Opiate Suicide Study in Patients with Major Depression

Protocol Number: 51536

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Table of Contents

1. Protocol summary:

1.1. Synopsis:

Title: Opiate Suicide Study in Patients with Major Depression

Study Description: Opioid abuse and addiction have become major public health problems in the U.S. over the past decade. More than 33,000 Americans die annually from opioid use and 2.1 million people annually misuse opioids the first time. Much opioid abuse follows use for physical pain, which is significantly more common in those with major depressive disorder. Indeed, 51% of individuals in the U.S. with an opioid use disorder have a mood and/or anxiety disorder. Depression at the time of knee replacement significantly increases the risk for chronic opioid use post-surgery. Accidental overdoses of opioids are accompanied by deaths due to suicide associated with increased risk of depression inherent in, or related to, opioid addiction and withdrawal. Adding to the complexity of the opioid problem, very low doses of buprenorphine--a partial mu opioid receptor agonist--has been reported to be effective (ie, within 2 weeks) in reducing suicidal behavior in patients with major depression or borderline personality disorder. (This has yet to be replicated.) In addition, single intravenous infusions of ketamine were recently reported in a meta-analysis to reduce suicidal ideation within 24 hours and to last for at least one week with about 55% of participants experiencing complete relief of suicidal symptoms. However, a recent esketamine intranasal study reportedly reduced suicidal behavior within 1 hour, but repeated doses resulted in significant differences from placebo in suicidal reduction only lasting 48 hrs. We present recently published data that ketamine's antidepressant effects are mediated largely via its mu opioid properties. Of interest, others have reported that ketamine can reduce the need for opioids post-surgery in patients prone to addiction. We propose to explore whether the strategy of a single intravenous ketamine infusion followed by low dose oral buprenorphine produces more robust and sustained anti-suicidal effects over a period of up to 4 weeks than does ketamine followed by placebo.

1.2. Objectives:

Primary Objective:

To test the hypothesis that in suicidal major depressives given a single ketamine infusion, oral low dose buprenorphine produces significantly greater anti-suicidal effects over 4 weeks than does placebo. To assess the potential relationship of improvement in depression, sleep or pain to improvement in suicidal ideation.

Secondary Objective:

To assess changes in depressive symptoms during the study period using validated clinical rating scales.

1.3. Endpoints:

Primary Endpoint: change in SSI scores from day 1 to day 31

Secondary Endpoint: change in MADRS/HAMD scores from day 1 to 31

Study Population: We will enroll 60 participants and employ a two-arm design with 30 subjects per arm. The target population is adults of all genders and ethnicities who are between 18 and 70 years of age with treatment-resistant MDD, or bipolar disorder type II with current Major Depressive Episode, with suicidal ideation, and who are otherwise in good general health.

Phase: this is a randomized phase II clinical trial.

Description of Sites/Facilities Enrolling Participants:

Stanford Department of Psychiatry and Behavioral Sciences: This study will be conducted within the Stanford Department of Psychiatry and Behavioral Sciences outpatient building. The outpatient building will provide both the office space and infrastructure for the screening / enrollment of participants, the delivery of study intervention, and the assessment of clinical outcomes.

Clinical and Translational Research Services Unit (CTRU): the CTRU is part of Spectrum (Stanford Center for Clinical and Translational Education), which is a multidisciplinary organizational center, partially supported by the NIH Clinical and Translational Science Award (CTSA). It provides research focused, ambulatory care and laboratory services to adult and pediatric study subjects. The CTRU offers bedside nursing, phlebotomy, dietary and laboratory specimen processing services in support of the Stanford research community. They work closely with the Stanford Biobank, where studies can utilize long term specimen storage. Many clinical research teams use the CTRU facility because it can meet the protocol lab and nursing care requirements (i.e. defined blood draw time windows) that may not be feasible within a standard hospital setting. The CTRU is at the frontier of precision health efforts across the research community. It is a primary backbone for accelerating the translation of bedside diagnostics and treatments and advancing research technologies into clinical applications. On average, the center is supporting over 350 clinical research studies annually for more than 200 faculty members. The studies stretch across multiple medical disciplines, and many are first-in-human trials, with novel therapies that have been discovered and developed at Stanford. The CTRU clinical team consists of highly specialized research nurses and other medical professionals to support these advanced human-subject trials. The laboratory personnel are set up to handle high-volume, longitudinal studies and disease registries that require advanced isolation and distribution of various biofluid and tissue specimens. The CTRU supports research services in multiple locations, with the primary research clinic on Welch Road being proximal to Stanford Hospital and Clinics. The phlebotomy and lab services are also located to maximize same-day clinical trial services, while more advanced cellular isolations and other novel methodologies for specimen processing are located at Arastradero Road.

