rate, and mild nausea and headache.[28] In order to maximize safety in clinical trials with psilocybin, a structured and supportive intervention protocol has been established for researchers to follow.[28,41]

Based on the available literature, researchers have not found evidence of addictive properties of psilocybin. Previous clinical studies with individuals with no or minimal (less than 10 lifetimes uses and no use within the last five years) history of hallucinogen use, who were given psilocybin in the context of a supervised and controlled research setting, concluded that, on follow-up, there were no incidents of illicit hallucinogens abuse in these subjects. Additionally, a retrospective analysis of the acute, short- and long-term subjective effects of psilocybin in healthy humans collected from previously conducted double-blind, placebo-controlled trials, revealed that the majority of participants reported "no change" in their psilocybin use following study drug sessions, as well as "no change" in their overall drug consumption habits (i.e. use of alcohol, nicotine, cannabis, MDMA). Those who did report changes often described decreased consumption after psilocybin[28,39]. Based on this evidence, it is not expected that the

hallucinogen-naïve participants in this study will develop dependence after psilocybin exposure.

2.3.4 Safety Considerations for Ketamine Administration

Ketamine is a dissociative anesthetic that is widely and safely used intravenously (IV) and orally in a clinical setting as a short-term anesthetic in doses ranging from 1-2 mg/kg administered IV, or 4-11 mg/kg administered intramuscularly. (Note: dissociative anesthesia is a form of anesthesia that lacks complete unconsciousness but is characterized by catatonia, catalepsy, and amnesia).[42] Ketamine is classified as an "atypical hallucinogen" due to its psychoactive properties. At certain doses it produces dissociative and psychomimetic effects similar to those of classic hallucinogens, including enhanced sensory perception, emotional connectedness, feeling of unreality, visual hallucinations, and altered perceptions of self and time.[43] Unlike classic hallucinogens, which are primarily mediated by agonist action at 5-HT_{2A} receptors, ketamine is a moderate affinity non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist.[44]

Ketamine's psychopharmacological effects are dose- and concentration-dependent.[45] Lower doses (i.e. 0.1 mg/kg administered IV over 40 minutes) induce a mild state of euphoria that is similar to that produced by a glass of wine, whereas higher subanesthetic doses (i.e. 0.5 mg/kg, IV over 40 minutes) produce alterations in sensory perception, feelings of unreality, and in some subjects mild psychosis.[42,43,45] Ketamine has been found to unfavorably affect cognition (i.e. decrease mental sharpness, recall, and recognition, as well as explicit and implicit memory) either during or shortly following administration.[43] During ketamine infusion, it is common for the perceptual effects to be

accompanied by anxiety. At doses where it alters perception, it also produces nystagmus and this symptom is associated with nausea and, in some cases, vomiting. In patients who are sensitive to ketamine-induced nausea, this symptom may be managed by pretreatment with odansetron, which does not seem to alter its therapeutic or psychological effects (Robert Ostroff, personal communication). In healthy subjects, ketamine typically produces a mild elevation in blood pressure and pulse rate that typically does not require medical intervention. Repeated ketamine administration appears to be safe when managed clinically. However, long-term heavy recreational use of ketamine, which can reach daily levels of 100-times the therapeutic dose, may lead to flashbacks, attentional, and other cognitive dysfunctions.[42,43,46-48]

Ketamine has proven to be a desirable drug due to its short half-life and lack of clinically significant severe adverse effects. In addition to its anesthetic action, it also possesses analgesic effects, anti-inflammatory effects, and antidepressant activity. Repeated subanesthetic ketamine has been shown to improve clinical outcomes for treatment resistant depression.[49-51]

2.4 Review of Relevant Methodology

2.4.1 Study Design and Possible Confounders

The unique challenges of conducting experimental research with psychedelics has been discussed extensively throughout the literature.[19,52-56] These challenges stem from the unique properties of psychedelic drugs and include design issues relating to subject selection, the difficulty of blinding to the subjective effects of the drug, and the possibility of complex interactions between psychological and environmental factors prior to, during, and after drug administration.

Prior hallucinogen experience

With regards to the selection of experimental subjects, an important consideration is a subject's prior hallucinogen experience. Previous studies have used varying selection criteria for hallucinogen experience. For example, the open-label study with psilocybin for AUD treatment required that individuals have no hallucinogen use in the previous 30 days, and lifetime use not exceeding 10 occasions.[24] In contrast, the open-label trial on nicotine dependence required all subjects to have had at least one prior and well-tolerated occasion of hallucinogen exposure.[23]

In this proposed study, we believe it will be important to enroll only hallucinogen-naïve participants so that they will not be able to recognize or differentiate between the psychedelic drug effects of psilocybin and ketamine due to a lack of previous experience. This will help to maintain the blind. This is particularly important in a trial with psychedelics because these drugs have been shown to be particularly susceptible to expectancy bias – that is, the individual's state of mind and expectations when taking the drug strongly influence the nature of the drug experience. Thus, minimizing expectancy bias enables us to better control the quality of the psychedelic experience. This selection criteria will also enable use to avoid selection bias, where individuals who have previously had positive experiences with hallucinogens may be more likely to participate.

Maintaining the double-blind

Maintaining the double-blind in studies with psychedelics is considerably difficult due to the pronounced acute subjective and objective effects of these drugs, which provide subjects and investigators with ample clues for identifying the experimental condition. To a certain degree, this problem is shared by other psychoactive drugs (i.e. stimulants, sedatives, and opioids) that produce discriminable effects, and typically, the

solution is to use an active placebo in lieu of an inert placebo. However, in trials with psychedelics, even active placebo has been easily distinguished from the experimental condition by participants and investigators.[29]

Previous psilocybin trials have used active controls such as niacin, ephedrine, and methylphenidate, due to their ability to induce some of the same mild physiological symptoms as psilocybin (i.e. sense of warmth, arousal, tingling sensation, and flushing, nervousness, and/or increased positive mood) without altering the subject's psychological state.[30,32] However, as Grob and his team discovered in their trial assessing the efficacy of psilocybin vs. niacin placebo in advanced stage cancer patients, "the drug order was almost always apparent to subjects and investigators whether the treatment was psilocybin or placebo." Similarly, Ross and his team concluded that staff guessed correctly 97% of the time whether the participant was administered psilocybin or niacin placebo rendering blinding completely unsuccessful. In fact, it is estimated that in RCTs with LSD or psilocybin, session monitors (therapists present during the drug sessions) were able to accurately discriminate between these experimental drugs and active placebos in 77-95% of the time.[55]

In other trials, very low ("placebo-like") doses of psilocybin have been used with the intention of providing noticeable psychoactive effects without the therapeutic effect of higher doses. In the psilocybin trial for OCD, a very low dose (25 μg/kg) psilocybin placebo was concluded to be an ineffective blind: "subjects experienced stronger than anticipated response to this dose, and its clinical effects were also greater than anticipated. This response to VLD impedes the use of VLD as a placebo comparator."[27] Another trial that used a very low dose of psilocybin as a placebo, had somewhat more

success in maintaining blinding, stating that "blinding procedures provided some protection against a priori monitor expectancy strongly determining outcomes of the psilocybin dose manipulation."

A limitation to a low-dose psilocybin placebo is that it is difficult to exclude the possibility that even a low-dose psilocybin placebo control may have some psychomimetic properties and partially contribute to treatment effects (as mentioned earlier). "A wiser choice," one investigator advises, "may be a control that has a different mechanism of action yet is still capable of producing similar psychoactive symptoms so that participants may remain blinded to their condition/treatment."[30] Heeding this advice, we have selected ketamine as the control condition in our study, since it closely mimics psilocybin's psychoactive effects, while still possessing a radically different mechanism of action from psilocybin.[57]

This design will be in contrast to Bogenschutz' current study on psilocybin for AUD, which is using diphenhydramine (50 mg) as an active control. (Diphenhydramine at this dose has a side effect profile that includes pupil dilation, facial flushing, hallucinations, and ataxic gait, which overlap with some of the physiologic side effects of psilocybin). We believe that blinding will be significantly compromised in this RCT.

Set and Setting

An individual's state of mind and expectations when taking a psychedelic, as well as the context (i.e. physical and interpersonal environment) in which the individual takes the drug significantly contribute to the overall quality of the drug experience. Consequently, the effects of hallucinogens can vary markedly from individual to individual and from session to session. This idea was introduced early on in psychedelic research, and dubbed "set and setting."[55,58,59] The elements of "set and setting" are

essential to account for within the design of a clinical trial on psychedelics because the overall quality of the drug experience is believed to mediate the persisting therapeutic effects of the drug.

Research to support this idea includes the finding that "pre-session negative mood consisting of anxiety or depression has been shown to significantly predict anxious or other negative experiences during the session."[41] In addition, work by Griffiths and his team with psilocybin in healthy individuals found that the presence/absence, and quality of the mystical experience during the drug's acute effects were significant predictors of beneficial change in volunteers. While research to systematically evaluate how specific elements such as set and setting may impact therapeutic outcomes is lacking, this idea is still generally accepted by psychedelic researchers.

Accordingly, Johnson and colleagues have published a set of guidelines for researchers to follow in order to control for the variables discussed here, maximize therapeutic potential, and ensure patient safety. These guidelines are based on previous research and are closely followed by researchers in this field. In addition to these guidelines, clinically validated instruments have been developed to qualify the dimensions of the drug experience and its overall intensity. All of the methods relevant to this proposal will be incorporated into our design (see Section 3.6.2).

Crossover Design

Taking into consideration the various challenges of RCTs with psychedelics, as well as our study's objectives, we selected a crossover design. Crossover designs have been used extensively in early-phase trials, including in studies with psilocybin in normal volunteers and individuals with anxiety and depressive disorders[19,30-32]. The most common type of crossover design consists of a two-period, two-treatment design wherein

subjects are randomly assigned to receive either treatment A and then B, or B and then A. A crossover design is ideal for studying treatment of chronic conditions in which clinical status is unlikely to change without treatment. It is also best for studying treatments that have rapidly evident effects.[60,61] A strength of this design is that it reduces between-patient variation, since subjects act as their own controls. Additionally, since all subjects receive the experimental treatment, the issue of excluding some individuals from a potentially beneficial treatment does not exist.

A limitation of the crossover design is the potential for carryover effects. Carryover occurs when the effect(s) of the treatment administered in the first period carryover into the second treatment period. In order to prevent carryover effects, we will include a four-week active washout period between treatments A and B (during which only MET will be administered). Based on previous research on the time course of acute effects of ketamine and psilocybin, we believe this length of washout is sufficient.[30-32,43,49,62] Another limitation is the possibility of a period effect, which occurs when the order in which the two treatments are administered affects the outcome. We will account for these limitations in our statistical analysis by running a between-group analysis to test the effect of the active intervention, and a within group analysis to test the effect of order.