Description of Study Intervention:

The ketamine infusion visit will last approximately 8 hours. All participants will receive a single intravenous infusion of ketamine at 0.5 mg/kg over 40 minutes. Participants will be monitored throughout the infusion and for a period of 3 hours post-infusion prior to discharge. A responsible adult must accompany participants and transport them home; driving to or from the visit is not permitted.

Pre-Visit Instructions
Participants will be instructed to fast (no food or beverages other than water) for 8 hours prior to the scheduled infusion and to remain fasting until 1-hour post-infusion, after which a meal will be provided. Participants will be required to abstain from alcohol, opioids, sedative medications (including benzodiazepines), and any other substances that may interfere with the ketamine response, as determined by the principal investigator, beginning the evening prior to and continuing beyond the day of the infusion.

At Day 3 (48 hours post-infusion), eligible participants will be randomized in a 1:1 ratio to one of two treatment arms:

1. Ketamine infusion followed by 4 weeks of buprenorphine (0.2–0.8 mg daily)
2. Ketamine infusion followed by 4 weeks of placebo

Infusion Procedure
A study physician will initiate and supervise the intravenous ketamine infusion. An intravenous (IV) catheter will be placed in a forearm vein for drug administration and potential supportive care. As a prophylactic antiemetic, ondansetron 4 mg IV may be administered 25–30 minutes prior to the infusion. Additional ondansetron (up to 12 mg within 2 hours) may be provided as needed. If ondansetron is ineffective, promethazine 25 mg IV may be administered for persistent nausea.
During the infusion, participants will be monitored by the study physician and trained research staff. Research personnel will conduct structured assessments of mood and dissociative symptoms during the infusion. Blood samples will be collected post-infusion to assess ketamine plasma levels.

Patients will be assessed weekly for 4 weeks during buprenorphine versus placebo treatment. The dosage of buprenorphine will be adjusted according to a prespecified protocol. Blood samples will be collected to assess for opioid activity (e.g., serum prolactin levels), drug blood levels, pupillary response, and their relationship to anti-suicidal effects. After 4 weeks buprenorphine or placebo will be discontinued and patients followed for 2 weeks to assess buprenorphine discontinuation symptoms, and recurrence of suicidal ideation.

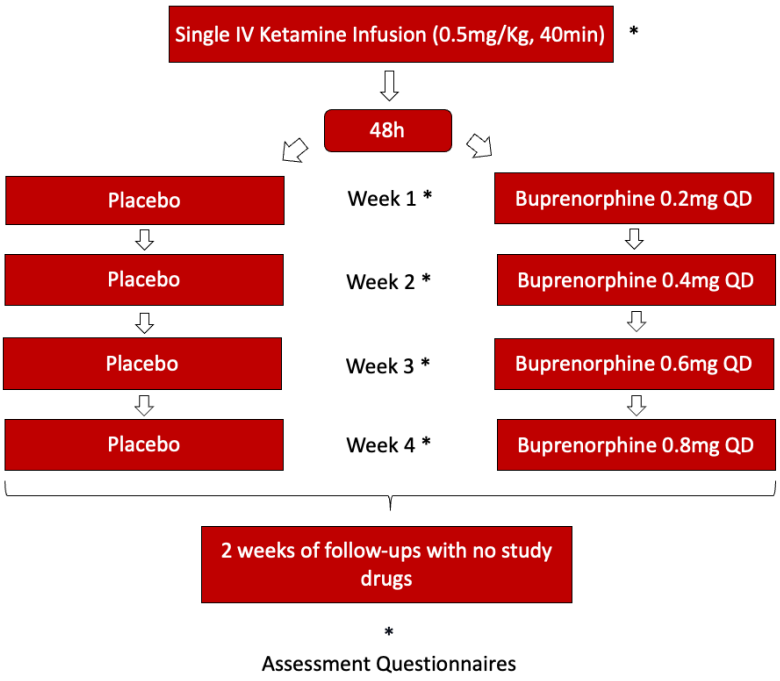
Study Duration:

The entire project is estimated to take approximately 42 months broken down into 36 months of data collection and 6 months of analysis.

Participant Duration:

The total duration for each participant from the time of screening to study completion is approximately 10 weeks.

1.4. Schema:



1.5. Schedule of Activities:

	Screen	Study Visits									
						Week 1	Week 2	Week 3	Week 4	Week 5	Week 6/ EOS
		Baseline	Day 1	Day 3	Day 5	Day 10	Day 17	Day 24	Day 31	Day 38	Day 45
					Phone	+/- 2 d	+/- 2 d	+/- 2 d	+/- 2 d	+/- 2 d	+/- 2 d
Inclusion/Exclusion Criteria	X										
Demographic data	X										
Consent	X										
Medical and Psychiatric History	X										
Physical Exam		X									
Neurological Exam		X	X**** *								X
Vital Signs		X	X	X		X	X	X	X	X	X
ECG*											X
Chemistry & CBC*		X									
Urine Toxicology Screen		X	X								
Urine Pregnancy Test		X	X								
Mini-International Neuropsychiatric Interview (M.I.N.I.)	X										
Massachusetts General Hospital Antidepressant Treatment Response Questionnaire (MGH-ATRQ)	X										
Montgomery-Åsberg Depression Rating Scale (MADRS)	X	X	X	X	X	X	X	X	X	X	X
Columbia Suicide Severity Rating Scale (C-SSRS)	X	X	X	X	X	X	X	X	X	X	X
Scale for Suicidal ideation (SSI)	X	X	X	X		X	X	X	X	X	X
Hamilton Depression Rating Scale 21-item (HAMD-21)	X	X	X	X	X	X	X	X	X	X	X
Hamilton Depression Rating Scale 6-item (HAMD-6)			X								
Clinical Global Impressions Severity (CGI-S)	X	X	X	X	X	X	X	X	X	X	X

	Screen	Study Visits									
						Week 1	Week 2	Week 3	Week 4	Week 5	Week 6/ EOS
		Baseline	Day 1	Day 3	Day 5	Day 10	Day 17	Day 24	Day 31	Day 38	Day 45
Adverse Childhood Experience (ACE) Questionnaire		X									
Snaith–Hamilton Pleasure Scale (SHAPS)				X		X	X	X	X	X	X
Beck Hopelessness Scale		X	X	X		X	X	X	X	X	X
Beck Depression Inventory II (BDI-II)		X	X	X		X	X	X	X	X	X
Ruminative Responses Scale				X		X	X	X	X	X	X
Insomnia Severity Index (ISI)		X		X		X	X	X	X	X	X
Brief Pain inventory (BPI)		X		X		X	X	X	X	X	X
Ketamine Infusion			X								
Pupillometry****			X	X		X	X	X	X	X	
Implicit Association Test-IAT		X		X					X		
Randomization (buprenorphine/placebo)				X							
Buprenorphine 0.2mg-0.8mg (10 SL/wk) Dispensed***				X		X	X	X			
Ketamine & Metabolites Blood Levels**			X								
Buprenorphine & Metabolites Blood Levels							X		X		
Prolactin Blood Levels			X **			X	X	X	X	X	
Clinician-Administered Dissociative States Scale (CADSS)**			X								
Visual Analogue Scale (VAS)**			X								
Subjective Opiate Withdrawal Scale (SOWS)										X	X
Clinician Opiate Withdrawal Scale (COWS)										X	X
Concise Health Risk Tracking Scale Self-Report (CHRT-SR)		X					X		X	X	X
Adverse Event Review		X	X	X	X	X	X	X	X	X	X
Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X