2.4.2 Primary and Secondary Outcomes

There are no generally accepted criteria for success in addiction treatment research.[19] In AUD research, there is a consensus to include alcohol consumption as a measure of treatment outcome, however, researchers debate over how to operationalize alcohol consumption. The FDA accepts complete abstinence and no HDD as clinical trial endpoints.[5] Dimensional measures that include abstinence are, time to first drink, time to

relapse, and longest duration of abstinence. Although long-term total abstinence is the most desirable outcome, recent evidence suggests that these endpoints may be overly strict and may not capture all individuals who respond to a medication. As the authors of Project MATCH point out, alcohol abusers demonstrate improved outcomes over time, therefore, a dichotomous measurement of abstinence or drinking is not sensitive to improvement.[63,64]

Other dimensional measures that have been proposed include percent days abstinent, percent heavy drinking days, and drinks per drinking day. The Alcohol Clinical Trials Initiative (ACTIVE) workgroup and affiliated researchers have advocated for such alternate endpoints, arguing that individuals who are able to reduce their alcohol consumption to low-risk levels during treatment do not substantially differ from abstainers in terms of healthcare utilization or medical costs and they are able to sustain this reduction in alcohol consumption over several years.[5]

In 2001, an NIAAA panel designated PHDD as the optimal outcome measure for future alcohol treatment efficacy trials because it can capture both abstinence and improvement over time.[63] Accordingly, many recent large-scale trials have used these alternative endpoints.[11,13,63-70] In keeping with the NIAAA recommendations and the trends of recent trials (including Bogenschutz's studies on psilocybin for AUD), this outcome measure is the most logical choice for this study; it will enhance validity by allowing for consistency in evaluation and cross-study comparisons.

In order to capture this data, the timeline follow-back (TFLB) instrument will be used. The TFLB is a daily drinking estimation method that been validated by the American Psychiatric Association and the NIAAA.[71] The NIAAA recommends it as the

measure of choice when drinking is variable or when relatively precise estimates of drinking are needed (i.e. frequency of drinking at specific levels). An alternative means of assessing DDE is through Form 90, however, TFLB has been determined the most psychometrically sound and widely used DDE method.[63] An important advantage of this method is that researchers are able to reanalyze the raw data to generate alternative drinking outcomes of interest not assessed in a study (i.e. percent days abstinent, days to first drinking day, number of days to first drink), which enhances reliability. Limitations of this method include that it requires more resources such as interviewer and participant time, training, and increased burden on the respondents, which could increase attrition rates.

The non-drinking outcome measures in this study will be three well-established mediators of addictive behavior – self-efficacy, craving and motivation – that have been implicated as significant predictors of treatment outcome in alcohol addiction and that are potentially modifiable through therapeutic use of classic hallucinogens.[72] Self-efficacy is, "the conviction that one can successfully execute behavior required to produce the [desired] outcomes."[72] It provides a means to predict and understand psychological changes that occur during treatment. Motivation can affect drinking by "[influencing] patients to seek, complete, and comply with treatment and make successful long term changes in drinking."[72] Hallucinogen treatment is theorized to enhance motivation through several mechanisms. During acute intoxication, hallucinogens are known to cause a subjective experience of mysticism and/or other novel psychological experiences or insights. This in turn may increase one's belief in the possibility of change (self-efficacy), heighten one's awareness of negative consequences, and change one's

perspective in favor of a greater desire to change, which together may enhance one's motivation.[72] MET may further facilitate this process by directly targeting motivation as the main mechanism of behavioral change.

Craving is a multi-dimensional construct which includes motivational, affective and cognitive components.[72] Many studies have demonstrated a positive relationship between craving intensity and relapse. While there are yet to be any clinical trials with hallucinogens to investigate the role of alcohol or drug craving in treatment, Bogenschutz recommends that future trials include assessment of craving to investigate this question. He hypothesizes that, "stimulation and persistent activation of serotonergic pathways could affect craving by diminishing attentional bias, normalizing stress response, improving mood, or diminishing anxiety.[72]

Additional measures will be included to capture the quality of the participants' acute hallucinogenic experience. This is an essential element of hallucinogenic trials since a basic principle of the psychedelic treatment model holds that the quality of the acute experience mediates long-term improvements in mental health.[33] Indeed, Bogenschutz and his team found this to be true in their pilot study on psilocybin for alcoholism which demonstrated that both mystical experience and broader measures of the intensity of subjective effects were associated with improvement in drinking.[24] "The patient's conscious experience during the drug's acute effects is essential for long-term clinical benefit," Bogenschutz explains.[73] The assessments used in this study to capture subjective experience of psilocybin will include the APZ Questionnaire (a version of the Altered States of Consciousness Rating Scale, ASCRS), to be completed by the participants, and a Monitor Session Rating Form (MSRF), to be completed by monitors

present during the drug sessions. (The MSRF will expand upon the subjective reports of the participants with monitor ratings of participants behavior and affect). The APZ is a clinically validated measure, commonly used throughout psychedelic research. In addition to capturing subjective data such as mood, perceptions, and cognitions, the APZ Questionnaire will also enable a characterization of the intensity of the experience, and inform researchers of possible safety considerations. By incorporating this well-established and commonly used measure into our study, the validity will be enhanced by enabling comparisons between other trials.

An assessment of the presence or absence of the mystical experience as well as its quality, is an important component of this study. The mystical experience will be assessed by the Mystical Experience Questionnaire (MEQ-30). Numerous clinical trials with psilocybin and other classic hallucinogens have attempted to evaluate the occurrence and character of individual mystical experiences that hallucinogens have been found to induce due to cumulative evidence over the years that it may serve as a valuable predictor of positive outcomes.[33,34,72,74-76]

Dating back to 1950s, Drs. Hoffer and Osmond noticed an unexpected effect of LSD in alcoholic patients: it seemed to induce an experience "so profound and impressive that [one's] life experience in the months and years to follow [would become] a continuing growth process." As other researchers at the time similarly noted, LSD evoked a "transcendent, overwhelming, conversion-like experience" in patients and, "clients who [made] successful recoveries often [attributed] their success to a spiritual experience or enlightenment." Bill Wilson (the founder of Alcoholics Anonymous) credits the spiritual experiences he had while using LSD as the impetus for his sobriety.

In his treatment model for Alcoholics Anonymous, he incorporates a similar concept, which emphasizes the importance of an experience of spiritual insight in the path to sobriety. [73] [77] Other Twelve-Step programs are similarly based on the idea that spiritual change can bring about recovery from addiction.[72]

Contemporary addiction research has examined the role of a spiritual experience in recovery. One large study on alcoholism treatment found that subjects who reported a recent spiritual awakening were found to have markedly increased rates of 12-month continuous abstinence compared to those who did not report this experience (odds ratio = 3.9).[78] In another study, 82% of individuals who reported a spiritual awakening between baseline and follow-up reported abstinence compared to 55% of those not reporting such an experience (55%) ($X2 = 26.48$, $p < 0.001$).[72,79] Recent studies with psilocybin have demonstrated that the self-reported "mystical" dimension experienced while taking psilocybin significantly predicts the lasting personal significance of the experience.[34,37] More research is needed to further investigate the role of the mystical experience in alcohol treatment.

2.4.3 Inclusion and Exclusion Criteria

The inclusion and exclusion criteria for this study are based on established guidelines for the safe administration of hallucinogens in human volunteers, as well as Bogenschutz and his team's pilot and RCT studies on psilocybin for AUD, and an ongoing study by McAndrew and her team on ketamine-assisted-therapy for AUD).[24,41,80,81] In accordance with the guidelines, all participants will be in good general health, as assessed by detailed medical history, physical examination, 12-lead ECG,

blood chemistry profile, hematology, and urinalysis. Pregnant women or those not practicing effective means of birth control will be excluded.

Due to the side effect of psilocybin and ketamine to moderately increase pulse and both systolic and diastolic blood pressure, volunteers will be excluded if they have uncontrolled hypertension (defined as a blood pressure exceeding 165 systolic and 95 diastolic (mmHg), averaged across four assessments on at least two separate days) or serious ECG abnormalities (i.e. evidence of ischemia or myocardial infarction)[28,41]. Participants taking the following medications on a chronic basis (greater than 30 days) will be excluded from the study due the potential of these medications to interact with psilocybin: tricyclic antidepressants, lithium, serotonin reuptake inhibitors, monoamine oxidase inhibitors, haloperidol.

Thorough psychiatric interviews using the Structured Clinical Interview-5, Alcohol Revised (SCID-5-AR) assessment will be conducted to identify and exclude individuals with contraindicated psychological disorders (see Appendix C). This psychiatric screening criteria is important for minimizing the chance (admittedly, already low) of precipitating a longer-term psychotic, or adverse emotional or behavioral reaction by hallucinogen administration.[28,41] It will also enable us to decrease the chance that symptoms from such disorders are inadvertently misattributed to the action of psilocybin or ketamine. Individuals with other medical conditions that will preclude safe participation in this study will be also be excluded (see Appendix C).

In order to minimize the potential for confounding, participants with a history of cocaine, psychostimulant, opioid or cannabis dependence within the previous 12 months will be excluded, as well as those participating in any formal treatment for alcohol

dependence (12-step meetings are not considered treatment). Participants must have a desire to stop or decrease their drinking, and at least two heavy drinking days (HDD) within the previous 30 days.

2.4.4 Intervention

Pharmacological intervention:

The two leading candidates for application in the treatment of addiction are LSD and psilocybin, as supported by the evidence presented here[19]. While LSD has the advantage of an extensive body of literature on alcoholism treatment trials from the 1950s-1970s, psilocybin, has other advantages. Among them, psilocybin has a shorter duration of action (four to six hours) compared to LSD (eight to twelve hours), making it more amenable than LSD to administer outpatient. Additionally, it has been found to be more strongly visual, less emotionally intense, more euphoric, and with fewer panic reactions and less chance of paranoia than LSD[30]. These properties, together with the evidence favoring psilocybin for the treatment of a variety of mental health disorders have led us to choose psilocybin as the intervention in this proposed study.

Psilocybin dose:

In keeping with the psychedelic treatment model (vs. the psycholytic treatment model; see "Psychosocial Intervention" section below for further information), we will use a single high dose of psilocybin (0.3 mg/kg) in conjunction with several treatment sessions. In completed clinical trials studying oral psilocybin, doses have ranged from 0.045 mg/kg (very low dose) to 0.428 mg/kg (very high dose), all of which were reported to be safe and without serious adverse events. In Bogenschutz's open-label trial on psilocybin for AUD, participants received 0.3 mg/kg during the first session, and 0.4 mg/kg during the second session. In his follow-up RCT, doses will range from 25 mg/70

kg to 40 mg/70 kg. In the study on tobacco dependence, oral psilocybin was administered at a low dose (20 mg/70 kg) and a high dose (30 mg/70 kg) with an option for a third dose (low or high). Based on these trials, we will administer 30 mg/70 kg of psilocybin in a single session. Additional support for using this high dose comes from the literature, which consistently demonstrates that higher doses of psilocybin lead to better outcomes.[19,28,34,37] Since all participants in this study will only be getting one dose of psilocybin, it makes sense to maximize the possibility for therapeutic efficacy. While a higher dose does increase the risk of adverse events, these events are typically non-serious and transient, resolving by the end of the dosing day. Furthermore, common adverse events such as fear and anxiety respond well to reassurance and have not required pharmacological intervention in previous studies.[28]

Ketamine dose:

Ketamine will be administered at a subanesthetic dose of 0.5 mg/kg during a 40-minute IV infusion in order to blind participants, care providers, and outcome assessors to the experimental treatment. This will be the first clinical trial with psilocybin to use ketamine as an active placebo. This dose was chosen due to evidence from previous experimental trials that it reliably exerted broad influences on consciousness and perception.[42,43] These effects typically emerge within 10 minutes of the start of the infusion, and subside within 40 minutes of treatment termination, similar to the time course of psilocybin's effects. (Note, little to no psychoactive effects were observed at the dose of 0.1 mg/kg).