*if no results within the past 6 months

**-5 min, 40, 80, 120, 180, 220 min

*** Weekly supply of rx provided. Varying dosage depending on response & tolerability.

****-5min, 40 min

***** @220 min / discharge

2. Introduction:

2.1. Background:

Opiate abuse and addiction have become major public health problems in the United States over the past decade (1). The profound increase in accidental deaths due to opioid overdose is accompanied

by an elevated risk of depression and suicide associated with opioid addiction and withdrawal (1). Although these underscore the negative consequences of opioid abuse, opioids appear to have antidepressant and anti-suicidal properties, as observed in preliminary clinical trials (2). For example, low doses of buprenorphine, a partial mu-opioid receptor (MOR) agonist and kappa opioid receptor (KOR) antagonist, have been reported to be effective as an antidepressant (2) and as an anti-suicidal agent in patients with major depressive disorder (MDD) or borderline personality disorder (3). Similarly, both major depressive and borderline personality disorder patients have altered mu-opioid receptor activity in PET studies (4,5). A recent Israeli study (3) reported that buprenorphine at low doses of 0.1/0.2-0.8 mg per day (mean dose=0.44mg per day) over four weeks reduced suicidal behavior in patients with major depression or borderline personality. The entry criterion was a score of $\geq$ 11 on the Scale for Suicide Ideation (SSI). The treatment was effective by 2 (but not at 1) weeks, with a mean 4.3-point reduction difference in SSI score, favoring the active drug over placebo. At study completion, the difference was 7.1 points. Antidepressant effects did not attain statistical significance. Withdrawal symptoms were not observed, although formal assessments of dependence/withdrawal were not incorporated into the design.

Another drug recently associated with MOR agonism is ketamine, an anesthetic with rapid-acting antidepressant and anti-suicidal effects (6). A recent meta-analysis indicated that single intravenous doses of ketamine produce significant anti-suicidal effects within 24 hours, lasting at least one week (7), and response rates were about 55%. The mechanisms of action underlying ketamine's antidepressant and anti-suicidal effects have previously been conceptualized broadly as NMDA antagonism (8), yet other candidate NMDA antagonists have not been proven to be effective antidepressants (9). Others have argued that ketamine may induce other glutamatergic effects, such as agonism at the AMPA receptor (10) and modulation of mTOR (11). However, our recent findings about ketamine's relationship with the mu-opioid receptor aligned with previous evidence that ketamine can reduce the need for opioids post-surgery in patients prone to addiction (12). This may, in part, reflect glutamatergic-related plasticity effects.

Several additional lines of evidence link ketamine to the opioid system. Ketamine has been successfully utilized for acute and chronic pain conditions (13). Naltrexone, a MOR antagonist used to block opioid effects, has been reported to be effective in ketamine dependence (14). In addition to binding MORs (15–17), ketamine binds to delta and kappa opioid receptors. In a preclinical model, its analgesic effects are blocked by mu and delta but not by kappa opioid antagonists or agonists, indicating a non-kappa opioid mechanism in ketamine's pain relief effects (18). Our recent report suggests the antidepressant effects of ketamine are mediated via MOR activity. Some of the ketamine's quantifiable physiological effects may reflect its engagement with the opioid system and, as such, may be helpful predictors of antidepressant response. Moreover, prolactin rises with exposure to opioids and ketamine but not to the NMDA antagonist memantine (19,20).