While ketamine has been administered orally in certain clinical contexts, there is far less research on the safety and pharmacodynamic effects of orally administered ketamine compared to IV-administered ketamine[82]. Thus, we will have to employ a

double dummy design in order to disguise the ketamine treatment from the experimental session with psilocybin.

While the potential for ketamine to confound results cannot be excluded, particularly given previous pilot work conducted in Russia in the 1990s that administered ketamine in conjunction with psychotherapy for the treatment of AUD, we do not anticipate this.[83] This previous work had serious methodological flaws preventing any significance conclusions on potential efficacy to be drawn. Furthermore, a more recent double-blind treatment trial investigating the therapeutic potential of NMDA receptor antagonists for AUD found that memantine did not have any significant effects on reducing drinking behavior in alcohol-dependent patients.[84]

Psychosocial intervention:

There are two treatment models which have consistently been used throughout clinical trials of psychedelic-assisted psychotherapy, and which have their origins in early research with LSD therapy for alcoholism in the 1950s[57]. The two models, termed psychedelic and psycholytic therapy, are based on different theoretical frameworks. Psychedelic therapy involves high doses of a psychedelic (typically LSD, 200-800 μg) administered once or on a few occasions, with the goal of inducing a "peak-psychedelic," or mystical, experience.[19,57]. In contrast, in the psycholytic model, low to moderate doses of hallucinogens (i.e. LSD 50-100 μg or psilocybin 10-15 mg) are administered on multiple occasions over months to years. The psycholytic treatment model incorporates psychedelics into traditional psychoanalytic therapy, in order to accelerate the therapeutic process.[26] The psychedelic model has been used across various populations including severe alcoholics, narcotic addicts, and individuals with existential anxiety related to cancer-diagnoses and depression, with reported success.[57,85-87] Most of the

studies within the addiction treatment field (both early and recent) have used the psychedelic model, including the two open-label trials on psilocybin-assisted psychotherapy for AUD and tobacco dependence. Thus, the psychedelic treatment model will be used in this study.

In keeping with the behavioral intervention used in Bogenschutz's trials on psilocybin for AUD, the psychosocial intervention utilized in this study will be MET. While alternative approaches could be used, such as CBT or TSF, the key elements believed to be driving change through hallucinogenic-assisted therapy are also central targets of MET (i.e. motivation), thus when paired, they can work synergistically to affect change. MET will be delivered using a structured approach that incorporates the principles of motivational interviewing established in the Motivational Enhancement Therapy Manual.[88]

2.5 Sample Size

The within group effect size was approximated from Bogenschutz's pilot study on psilocybin for AUD. In this study it was found that PHDD decreased during the four-week period following psilocybin administration relative to the baseline by a mean difference (SD) of 26.0 (22.4), 95% CI 8.7-43.2, $p = 0.008$. Based on this data, we estimated a slightly more conservative difference of effect between psilocybin and ketamine of $d = 1.0$. Due to an absence of data on the level of outcome in the ketamine group, we estimated the effect of ketamine to be half the magnitude of the effect of psilocybin ($d = 0.5$). This calculation yielded a sample size of 57.

2.6 Conclusion

New treatments are needed for AUD, and this new era of psychedelic research has produced significant evidence for the promise of psilocybin-assisted therapy as a novel

treatment option for AUD. This proposed study will aim to help fill the gaps in current research. It is our hope that our results will provide further evidence for the therapeutic role of psilocybin in addiction and that our study design may serve as a model for future RCTs with psychedelics.

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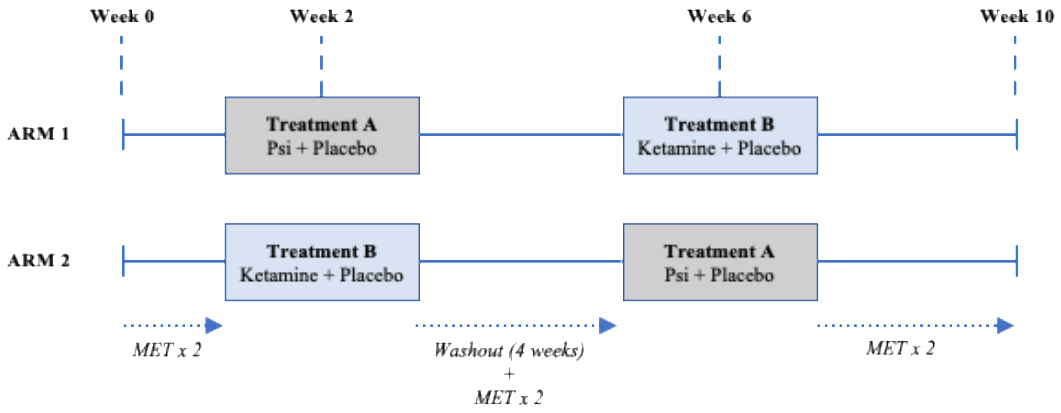
Chapter 3 – Study Methods

3.1 Study Design

This study will be a 10-week randomized, double-blind, active-placebo-controlled crossover trial to evaluate the effect of psilocybin-assisted treatment on drinking outcomes relative to a ketamine control. A double-dummy design will be employed in order to disguise psilocybin from ketamine (see Figure 1). Participants will be randomly assigned to two separate dosing sequences: (1) psilocybin and ketamine placebo, followed by ketamine and psilocybin placebo or, (2) ketamine and psilocybin placebo, followed by psilocybin and ketamine placebo. The drug administration sessions will occur within the context of 12 psychosocial sessions.

Figure 1: Intervention Design



3.2 Study Population and Sampling

The study population will include English-speaking adults, aged 25-65 with a diagnosis of alcohol use disorder (in accordance with DSM-V criteria). Resources from the Yale Center for the Translational Neuroscience of Alcoholism (CTNA), the VA Alcohol Research Center (ARC), the Connecticut Mental Health Center (CMHC), and the Alcoholism Treatment Center at Yale will be utilized for support in enrolling subjects; clinicians at these sites will be informed of this study and asked to refer eligible

and interested patients. Convenience sampling will be used to include heavy drinkers who are motivated to seek help.

Participants will also be recruited from the general population using advertising and recruitment media (i.e. Craigslist, Google, Twitter, Facebook, cable TV, and print advertising and flyers). Advertisements will be designed to target heavy drinkers at places and times they are expected likely to consider getting help for their drinking (i.e. late-night TV ads, early morning radio and TV ads, and print advertising in heavily trafficked urban areas).

For those individuals interested in participating who have provided verbal consent, a pre-screen phone interview will be given to determine initial eligibility. Those who pass this screening will be scheduled for an in-person screening visit at the Alcoholism Treatment Center at Yale, where a trained research staff member will administer the SCID-5-RV to provide a diagnosis of AUD[1]. Eligible subjects must meet the inclusion and exclusion criteria outlined below in order to be invited. Once invited, all participants will be randomly assigned to a treatment sequence.

3.3 Eligibility

Eligibility will be determined through assessment of the patient by a clinician, or other trained study personnel. The subject's clinical and medical information will be reviewed by the research staff for any contraindications to research participation. The inclusion and exclusion criteria will be used as a guide for eligibility. See Appendix C for full inclusion/exclusion criteria.

In preparation of drug administration sessions participants must agree to: (1) Ingest only alcohol-free liquids after 24:00 (midnight) the evening before the drug administration session, and refrain the day of and the day after each drug administration

session. (2) Refrain from the use of any psychoactive drug, with the exception of caffeine or nicotine, within 24 hours of each drug administration session (3) Not use caffeine or nicotine for two hours before and six hours after ingesting the drug, or until therapists deem it safe to do so.

3.4 Subject Protection and Confidentiality

Prior to recruitment, we will attain Institutional Review Board (IRB) approval through the Integrated Research Enterprise Solution-IRB submission system. All necessary accompanying documents will be accessed through this system and submitted along with the protocol application (see Appendices D-F). Study goals, timeline, procedures, confidentiality practices, and all potential risks, discomforts, and benefits of participation will be clearly outlined. Once IRB approval is obtained, a separate Investigational New Drug (IND) application will be submitted.

Protection of participants' research data will be compliant with Yale University Procedure 400 PR.1 and the Health Insurance Portability and Accountability Act (HIPAA). All identifiable research data, including recruitment and screening information and code keys will be stored on a database located on a secure Yale-ITS network. Access to the database will be password protected.

All subjects considered for participation in this study will be given an informed consent and a thorough explanation of the study. All consents will be appropriately documented. Risks to participants will be minimized. Selection of participants will be equitable, and will not inappropriately exclude based on gender, race, age or other criteria. We will not specifically recruit for a category of subjects that require special safeguards (i.e. children, non-English speaking, prisoners, pregnant women). Subjects

who are females of childbearing potential will require the following additional safeguards/considerations upon their enrollment in the study (see Appendix C).

3.5 Study Variables and Measures

The intervention will be synthetic psilocybin (0.3 mg/kg) and its control will be an inert capsule. Both pills will be delivered by a blinded pharmacist from the Yale Investigational Pharmacy and swallowed with 100 ml. of water. The active control will be intravenous ketamine 0.5 mg/kg and its control will be intravenous saline 0.9%, both of which will be infused over 40 minutes by an anesthesiologist from Yale who will be blinded**.**

The primary outcome (dependent variable) will be mean percent heavy drinking days in each treatment arm, which will be measured with the TLFB method (a calendar-based form in which people provide retrospective estimates of their daily drinking over a designated time period) at baseline, weeks two, six and 10. Heavy drinking days will be defined as days during which participants consume five or more standard drinks (14 g of alcohol) if male, or four or more standard drinks if female.

Several secondary outcomes will be measured. Motivation to change drinking behavior (assessed with SOCRATES 8A; see Appendix G), self-efficacy (assessed with the AASE; see Appendix H), and craving (assessed with PACS; see Appendix I) will be measured at baseline, one day prior to dosing sessions, and one day after dosing sessions. The acute subjective drug experience (assessed with the APZ Questionnaire) and the mystical experience (assessed with the Mysticism Scale) will be collected seven hours following dosing sessions. The APZ is a 72-item yes/no questionnaire and data will be expressed as a percentage of maximum possible score. The mystical experience (assessed with the MEQ 30) will be measured seven hours following drug administration at weeks

two and six. The MEQ 30 will generate a total score, as well as four empirically derived factors: mystical; positive mood; transcendence of time and space; and ineffability. The monitor ratings (assessed with the MSRF) will be collected during the first six hours following drug administration at weeks two and six. The MSRF will involve scoring several dimensions of the participant's mood or behavior, which will be rated on a 5-point scale from 0 to 4 and expressed as peak scores. Data will be the mean of the two monitor ratings at each time point.

Safety assessments will include: adverse events (collected on an adverse events case report form) that will be monitored at every study visit. Cardiovascular measures (systolic and diastolic blood pressure, heart rate) will be assessed during medication sessions at the following time points: 30, 60, 90, 120, 180, 240, 300 160 minutes post-dose administration.