Taken together, such data suggest that, although agents with MOR properties can present a risk to patients (21), they can also be harnessed to provide rapid symptom relief for patients at elevated risk for suicide (2). In our original grant application, we propose to answer several key questions that promise to elucidate and optimize the use of buprenorphine and ketamine in high-suicide-risk patients. Thus, buprenorphine provides hope for acute treatment but is not rapid in the onset of effect. Because of its MOR properties, prolonged use could be associated with tachyphylaxis and dependence (22). As a result,

we proposed to examine the potential use of buprenorphine as a follow-up to intravenous ketamine to increase the degree, speed, and duration of response to buprenorphine and to prolong the anti-suicidal effects of ketamine. The proposed dose of buprenorphine (0.2-0.8 mg per day) mirrors those used by Yovell and colleagues. Novel from the previous proposal, we will also assess implicit suicidal cognition and its potential mechanisms and moderators of anti-suicidal effects.

2.2. Preliminary data:

Our group a few years ago reported (6) on a trial of naltrexone, a MOR antagonist, to block the antidepressant effects of ketamine. We hypothesized that patients who responded to ketamine alone (50% reduction in HDRS 17 score at day 1) would show a significant diminution in response when given 50mg of the MOR antagonist, naltrexone, 45 minutes orally before the infusion. We used a double-blind, within-subjects crossover design to compare naltrexone's and placebo's effects. Patients received two open-label intravenous infusions of ketamine approximately one month apart and at the typical 0.5mg per kg dose over 40 minutes. Although we had initially indicated we would study patients twice at an interval of 4 weeks, the interval range was adjusted to 2-16 weeks to accommodate patients who showed no response and those who showed unexpectedly long responses (actual range 21-63 days; mean=42 days). Patients were assessed in the first 4 hours post-infusion and then at days 1,3,5,7, and 14 post-infusion. Thereafter, we assessed patients every two weeks. We proposed to study 30 patients with major depression and perform an interim analysis at the halfway point. Of the 16 patients who consented, one was excluded because of a positive urine drug screen and another for an undisclosed medical condition. Of the remaining 14, two received one infusion only. Of the 12 who crossed over, 7 responded to ketamine alone. These served as the basis for testing the mechanism of action. Of these, significantly more significant differences in HDRS change score in patients given ketamine plus placebo versus ketamine plus naltrexone (mean decrease=22.3 vs. 5.6 respectively, p=.04) or at day 3 (mean=20,1 versus 6.7, p<.01) were observed—See Figure 1.

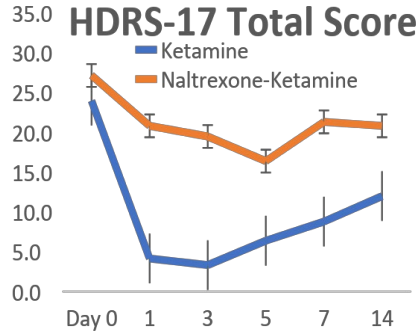


Figure 1: Mean HDRS-17 in n=7 crossover patients who responded to ketamine

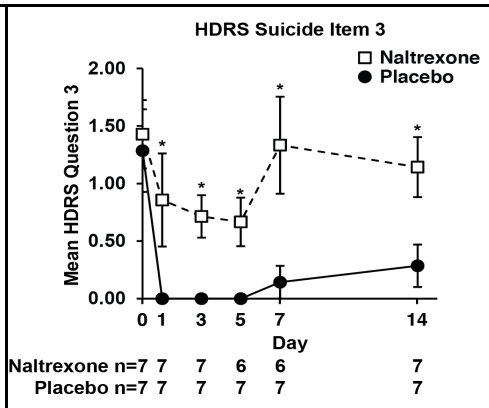


Figure 2: Mean HDRS Suicide Item 3 in n=7 crossover patients who responded to ketamine

No differences were observed in the total HDRS score by day 5. There were no differences in scores on the CADSS, a measure of dissociation. These data indicate that the antidepressant effects of ketamine are

largely mediated through MOR and suggest that dissociative properties are not necessary for antidepressant response. Although patients were not recruited for suicidal behavior on the HDRS suicide item, significant differences were observed at days 1, 3, 5, 7, and 14 ($p<.05$)—See Figure 2. Similarly, significant differences were observed on those days for the MADRS suicide item 10; on the mean CSSRS total score, significance was observed at days 3, 7, and 14 (See Figures 3 and 4.).