Additional outcomes that will be collected at baseline include demographic and clinical characteristics of study participants as follows: sex (male, female), age (mean (SD)), race (White, Black, Hispanic, Asian, Other), highest level of education (high school or less, some college, college, graduate/professional degree), religious/spiritual beliefs (atheist/agnostic, Jewish, Catholic, Christian, other faith/tradition), mean duration of alcohol dependence (in years), current tobacco use (yes/no), current marijuana use (yes/no), previous alcohol treatment (yes/no; if yes, indicate).

Alcohol withdrawal will be assessed with CIWA-Ar, (reported as a score from 0-70, where ≥ 10 is indicative of alcohol withdrawal) at baseline and each drug administration session. Urine pregnancy tests (UPT) for women of childbearing potential will be collected at baseline and prior to each drug administration session. Breath Alcohol

Concentration (BAC) and Urine toxicology screens will be measured at baseline and every subsequent visit in order to ensure safety of treatment and validity of assessments. See Figure 2 for an outline of data collection timepoints.

3.6 Methodology Considerations

At the medical screening visit, subjects will undergo a complete history and physical examination and the following tests will be performed: ECG, liver function tests, complete blood count, blood chemistries, urinalysis, serum pregnancy test, and body mass index. Based on this data, subjects eligible for participation will be enrolled into the study. Within two weeks of this screening, the first visit will take place. At this visit subjects will meet with the study team including the therapists who will lead the MET sessions and drug administration sessions. They will complete all baseline assessments and be provided with a calendar of the study visits. Someone from the study team will also orient them to the room where the drug administration sessions will take place, and participants will be given an opportunity to address and questions or concerns they have. After the baseline visit, participants will have four separate visits scheduled over a two-week period – the first two visits will be MET sessions and the subsequent two will be preparation sessions. At week two the first drug administration session will occur. A four-week washout period will follow. During this period there will be a debriefing session (the day after the drug session), two MET sessions at weeks three and four, respectively, and a preparation session at week six the day prior to the second drug administration session. Following the second drug administration session another debriefing session will follow the next day, and then MET sessions will occur at weeks seven, eight, and nine. (See Appendix J).

The following resources will be used to develop and standardize the content for the drug administration sessions and psychosocial intervention: (1) Project MATCH Motivational Enhancement Therapy Manual (2) Human Hallucinogen Research: Guidelines for Safety (3) Supplementary Materials from Bogenschutz's Pilot Study and RCT.[2-6] A brief summary of what this will entail will follow.

3.6.1 Drug Administration Sessions

No more than one patient will be in a drug administration session on any given day. Patients will arrive at the research facility in the morning (8:00-9:00 am) and complete all necessary interim assessments. They will be taken to the dosing room where they will be invited to relax on a bed in a supine or reclined position with eyeshades while music is played through high-quality stereo speakers and earphones. The two session monitors will sit on either side of the bed and will be present for the duration of the session. Dosing will take place at approximately 10:30 am. Additional measurements will be collected as necessary throughout the sessions, as stipulated in Section 3.6. Tranquilizing medications (oral lorazepam and risperidone) will be on hand for administration if necessary. Monitors will adopt a non-directive, supportive approach, allowing the patient to experience a mostly uninterrupted inner "journey". Upon the session's completion, patients will be picked up from the facility by a close friend or relative who will bring them home and stay overnight with them.

3.6.2 Psychosocial Intervention

The psychosocial intervention will comprise a total of 12 sessions: seven MET sessions, three preparation sessions and two debriefing sessions. The psychosocial intervention will be delivered by a team of two therapists (session monitors) who will be

present at every session, including the two drug administration sessions. One of the therapists will perform the MET sessions, while the other will be responsible for preparation before, support during, and debriefing after the drug administration sessions. Therapy sessions will be audio-recorded and coded using the Motivational Interviewing Treatment Integrity coding system by a rater trained to reliability.[7]

The goal of the first preparation sessions will be to conduct a detailed life review, including information about the participant's history, current situation, personality, relationships, goals, etc., and to facilitate the development of rapport between the participants and the therapists. The second preparatory session will include a review of motivation and expectations for the study, detailed information about the physiological and psychological effects of the drugs, and advice on how to deal with potential dysphoric reactions to the drugs. The participant will be introduced to the aspects of the dosing sessions and oriented to the room in which the session will take place. At all preparatory sessions, the participant will be given the opportunity to address questions, concerns, hopes, and fears related to the drug sessions.

De-briefing sessions will occur the day after each dosing session to allow the participant to reflect on his experience during the dosing session. Open-ended questioning techniques will be used to encourage the participant to discuss his experience freely. Motivational interviewing techniques will be used to discuss how the session has affected the participant's relationship to alcohol and desire to change drinking behavior.

3.6.3 Blinding of Intervention

Double-blind randomization will be maintained by the Yale New Haven Hospital (YNHH) Investigational Pharmacy, with joint-assistance from the CTNA. Psilocybin and

its placebo will be prepared in identical opaque 0 gelatin capsules. The ketamine and saline solutions will be supplied in identical 50-ml syringes containing either 0.9% saline or ketamine with the additional volume of saline to total 50 ml. Participants, study therapists, investigators, and outcome assessors will be blinded to the drug administration conditions. At the end of each dosing session, the session monitors will record their guesses as to whether the participants received psilocybin or ketamine. Participants will not be asked to record their guesses as to which drug they receive on dosing session days.

3.6.4 Blinding of Outcome

Trained research staff will administer the TLFB to collect drinking data on every participant. Session monitors will be blinded to the data until the end of the experimental period at week 10.

3.6.5 Assignment of Intervention

Participants will be equally randomized to the two different dosing sequences via a random-numbers chart. Randomization will not stratify for any demographic or clinical characteristics. The randomization list will be kept with other study documents in a secure location, available only to administrative staff. Upon entry of a new participant to the trial, administrative staff will consult the allocation sequence and provide this information unblinded to Yale pharmacy staff who will prepare the drugs. The pharmacist who delivers the medication and the anesthesiologist to administer the infusions will be blinded to the treatments.

3.6.6 Adherence

Incentives such as monetary compensation or vouchers will not be used in this study. It is our hope that in selecting only individuals with a motivation to change their

problematic drinking behaviors that participants will remain in the study until its completion. The relatively short length of the study period (10 weeks) will hopefully facilitate participant adherence. Nevertheless, some degree of dropout is nearly inevitable, so we have accounted for dropout in our sample size calculation.

3.6.7 Monitoring of Adverse Events:

In order to monitor for any adverse events (AE) vital signs will be obtained at each visit and at multiple timepoints throughout the drug sessions (see Section 3.6). Any adverse events that do occur will be collected on an AE case report form at the end of the session.

3.7 Data collection

Data for the primary outcome, mean PHDD, will be collected with the TLFB method by a trained member of the study team at Baseline (data for previous 90 days); week 2 (data for previous two weeks); week 6 (data for previous 4 weeks); and week 10 (data for previous 4 weeks). A trained study staff member will administer all additional questionnaires and assessments. The below figure outlines the specific timepoints of data collection.

Figure 2: Data collection schedule for outcome measures and assessments

Assessment Schedule		Baseline	1-day pre-Dose 1	Dose 1	1-day post-Dose 1	1-wk post-Dose 1	2-wks post-Dose 1	3-wks post-Dose 1 1-day pre-Dose 2	Dose 2	1-day post-Dose 2	1-2 wks post-Dose 2	2-3 wks post-Dose 2	4 wks post-Dose 2
Safety Assessments	Adverse Events			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	CIWA-Ar	✓		✓					✓				
	UPT/BAC	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	BP/HR	✓		✓					✓				
Primary Outcome	Mean PHDD	✓	✓					✓				✓	✓
Secondary Outcomes	Motivation (SOCRATES-8A)	✓		✓		✓			✓		✓		
	Self-efficacy (AASE)	✓		✓		✓			✓		✓		
	Craving (PACS)	✓		✓		✓			✓		✓		
	Mystical Experience (MEQ-30)	✓		✓		✓			✓		✓		
	Acute hallucinogen experience (APZ-Q)			✓					✓				
	Monitor ratings (MSRF)			✓					✓				

3.8 Sample Size Calculation

We used a t-test calculator to calculate sample size. Assuming a confidence level of 1%, an effect size of $d = 1.0$, and a standard deviation of 22.4 to test a two-sided hypothesis for a power of 80% and 10% dropout, we determined that we will need 57 subjects. We corrected the assumption for the confidence level due to the multiple comparisons that would be tested in a crossover design.

3.9 Analysis

Descriptive statistics (means and proportions) will be used to describe the baseline demographic and clinical characteristics of the study sample. Simple inferential statistics will be used to compare the characteristics between the two dose-sequence groups at baseline. T-tests will be used to compare continuous variables, and chi-square tests will be used to compare categorical variables.

Between and within-group comparisons will be made for the primary outcome and all secondary outcomes (motivation, self-efficacy, craving, mystical experience, and

acute subjective effects). For the primary outcome of mean PHDD, the between-group analysis will test the effect of the active intervention (i.e. the difference in mean PHDD post-psilocybin in Arm 1 vs. the mean PHDD post-ketamine in Arm 2), and the within-group analysis will test the effect of order. To test for these comparisons we will first test the data for skewedness with the Kolmogorov-Smirnov and Shapiro-Wilk tests. If the data are not skewed, within-group changes will be analyzed with a paired t-test and between-group comparisons will be analyzed with an unpaired t-test. Additionally, mean changes in PHDD and all secondary measures at all timepoints will be analyzed using repeated measure ANOVA. If the data are skewed, the Wilxocon signed-rank test will be used in place of the paired t-test and the non-parametric ANOVA-type statistic will be used in place of the repeated measures ANOVA.[8]

3.10 Timeline and Resources

Resources from the CTNA, ARC, CMHC, Psychotherapy Development Research Center, and the Alcoholism Treatment Center at Yale will be utilized for this study. They will provide a trained clinician to administer the clinical diagnostic interview and medical screening, and trained staff to monitor subject recruitment, generate the randomization list, oversee self-reports and clinician-administered reports, and perform data analyses. The YNHH Investigational Pharmacy will prepare the experimental drugs, and a YNHH anesthesiologist will administer the intravenous solutions.

The recruitment period will last 12 months. Participants will be enrolled until the target sample size of 56 individuals has been met. Upon enrollment, each participant will be randomized to one of the two treatment sequences. Participants will not need to wait until the target sample size is reached to achieve treatment since each participant will act

as his/her own control. The treatment period will last a total of ten weeks. The entire study period from recruitment to last follow-up is estimated to last 24 months.

3.11 References:

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Chapter 4 – Conclusion

4.1 Strengths and Limitations

There are multiple converging but preliminary lines of evidence that heighten our interest in testing psilocybin for AUD. In the last couple of decades researchers have built upon the foundational work of their predecessors with enhanced study designs that incorporate methods such as randomization, blinding, and a control-arm. Our study will be the second to examine, in a randomized, placebo-controlled, double-blind fashion, the efficacy of psilocybin on drinking outcomes in individuals with AUD. It will be a necessary step to advance to the next phase of clinical research: Phase 3 trials.

One significant advantage of our study will be the use of ketamine as an active control for psilocybin. This sets our study apart from previous psilocybin (and other psychedelic) trials by incorporating another hallucinogen as the control condition. We expect that this will preserve the blind and in turn minimize expectancy bias and enhance validity. Despite evidence laid out in previous sections to the contrary, it is possible that ketamine will have a positive effect on drinking outcomes, which could confound our results. To address this, we have performed our sample size calculation accordingly, and estimated the effect of ketamine to be half the magnitude of the effect of psilocybin. Given the consistently large effect sizes detected for psilocybin in previous studies, we still expect to detect a statistically significant difference in effect between psilocybin and ketamine.

Some advantages of this proposed study distinguish it from Bogenschutz's RCT. First, the decision to include only hallucinogen-naïve individuals will help minimize expectancy bias on the part of participants, who will not necessarily be able to distinguish between the psychedelic drug effects due to lack of previous experience. Additionally,

this will prevent selection bias by avoiding recruiting individuals who previously had positive experiences with hallucinogens. The incorporation of a crossover design will reduce between-patient variation since subjects will act as their own controls, and will also allow for a smaller sample size, which will conserve study resources. A limitation of the crossover design is that it may lead to carryover and period effects. While we cannot be certain that the designated four-week washout period will be adequate, previous evidence supports that this length of time will be sufficient for any remaining acute drug effects to dissipate. We will further address these potential weaknesses by performing between- and within-group statistical analyses of the data.

Additional limitations of this study include those inherent to psychedelic research in general, which were mentioned in Chapter 2. While these challenges are formidable, current research provides hope that they are surmountable.

4.2 Clinical and Public Health Significance

The potential advantages of a targeted intervention with psilocybin-assisted therapy for the treatment of AUD are numerous. Despite significant progress in alcoholism research over the past several decades, AUD remains a significant global health burden, in need of alternative treatment options with greater efficacy in a broader range of individuals.[1,2] Current research indicates that psilocybin-assisted psychotherapy may be the answer. If this therapy were to be approved, it would offer a cheaper, faster alternative to current treatments, making it more accessible to a wider population. Adherence would be less of a concern: instead of chronic daily pills (and their associated costs and adverse effects), this therapy (if shown to be efficacious) would offer the promise of long-term beneficial effects from just a single drug-administration session. Additionally, unlike any single treatment today, this therapy addresses multiple domains

of addictive behavior, which the NIAAA has identified as necessary targets of future alcoholism research (i.e. craving, self-efficacy, motivation).[3,4] Such an integrative approach could potentially treat a greater spectrum of the disease.

In order to prove the clinical efficacy of these drugs, additional Phase 2 placebo-controlled, double-blind, randomized controlled trials are needed to further demonstrate feasibility safety and efficacy.

Bogenschutz predicts that "the therapeutic use of psychedelics in the treatment of addiction … will continue to increase in coming years, possibly leading to approved clinical uses for these medications."[5] While there is still a long road ahead before psilocybin potentially becomes an FDA-approved treatment of addiction, the very recent approval of esketamine (a ketamine derivative) for treatment-resistant depression indicates that, perhaps, Bogenschutz's predictions are not as far off as once thought.

4.3 References

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APPENDICES

Appendix A: Concept Table

Concept	Psilocybin / Psychedelic-Assisted Therapy	Ketamine / Psychedelic-Assisted therapy	Alcohol Use disorder
Keywords/ MeSH Terms	Psilocybin, psilocybin/therapeutic use, psilocybin/administration and dosage, psilocybin/history, Psilocybin/pharmacokinetics, Psilocybin/pharmacology	Ketamine/therapeutic use, ketamine/administration and dosage, ketamine/pharmacokinetics, ketamine/pharmacology	Alcoholism, alcoholism/drug therapy, alcoholism/prevention and control, lcoholism/therapy
Related Terms	Hallucinogen*, psi, psychedelic, indole alkaloid, tryptamine*, entheogen, psychotropic, serotonergic, psychedelic, 5-HT2A receptors agonist, mushroom, mental disorders/drug therapy, psychotherapy, therapy, behavioral intervention, cognitive behavioral therapy, motivational interviewing, motivational enhancement therapy, MET, CBT	Ketamine hydrochloride, esketamine, calypso, kalipsol, ketanest, ketaset, ketalar, (-)-Ketamine, S-ketamine, L-ketamine, ketaved psychotherapy, therapy, behavioral intervention, cognitive behavioral therapy, motivational interviewing, motivational enhancement therapy, MET, CBT	Addiction, AUD, alcohol dependence, alcohol addiction, heavy drinking, chronic alcoholic, problematic drinking, alcohol abuse, substance use, substance abuse, substance use disorder, addiction treatment, chronic alcohol intoxication

Appendix B: Sample size calculator

Continuous Endpoint, Two Independent Sample Study

Sample Size	
Group 1	52
Group 2	52
Total	**104**

Study Parameters	
Mean, group 1	26
Mean, group 2	11
Alpha	0.01
Beta	0.2
Power	0.8

$$k = \frac{n_2}{n_1} = 1$$

$$n_1 = \frac{(\sigma_1^2 + \sigma_2^2/K)(z_{1-\alpha/2} + z_{1-\beta})^2}{\Delta^2}$$

$$n_1 = \frac{(22.4^2 + 22.4^2/1)(2.58 + 0.84)^2}{15^2}$$

$$n_1 = 52$$

$$n_2 = K * n_1 = 52$$

$\Delta = |\mu_2 - \mu_1|$ = absolute difference between two means
σ_1, σ_2 = variance of mean #1 and #2
n_1 = sample size for group #1
n_2 = sample size for group #2
α = probability of type I error (usually 0.05)
β = probability of type II error (usually 0.2)
z = critical Z value for a given α or β
k = ratio of sample size for group #2 to group #1

*Note: we calculated sample size for a within-group comparison, yielding N = 52. After accounting for a 10% dropout the final sample size became N = 57 subjects.

Source: https://clincalc.com/Stats/SampleSize.aspx?example

Appendix C: Table of inclusion and exclusion criteria

Inclusion Criteria	Exclusion Criteria
➢ Desire to stop or decrease their drinking ➢ Have at least two heavy drinking days in the past 30 days ➢ Not participating in any formal treatment for alcohol dependence (12-step meetings are not considered treatment) ➢ English speaking- able to understand the process of consent and the risks and benefits associated with the study, and able to provide voluntary informed consent ➢ Must sign a medical release for the investigators to communicate directly with their therapist and doctors to confirm a medication and/or medication history ➢ Are willing to be driven home after the drug administration sessions by a driver arranged by the subject who will also stay overnight with the subject ➢ Must provide a contact (relative, spouse, close friend, or other caregiver) who is willing and able to be reached by the Clinical Investigators in the event of a participant becoming suicidal. ➢ If female of childbearing potential, are willing to use approved form of contraception from screening until after the psilocybin administration sessions ➢ Able to provide adequate locator information ➢ No prior history of hallucinogen use	➢ The following medical conditions: seizure disorder, significantly impaired liver function, coronary artery disease, heart failure, uncontrolled hypertension (>165/95), history of cerebrovascular accident, asthma, hyperthyroidism, narrow-angle glaucoma, stenosing peptic ulcer, pyloroduodenal obstruction, symptomatic prostatic hypertrophy, bladder-neck obstruction. ➢ The following psychiatric conditions: schizophrenia or other psychotic disorders, bipolar I or II disorder, current major depressive episode, current post-traumatic stress disorder, current suicidality or history of medically serious suicide attempt ➢ Cognitive impairment (Folstein Mini Mental State Exam score <26) ➢ Family history of schizophrenia, schizoaffective disorder (first- or second-degree relatives), or bipolar disorder type 1 (first degree relatives) ➢ Cocaine, psychostimulant, opioid or cannabis dependence (past 12 months) ➢ Current (past 30 days) or non-medical use of cocaine, psychostimulants (i.e. dextroamphetamine, methamphetamine, methylphenidate, ephedrine, phenylpropanolamine, and other anorectics and decongestants) or opioids. ➢ Significant alcohol withdrawal (CIWA-Ar score >7. Patients presenting at screening in withdrawal may be referred for detoxification and reassessed within 30 days) ➢ Serious ECG abnormalities (i.e. evidence of ischemia or MI) ➢ Serious abnormalities of CBC or chemistries ➢ Active legal problems with the potential to result in incarceration

	➢ Pregnancy or lactation ➢ Need to take the following medications: antidepressants, antipsychotics, psychostimulants, treatments for addictions, other dopaminergic or serotonergic agents, lithium, anticonvulsants) ➢ High risk of adverse emotional or behavioral reaction based on investigator's clinical evaluation (i.e. evidence of serious personality disorder, antisocial behavior, serious current stressors, lack of meaningful social support)

Appendix D: Informed consent form

CONSENT FOR PARTICIPATION IN A RESEARCH PROJECT
200 FR. 1 (2016-2)
YALE UNIVERSITY SCHOOL OF MEDICINE – YALE-NEW HAVEN HOSPITAL

Study Title: Psilocybin-Assisted Psychotherapy for Alcohol Use Disorder: A Double-Blind Randomized Control Trial

Principal Investigator: John Krystal, MD

You are invited to participate in a research study designed to look at whether psychedelic-assisted treatment with psilocybin of alcohol use disorder (AUD) is clinically useful. Specifically, this study aims to: (1) characterize the acute effects of psilocybin in alcoholic patients (2) evaluate the effect of psilocybin treatment on drinking outcomes relative to a ketamine control. You are being asked to participate because you have been identified as someone who meets the eligibility requirements for our study.

In order to decide whether or not you wish to be a part of this research study you should know enough about its risks and benefits to make an informed decision. This consent form gives you detailed information about the research study, which a member of the research team will discuss with you. This discussion should go over all aspects of this research: its purpose, the procedures that will be performed, any risks of the procedures, possible benefits and possible alternative treatments. Once you understand the study, you will be asked if you wish to participate; if so, you will be asked to sign this form.

Description of Procedures

Guidelines:

- Psilocybin and ketamine are classified as hallucinogens due to their ability to induce the following effects in humans: broad influences on consciousness and perception, including dissociation, distortions in visual, auditory, or somatosensory stimuli, or alterations in the perception of self or time, conceptual disorganization, hallucinations.
- You will be randomly assigned to one of the two treatment sequences (both sequences receive identical treatments, just in a different order – i.e. AB/BA or BA/AB). The treatments you will receive will be both pharmacological and psychosocial in nature.
- The pharmacological intervention will consist of two drug sessions. At each drug session both a pill and an intravenous treatment will be administered; the combination will always consist of an active treatment (moderate to high doses of either psilocybin or ketamine) paired with an inactive one (a placebo pill or IV saline solution); whichever combination you receive at the first session, you will receive the alternate at the second session, so that by the end of the trial you will

have received both ketamine and psilocybin. The purpose of creating to dosing sequences is to disguise which drug you will be getting at each session so as to preserve the integrity of the experiment.

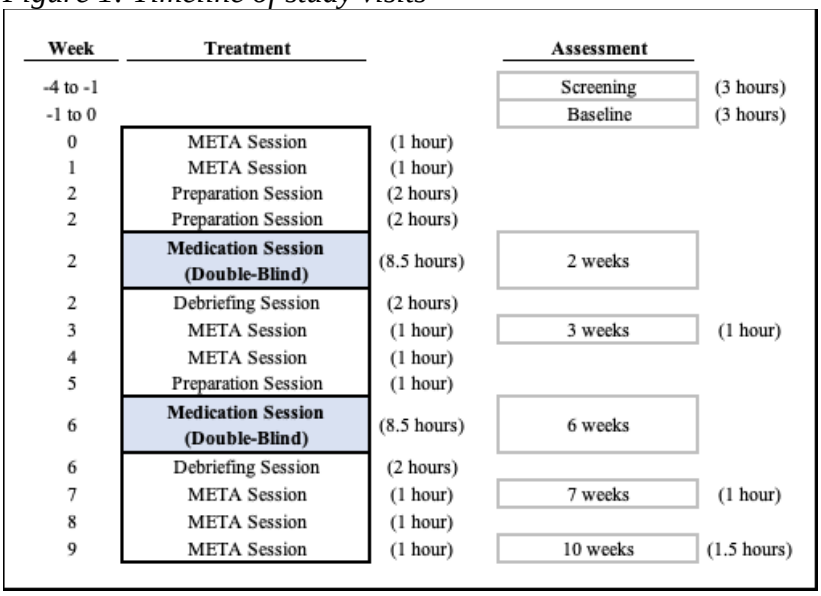
- The psychosocial treatment will consist seven sessions of motivational enhancement therapy, three preparation sessions, and two debriefing sessions. Content of therapy, preparation, and debriefing sessions may vary according to the participant's needs; however, all sessions will follow the same standardized guidelines. These additional treatment components have been standardized in previous research, and are necessary components of psychedelic-assisted therapy to ensure your safety throughout the trial and maximize potential beneficial treatment effects. (See image below for outline of study visits). All study visits will take place at the Alcohol Treatment Center at Yale
- Motivational enhancement therapy (MET) is a common intervention for the treatment of alcohol dependence. It consists of a patient-centered therapy that aims to produce rapid internally-motivated changes by exploring and resolving ambivalence towards behavior.
- Preparation sessions will consist of a review of motivation and expectations for the study, detailed information about the physiological and psychological effects of the drugs, and advice on how to deal with potential dysphoric reactions to the drugs. At your first dosing session you will be oriented to the room in which the drug sessions will take place, shown the eye shades and headphones to be worn, and played a sample of the music to be played.
- Debriefing sessions will occur on the following each drug administration session to allow you participant to reflect on his experience during the drug administration session.
- During study visits you will be asked to complete questionnaires about your drinking behavior and aspects related to your drinking such as self-efficacy, craving, and motivation. The data from these questionnaires will be used to help us analyze the efficacy of the intervention.
- Biological samples will be collected at an in-person screening visit in order to determine study eligibility (i.e. ECG, liver function tests, complete blood count, blood chemistries, urinalysis, and serum pregnancy test if female of child-bearing potential). Alcohol withdrawal will be assessed at a baseline visit and both drug administration sessions. Breath alcohol concentration will be collected at every visit in order to ensure your safe participation in the study.
- All data collected as part of this study will remain confidential; it will not be included in your medical records nor will it be accessible to your medical providers.

If you agree to participate in this study, you will be asked to attend all study visits outlined above. See figure below for further clarification.

A description of this clinical trial will be available on *http://www.ClinicalTrials.gov*, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

You will be told of any significant new findings that are developed during the course of your participation in this study that may affect your willingness to continue to participate.

Figure 1: Timeline of study visits



Risks and Inconveniences

Guidelines:

- Ketamine and psilocybin have similar psychopharmacological effects. Lower doses of these drugs may induce a mild state of euphoria that is similar to that produced by a glass of wine, whereas higher subanesthetic doses (i.e. 0.5 mg/kg, IV over 40 minutes) produce alterations in sensory perception, feelings of unreality, and in some subjects mild psychosis. These drugs have also been found to affect cognition (i.e. decrease mental sharpness, recall, and recognition) either during or shortly following administration. At doses perception-altering doses, these drugs may produce nausea and, in some cases, vomiting; this symptom may be managed by pretreatment with odansetron. In healthy subjects, these drugs typically produce a mild elevation in blood pressure and pulse rate that typically does not require medical intervention. Repeated ketamine administration appears to be safe when managed clinically. However, long-term heavy recreational use of ketamine, which can reach daily levels of 100-times the therapeutic dose, may lead to flashbacks, attentional, and other cognitive dysfunctions. Participation in this study may involve risks that are currently not known.

- There is a federal law called the Genetic Information Nondiscrimination Act (GINA) that, in general, makes it illegal for health insurance companies, group health plans, and most employers, except those with fewer than 15 employees, to discriminate against you based on your genetic information. However, it does not

protect you against discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.

Contrast Risks and Procedures Statements.

Having an intravenous (IV) line placed is a very safe procedure. There is a slight chance that multiple needle-sticks will be needed to make sure the IV is placed correctly. You might feel a small amount of pain when the IV is placed but it does not last very long. A bruise or a minor infection might develop where the IV is placed. A bruise will go away by itself and it might help if you wrap a warm towel around your arm. Infections can also be treated if necessary.

You should tell your principal investigator: (1) if you are pregnant or breast feeding, (2) if you have a history of kidney disease, seizure, asthma, or allergic respiratory disorders, and (3) if you have anemia or disease that affects red blood cells.

Benefits

Guidelines:

- There remains substantial room for the development of effective treatment alternatives for AUD and classic hallucinogens, particularly psilocybin, have shown promise in early studies. Recently completed proof-of-concept studies of psilocybin in conjunction with psychotherapy for nicotine and alcohol dependence demonstrated that the intervention led to substantial decreases in use of the target substance. Your participation in this study will help us to further understand the therapeutic role psilocybin for the treatment of AUD, with the possibility that in the future this treatment could become an approved alternative for many patients afflicted with this disease.
- The proposed psilocybin intervention as a treatment for AUD is still under investigation and currently unproven, thus we cannot guarantee that you will benefit from this treatment. However, MET is an established treatment for AUD and it is reasonable to expect

Economic Considerations

Guidelines:

- You will be compensated for any costs involved in transporting to and from the study center. According to the rules of the Internal Revenue Service (IRS), payments that are made to you as a result of your participation in a study may be considered taxable income.
- All costs associated with the medical screening visit (i.e. physical exam, laboratory tests) and all treatment interventions (drug sessions and therapy visits) will be covered by the study.

Treatment Alternatives/Alternatives

Guidelines:

Current treatment options for AUD consist of pharmacological interventions, behavioral therapy, and mutual support groups. The FDA has approved only three drugs for AUD: Naltrexone, Acamprosate, and Disulfiram, and these medications display poor efficacy, low adherence rates, or adverse effects at a population level.[1] Empirically-validated behavioral interventions include cognitive behavioral therapy, motivational interviewing, and marital and family counseling. Mutual support treatment groups include Alcoholics Anonymous and other 12-step programs.

Confidentiality

Guidelines:

Except as permitted by law, your health information will not be released in an identifiable form outside of the Yale University research team. Examples of information that we are legally required to disclose include abuse of a child or elderly person, or certain reportable diseases. Note, however, that your records may be reviewed by those responsible for the proper conduct of research such as the Yale University Human Research Protection Program, Yale University Human Subjects Committee or representatives of the U.S. Department of Health and Human Services. The information about your health that will be collected in this study includes:

- Baseline medical information (i.e. relevant current or past medical conditions, medication use, substance use)
- History of alcohol use disorder (i.e. date of first diagnosis, previous treatments received)
- Baseline biological data (i.e. blood tests, ECG) as mentioned above
- Any personal material disclosed during therapy sessions

Information may be re-disclosed if the recipients are not required by law to protect the privacy of the information. At the conclusion of this study, any identifying information related to your research participation will be de-identified, rendering the data anonymous. Authorized representatives of the Food and Drug Administration (FDA) and the manufacturer of the drug being tested may need to review records of individual subjects. As a result, they may see your name; but they are bound by rules of confidentiality not to reveal your identity to others.

Guidelines:

If you are injured while on study, seek treatment and contact the study doctor as soon as you are able.

Yale School of Medicine, Yale-New Haven Hospital, and the Connecticut Mental Health Center do not provide funds for the treatment of research-related injury. If you are injured as a result of your participation in this study, treatment will be provided. You or your

insurance carrier will be expected to pay the costs of this treatment. No additional financial compensation for injury or lost wages is available.

You do not give up any of your legal rights by signing this form.

Voluntary Participation and Withdrawal

Guidelines:
Participating in this study is voluntary. You are free to choose not to take part in this study. Refusing to participate will involve no penalty or loss of benefits to which you are otherwise entitled (such as your health care outside the study, the payment for your health care, and your health care benefits). However, you will not be able to enroll in this research study and will not receive study procedures as a study participant if you do not allow use of your information as part of this study.

Withdrawing From the Study

If you do become a subject, you are free to stop and withdraw from this study at any time during its course. To withdraw from the study, you can call a member of the research team at any time and tell them that you no longer want to take part. This will cancel any future appointments.
The researchers may withdraw you from participating in the research if necessary (i.e. if you are no longer compliant with exclusion/inclusion criteria of this study, or if you experience serious adverse side effects from the drug(s)). Withdrawing from the study will involve no penalty or loss of benefits to which you are otherwise entitled. It will not harm your relationship with your own doctors or with New Haven Hospital or the Connecticut Mental Health Center. We would still, at your request, refer you to a clinic or doctor who can offer you treatment.

When you withdraw from the study, no new health information identifying you will be gathered after that date. Information that has already been gathered may still be used and given to others until the end of the research study, as necessary to insure the integrity of the study and/or study oversight.

Questions

We have used some technical terms in this form. Please feel free to ask about anything you don't understand and to consider this research and the consent form carefully – as long as you feel is necessary – before you make a decision.

Authorization

I have read (or someone has read to me) this form and have decided to participate in the project described above. Its general purposes, the particulars of my involvement and possible hazards and inconveniences have been explained to my satisfaction. My signature also indicates that I have received a copy of this consent form.

Name of Subject:_____

Signature:_____

Relationship:_____

Date:_____

_____ _____
Signature of Principal Investigator Date

or

_____ _____
Signature of Person Obtaining Consent Date

If you have further questions about this project or if you have a research-related problem, you may contact the Principal Investigator John Krystal, MD.
If, after you have signed this form you have any questions about your privacy rights, please contact the Yale Privacy Officer at 203-432-5919. If you would like to talk with someone other than the researchers to discuss problems, concerns, and questions you may have concerning this research, or to discuss your rights as a research subject, you may contact the Yale Human Investigation Committee at (203) 785-4688.

Appendix E: Verbal consent form

Information Sheet
Verbal Consent for Participation in a Research Study
200 FR 9 (2017-2)

YALE UNIVERSITY SCHOOL OF MEDICINE – YALE-NEW HAVEN HOSPITAL

Study Title: Psilocybin-Assisted Psychotherapy for Alcohol Use Disorder: A Double-Blind Randomized Control Trial

Principal Investigator: John Krystal, MD

Introduction

You are being asked to join a research study. The following information will explain the purpose of the study, what you will be asked to do, and the potential risks and benefits. You should ask questions before deciding whether you wish to participate, or at any time during the course of the study.

Purpose

The purpose of this study is to further clarify whether psilocybin-assisted treatment of AUD is clinically useful. You are being asked to participate because you have been identified as someone who meets the eligibility requirements for our study.

Procedures

If you choose to participate in the study, you will be asked to fully comply with the procedures of our study, which are described as follows:

- You will be randomly assigned to one of the two treatment sequences (both sequences receive identical treatments, just in a different order – i.e. AB/BA, BA/AB)
- Treatment will consist of two blinded drug administration sessions, seven sessions of motivational enhancement therapy, three preparation sessions, and two debriefing sessions. Content of therapy, preparation, and debriefing sessions may vary according to the participant's needs, however, all sessions will follow the same standardized guidelines
- Biological samples will be collected at an in-person screening visit in order to determine study eligibility (i.e. ECG, liver function tests, complete blood count, blood chemistries, urinalysis, and serum pregnancy test if female of child-bearing potential). Alcohol withdrawal will be assessed at a baseline visit and both drug administration sessions. Breath alcohol concentration will be collected at every visit in order to ensure your safe participation in the study.

- All data collected as part of this study will remain confidential; it will not be included in your medical records nor will it be accessible to your medical providers.

Possible Benefits

This research may or may not benefit you directly. However, knowledge gained from the results may help us to better understand the efficacy of psychedelic-assisted therapy for the treatment of alcohol use disorder.

Possible Risks

Your part in this research study consists solely of abiding to the protocol as specified above. This study does require you to have treatments, including the administration of drugs which are not currently approved for clinical use by the U.S. Food and Drug Administration. The potential exists for anticipated and/or unanticipated adverse events, serious or otherwise, to occur. Additionally, there is a slight risk regarding the confidentiality of your participation in this study, if information about you becomes known to persons outside this study. The researchers are required to keep your study information confidential, however, so the risk of breach of confidentiality is very low.

Alternatives to Participation

Study staff will provide you will all information on alternative treatment options. Your participation in this study is voluntary. You are free to choose not to take part in this study at any time.

Privacy / Confidentiality

To protect your confidentiality, your name and other identifying information will not be recorded on any study documents. We will only collect information that is needed for research. Only the researchers involved in this study and those responsible for research oversight will have access to the information you provide.

Research Authorization:

Except as permitted by law, your health information will not be released in an identifiable form outside of the Yale University research team. Examples of information that we are legally required to disclose include abuse of a child or elderly person, or certain reportable diseases. Note, however, that your records may be reviewed by those responsible for the proper conduct of research such as the Yale University Human Research Protection Program, Yale University Human Subjects Committee [or representatives of the U.S. Department of Health and Human Services or the name of research sponsor if applicable). The information about your health that will be collected in this study includes:

- Baseline medical information (i.e. relevant current or past medical conditions, medication use, substance use)
- History of alcohol use disorder (i.e. date of first diagnosis, previous treatments received)
- Baseline biological data (i.e. blood tests, ECG) as mentioned above
- Any personal material disclosed during therapy sessions

Information may be re-disclosed if the recipients are not required by law to protect the privacy of the information. At the conclusion of this study, any identifying information related to your research participation will be de-identified, rendering the data anonymous.

By agreeing to participate in this study, you authorize the use and/or disclosure of the information described above for this research study. The purpose for the uses and disclosures you are authorizing is to ensure that the information relating to this research is available to all parties who may need it for research purposes.

This authorization to use and disclose your health information collected during your participation in this study will never expire.

Voluntary Participation

Participation in this study is completely voluntary. You are free to decline to participate, to end participation at any time for any reason, or to refuse to answer any individual question at any time. Refusing to participate will involve no penalty or loss of benefits to which you are otherwise entitled (such as your health care outside the study, the payment for your health care, and your health care benefits). By providing verbal consent, you have not given up any of your legal rights.

Questions

You have heard the above description of the research study. You have been told of the risks and benefits involved and, at this point, all of your questions regarding the study have been answered.

If you have any further questions about this study, you may contact the investigator, John Krystal, MD. If you would like to talk with someone other than the researchers to discuss problems, concerns, and questions you may have concerning this research, or to discuss your rights as a research subject, you may contact the Yale Human Investigation Committee at (203) 785-4688.

Appendix F: Data and safety monitoring plans form

Data and Safety Monitoring Plans (DSMP)
420 FR.1

Greater Than Minimal Risk DSMP

1. Personnel responsible for the safety review and its frequency:

The principal investigator will be responsible for monitoring the data, assuring protocol compliance, and conducting the safety reviews at the specified frequency, which must be conducted at a minimum of every 6 months (including when reapproval of the protocol is sought). During the review process, the principal investigator (monitor) will evaluate whether the study should continue unchanged, require modification/amendment, or close to enrollment. Either the principal investigator, the IRB or Yale Data and Safety Monitoring Committee (DSMC) have the authority to stop or suspend the study or require modifications.

2. The risks associated with the current study are deemed greater than minimal for the following reasons:

1. We do not view the risks associated with psilocybin and ketamine as minimal risks.
2. Given the now established safety and validity of the current study drugs in our prior work, we do not view the proposed studies as high risk.

Although we have assessed the proposed study as one of greater than minimal risk, the potential exists for anticipated and/or unanticipated adverse events, serious or otherwise, to occur since it is not possible to predict with certainty the absolute risk in any given individual or in advance of first-hand experience with the proposed study methods. Therefore, we provide a plan for monitoring the data and safety of the proposed study as follows:

3. Attribution of Adverse Events:
Adverse events will be monitored for each subject participating in the study and attributed to the study procedures / design by the principal investigator John Krystal, MD., according to the following categories:

a.) Definite: Adverse event is clearly related to investigational procedures(s)/agent(s).
b.) Probable: Adverse event is likely related to investigational procedures(s)/agent(s).
c.) Possible: Adverse event may be related to investigational procedures(s)/agent(s).
d.) Unlikely: Adverse event is likely not to be related to the investigational procedures(s)/agent(s).
e.) Unrelated: Adverse event is clearly not related to investigational procedures(s)/agent(s).

4. Plan for Grading Adverse Events:

The following scale will be used in grading the severity of adverse events noted during the study:

1. Mild adverse event
2. Moderate adverse event
3. Severe

5. Plan for Determining Seriousness of Adverse Events:

Serious Adverse Events:
In addition to grading the adverse event, the PI will determine whether the adverse event meets the criteria for a Serious Adverse Event (SAE). An adverse event is considered serious if it results in any of the following outcomes:

1. Death;
2. A life-threatening experience in-patient hospitalization or prolongation of existing hospitalization;
3. A persistent or significant disability or incapacity;
4. A congenital anomaly or birth defect; OR
5. Any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

An adverse event may be graded as severe but still not meet the criteria for a Serious Adverse Event. Similarly, an adverse event may be graded as moderate but still meet the criteria for an SAE. It is important for the PI to consider the grade of the event as well as its "seriousness" when determining whether reporting to the IRB is necessary.

6. Plan for reporting UPIRSOs (including Adverse Events) to the IRB

The principal investigator will report the following types of events to the IRB:

Any incident, experience or outcome that meets ALL 3 of the following criteria:

1. Is unexpected (in terms of nature, specificity, severity, or frequency) given (a) the research procedures described in the protocol-related documents, such as the IRB-approved protocol and informed consent document and (b) the characteristics of the subject population being studied; AND
2. Is related or possibly related to participation in the research (*possibly related* means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); AND
3. Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, legal, or social harm) than was previously known or recognized.

Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs) may be medical or non-medical in nature, and include – but are not limited to – *serious, unexpected, and related adverse events* and *unanticipated adverse device effects*. ***Please note*** that adverse events are reportable to the IRB as UPIRSOs **only** if they meet all 3 criteria listed above.

These UPIRSOs/SAEs will be reported to the IRB in accordance with IRB Policy 710, using the appropriate forms found on the website. All related events involving risk but not meeting the *prompt* reporting requirements described in IRB Policy 710 should be reported to the IRB in summary form at the time of continuing review. If appropriate, such summary may be a simple brief statement that events have occurred at the expected frequency and level of severity as previously documented**.** In lieu of a summary of external events, a current DSMB report can be submitted for research studies that are subject to oversight by a DSMB (or other monitoring entity that is monitoring the study on behalf of an industry sponsor).

7. Plan for reporting adverse events to co-investigators on the study, as appropriate the protocol's research monitor(s), e.g., industrial sponsor, Yale Cancer Center Data and Safety Monitoring Committee (DSMC), Protocol Review Committee (PRC), DSMBs, study sponsors, funding and regulatory agencies, and regulatory and decision-making bodies.

For the current study, the following individuals, funding, and/or regulatory agencies will be notified:

□ All Co-Investigators listed on the protocol.
□ Food and Drug Administration
□ Study Sponsor

The principal investigator John Krystal, MD., will conduct a review of all adverse events upon completion of every study subject. The principal investigator will evaluate the frequency and severity of the adverse events and determine if modifications to the protocol or consent form are required.

Please note: For any study that may be considered high risk, the IRB will be more focused on the safety requirements for the study and a DSMB will likely be required.

Appendix G: Personal Drinking Questionnaire (SOCRATES-8A)

Name:_____ Date:_____

Personal Drinking Questionnaire (SOCRATES 8A)

Instructions: Please read the following statements carefully. Each one describes a way that you might (or might not) feel *about your drinking.* For each statement circle one number from 1 to 5 to indicate how much you agree or disagree with it *right now.* Please circle one and only one number for every statement.

	NO! Strongly Disagree	**No** Disagree	**?** Undecided Or Unsure	**Yes** Agree	**YES!** Strongly Agree
1. I really want to make changes in my drinking.	1	2	3	4	5
2. Sometimes I wonder if I am an alcoholic.	1	2	3	4	5
3. If I don't change my drinking soon, my problems are going to get worse.	1	2	3	4	5
4. I have already started making some changes in my drinking.	1	2	3	4	5
5. I was drinking too much at one time, but I've managed to change my drinking.	1	2	3	4	5
6. Sometimes I wonder if my drinking is hurting other people.	1	2	3	4	5
7. I am a problem drinker.	1	2	3	4	5
8. I'm not just thinking about changing my drinking, I'm already doing something about it.	1	2	3	4	5
9. I have already changed my drinking, and I am looking for ways to keep from slipping back to my old pattern.	1	2	3	4	5
10. I have serious problems with drinking.	1	2	3	4	5
11. Sometimes I wonder if I am in control of my drinking.	1	2	3	4	5
12. My drinking is causing a lot of harm.	1	2	3	4	5
13. I am actively doing things now to cut down or stop drinking.	1	2	3	4	5
14. I want help to keep from going back to the drinking problems that I had before.	1	2	3	4	5
15. I know that I have a drinking problem.	1	2	3	4	5
16. There are times when I wonder if I drink too much.	1	2	3	4	5
17. I am an alcoholic.	1	2	3	4	5
18. I am working hard to change my drinking.	1	2	3	4	5
19. I have made some changes in my drinking, and I want some help to keep from going back to the way I used to drink.	1	2	3	4	5

Scoring the Stages of Change Readiness and Treatment Eagerness Scale (SOCRATES)

SOCRATES is an experimental instrument designed to assess readiness for change in alcohol abusers. The instrument yields three factorially-derived scores: Recognition, Ambivalence, and Taking Steps.

Three subscale scores are obtained from the SOCRATES:
Recognition (sum of items 1, 3, 7, 10, 12, 15 & 17) (score range 7 – 35)
Ambivalence (sum of items 2, 6, 11 & 16) (score range 4 – 20)
Taking Steps (sum of items 4, 5, 8, 9, 13, 14, 18 & 19) (score range 8 – 40)

The following discussion is provided as general guidelines for interpretation of scores, but it is wise in an individual case also to examine individual item responses for additional information.

RECOGNITION

HIGH scorers directly acknowledge that they are having problems related to their drinking, tending to express a desire for change and to perceive that harm will continue if they do not change.

LOW scorers deny that alcohol is causing them serious problems, reject diagnostic labels such as "problem drinker" and "alcoholic," and do not express a desire for change.

AMBIVALENCE

HIGH scorers say that they sometimes *wonder* if they are in control of their drinking, are drinking too much, are hurting other people, and/or are alcoholic. Thus a high score reflects ambivalence or uncertainty. A high score here reflects some openness to reflection, as might be particularly expected in the contemplation stage of change.

LOW scorers say that they *do not wonder* whether they drink too much, are in control, are hurting others, or are alcoholic. Note that a person may score low on ambivalence *either* because they "know" their drinking is causing problems (high Recognition), *or* because they "know" that they do not have drinking problems (low Recognition). Thus a low Ambivalence score should be interpreted in relation to the Recognition score.

TAKING STEPS

HIGH scorers report that they are already doing things to make a positive change in their drinking, and may have experienced some success in this regard. Change is underway, and they may want to help to persist or to prevent backsliding. A high score on this scale has been found to be predictive of successful change.

LOW scorers report that they are not currently doing things to change their drinking, and have not made such changes recently.

Decile Scores	Recognition	Ambivalence	Taking Steps
90 very high		19 – 20	39 – 40
80		18	37 - 38
70 High	35	17	36
60	34	16	34 - 35
50 Medium	32 – 33	15	33
40	31	14	31 - 32
30 Low	29 – 30	12 – 13	30
20	27 – 28	9 – 11	26 - 29
10 Very Low	7 – 26	4 – 8	8 - 25

Citation: Miller WR, Tonigan JS. Assessing drinkers' motivation for change: The Stages of Change Readiness and Treatment Eagerness Scale (SOCRATES). Psychology of Addictive Behaviors 10:81-89, 1996.

Appendix H: Alcohol Abstinence Self-Efficacy Scale

{Module Name} Module

Alcohol Abstinence Self-Efficacy Scale

Agency Name: _____ **Site Name:** _____

ID #: _____ **Date:** __ __ / __ __ / __ __ __ __

Listed below are a number of situations that lead some people to drink. We would like to know **how TEMPTED you may be to drink in each situation**. Check the answer that best describes the feelings of temptation in each situation at the present time.

	TEMPTED				
SITUATION	**Not at all**	**Not very**	**Moderately**	**Very**	**Extremely**
1. When I am in agony because of stopping or withdrawing from alcohol use	❑0	❑1	❑2	❑3	❑4
2. When I have a headache	❑0	❑1	❑2	❑3	❑4
3. When I am feeling depressed	❑0	❑1	❑2	❑3	❑4
4. When I am on vacation and want to relax	❑0	❑1	❑2	❑3	❑4
5. When I am concerned about someone	❑0	❑1	❑2	❑3	❑4
6. When I am very worried	❑0	❑1	❑2	❑3	❑4
7. When I have the urge to try just one drink to see what happens	❑0	❑1	❑2	❑3	❑4
8. When I am being offered a drink in a social situation	❑0	❑1	❑2	❑3	❑4
9. When I dream about taking a drink	❑0	❑1	❑2	❑3	❑4
10. When I want to test my willpower over drinking	❑0	❑1	❑2	❑3	❑4
11. When I am feeling a physical need or craving for alcohol	❑0	❑1	❑2	❑3	❑4
12. When I am physically tired	❑0	❑1	❑2	❑3	❑4
13. When I am experiencing some physical pain or injury	❑0	❑1	❑2	❑3	❑4
14. When I feel like blowing up because of frustration	❑0	❑1	❑2	❑3	❑4
15. When I see others drinking at a bar or at a party	❑0	❑1	❑2	❑3	❑4
16. When I sense everything is going wrong for me	❑0	❑1	❑2	❑3	❑4
17. When people I used to drink with encourage me to drink	❑0	❑1	❑2	❑3	❑4
18. When I am feeling angry inside	❑0	❑1	❑2	❑3	❑4
19. When I experience an urge or impulse to take a drink that catches me unprepared	❑0	❑1	❑2	❑3	❑4
20. When I am excited or celebrating with others	❑0	❑1	❑2	❑3	❑4

ID #: _____ Date: ___ ___ / ___ ___ / ___ ___ ___ ___

Listed below are a number of situations that lead some people to drink. We would like to know **how CONFIDENT are you that you WOULD NOT drink in each situation.** Check the answer that best describes the feelings of confidence in each situation at the present time.

	CONFIDENCE				
SITUATION	**Not at all**	**Not very**	**Moderately**	**Very**	**Extremely**
21. When I am in agony because of stopping or withdrawing from alcohol use	❑0	❑1	❑2	❑3	❑4
22. When I have a headache	❑0	❑1	❑2	❑3	❑4
23. When I am feeling depressed	❑0	❑1	❑2	❑3	❑4
24. When I am on vacation and want to relax	❑0	❑1	❑2	❑3	❑4
25. When I am concerned about someone	❑0	❑1	❑2	❑3	❑4
26. When I am very worried	❑0	❑1	❑2	❑3	❑4
27. When I have the urge to try just one drink to see what happens	❑0	❑1	❑2	❑3	❑4
28. When I am being offered a drink in a social situation	❑0	❑1	❑2	❑3	❑4
29. When I dream about taking a drink	❑0	❑1	❑2	❑3	❑4
30. When I want to test my willpower over drinking	❑0	❑1	❑2	❑3	❑4
31. When I am feeling a physical need or craving for alcohol	❑0	❑1	❑2	❑3	❑4
32. When I am physically tired	❑0	❑1	❑2	❑3	❑4
33. When I am experiencing some physical pain or injury	❑0	❑1	❑2	❑3	❑4
34. When I feel like blowing up because of frustration	❑0	❑1	❑2	❑3	❑4
35. When I see others drinking at a bar or at a party	❑0	❑1	❑2	❑3	❑4
36. When I sense everything is going wrong for me	❑0	❑1	❑2	❑3	❑4
37. When people I used to drink with encourage me to drink	❑0	❑1	❑2	❑3	❑4
38. When I am feeling angry inside	❑0	❑1	❑2	❑3	❑4
39. When I experience an urge or impulse to take a drink that catches me unprepared	❑0	❑1	❑2	❑3	❑4
40. When I am excited or celebrating with others	❑0	❑1	❑2	❑3	❑4

Reference: DiClemente CC; Carbonari JP; Montgomery RPG; Hughes SO. The Alcohol Abstinence Self-Efficacy Scale. Journal of Studies on Alcohol 1994;55:141-148.

ALCOHOL ABSTINENCE SELF-EFFICACY (AASE)

NEGATIVE AFFECT

18 or 38. When I am feeling angry inside
16 or 36. When I sense everything is going wrong for me
3 or 23. When I am feeling depressed
14 or 34. When I feel like blowing up because of frustration
6 or 26. When I am very worried

SOCIAL/POSITIVE

15 or 35. When I see others drinking at a bar or at a party
20 or 40. When I am excited or celebrating with others
4 or 24. When I am on vacation and want to relax
17 or 37. When people I used to drink with encourage me to drink
8 or 28. When I am being offered a drink in a social situation

PHYSICAL AND OTHER CONCERNS

2 or 22. When I have a headache
12 or 32. When I am physically tired
5 or 25. When I am concerned about someone
13 or 33. When I am experiencing some physical pain or injury
9 or 29. When I dream about taking a drink

CRAVING AND URGES

1 or 21. When I am in agony because of stopping or withdrawing from alcohol use
7 or 27. When I have the urge to try just one drink to see what happens
11 or 31. When I am feeling a physical need or craving for alcohol
10 or 30. When I want to test my willpower over drinking
19 or 39. When I experience an urge or impulse to take a drink that catches me unprepared

Appendix I: Penn Alcohol Craving Scale (PACS)

Penn Alcohol Craving Scale (PACS)

PLEASE READ EACH ITEM CAREFULLY AND CIRCLE THE NUMBER THAT BEST DESCRIBES YOUR CRAVING *DURING THE PAST WEEK.*

1. During the past week *how often* have you thought about drinking or about how good a drink would make you feel?
   - 0 Never (0 times during the past week)
   - 1 Rarely (1 to 2 times during the past week)
   - 2 Occasionally (3 to 4 times during the past week)
   - 3 Sometimes (5 to 10 times during the past week or 1 to 2 times per day)
   - 4 Often (11 to 20 times during the past week or 2 to 3 times per day)
   - 5 Most of the time (20 to 40 times during the past week or 3 to 6 times per day)
   - 6 Nearly all of the time (more than 40 times during the past week or more than 6 times per day)

2. At its most severe point, *how strong* was your craving during the past week?
   - 0 None at all
   - 1 Slight, that is a very mild urge
   - 2 Mild urge
   - 3 Moderate urge
   - 4 Strong urge, but easily controlled
   - 5 Strong urge and difficult to control
   - 6 Strong urge and would have drunk alcohol if it were available

3. During the past week *how much time* have you spent thinking about drinking or about how good a drink would make you feel?
   - 0 None at all
   - 1 Less than 20 minutes
   - 2 21 to 45 minutes
   - 3 46 to 90 minutes
   - 4 90 minutes to 3 hours
   - 5 Between 3 to 6 hours
   - 6 More than 6 hours

4. During the past week *how difficult would it have been to resist* taking a drink if you had known a bottle were in your house?
   - 0 Not difficult at all
   - 1 Very mildly difficult
   - 2 Mildly difficult
   - 3 Moderately difficult
   - 4 Very difficult
   - 5 Extremely difficult
   - 6 Would not be able to resist

5. Keeping in mind your responses to the previous questions, please rate your overall *average alcohol craving* for the past week.
   - 0 Never thought about drinking and never had the urge to drink
   - 1 Rarely thought about drinking and rarely had the urge to drink
   - 2 Occasionally thought about drinking and occasionally had the urge to drink
   - 3 Sometimes thought about drinking and sometimes had the urge to drink
   - 4 Often thought about drinking and often had the urge to drink
   - 5 Thought about drinking most of the time and had the urge to drink most of the time
   - 6 Thought about drinking nearly all of the time and had the urge to drink nearly all of the time

Appendix J: Proposed protocol timeline for study visits and assessments

Week	Treatment		Assessment	
-4 to -1			Screening	(3 hours)
-1 to 0			Baseline	(3 hours)
0	META Session	(1 hour)		
1	META Session	(1 hour)		
2	Preparation Session	(2 hours)		
2	Preparation Session	(2 hours)		
2	**Medication Session (Double-Blind)**	(8.5 hours)	2 weeks	
2	Debriefing Session	(2 hours)		
3	META Session	(1 hour)	3 weeks	(1 hour)
4	META Session	(1 hour)		
5	Preparation Session	(1 hour)		
6	**Medication Session (Double-Blind)**	(8.5 hours)	6 weeks	
6	Debriefing Session	(2 hours)		
7	META Session	(1 hour)	7 weeks	(1 hour)
8	META Session	(1 hour)		
9	META Session	(1 hour)	10 weeks	(1.5 hours)

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