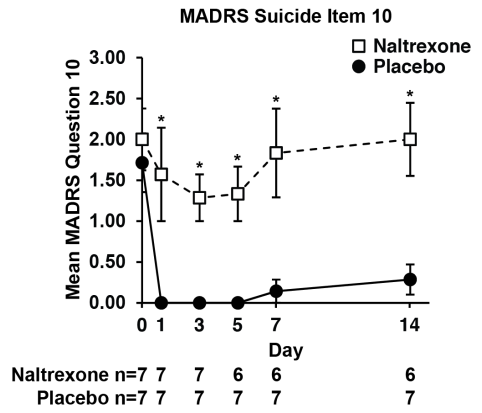


Figure 3: Mean MADRS Suicide Item 10 in 7 crossover participants who responded to ketamine

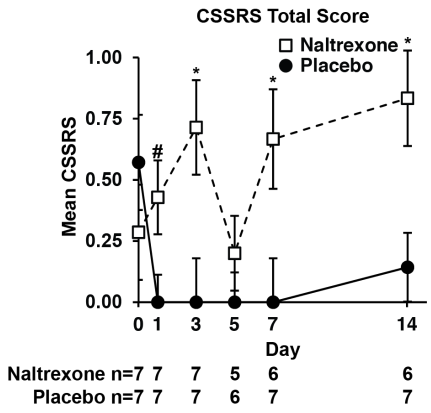


Figure 4: Mean CSSRS total score in 7 crossover participants who responded to ketamine

2.3. Risk and Benefit Assessment:

2.3.1. Known Potential Risks:

Taking Ketamine may cause one or more of the side effects listed below.

Common side effects of ketamine are:

- fast, irregular heartbeat
- increased blood pressure
- clear dreams that may seem real
- confusion or irritation
- floating sensation (feeling “out-of-body”) lasting from minutes to hours
- hallucinations (seeing or hearing things that are not really there)
- decreased rate of breathing, coughing
- nausea, vomiting
- twitching, muscle jerks, and muscle tension
- increased saliva (spit)
- increased thirst
- headaches
- metallic taste
- constipation
- blurry or double vision

Ketamine is known to have a significant potential for addiction in some individuals. Individuals should not participate in this study if they have any history of addiction to a drug or to alcohol.

Taking Buprenorphine may cause one or more of the side effects listed below.

Risks of Buprenorphine

- Headache
- Nausea
- Vomiting
- Excessive Sweating
- Constipation
- Fatigue
- Dry Mouth
- Insomnia
- Pain
- Signs and Symptoms of withdrawal

The study drugs, both buprenorphine and the matched placebo, in this study are being administered sublingually (i.e. under the tongue). Occasionally with this administration there can be a burning sensation or pain in the mouth during the process of dissolving.

Buprenorphine is often used to treat opiate addiction but this medication can also have a risk of abuse. Due to this risk, the study physicians will closely monitor enrolled subjects for drug or alcohol use in addition to close monitoring of other medications they may take on a daily basis. Subjects should not take part in this trial if they have a history of addiction.

Risk of Allergic Reaction

As with any drug, an allergic reaction can occur. Allergic reactions can be mild or more serious, and can even result in death. If the patients think they are having an allergic reaction, we recommend them to call the study doctor right away.

Confidentiality

Your identity will be kept as confidential as possible as required by law. However, there is always some risk that even de-identified information might be re-identified. Your personal health information related to this study may be disclosed as authorized by you. Your research records may be disclosed outside of Stanford, but in this case, you will be identified only by a unique code number. Information about the code will be kept in a secure location and access limited to research study personnel.

The results of this research study may be presented at scientific or medical meetings or published in scientific journals. However, your identity will not be disclosed.

Patient information may be provided to Federal and other regulatory agencies as required.

Alternative Treatments and Procedures

There are other treatments available for your depression. These include a variety of antidepressant medications such as fluoxetine (Prozac), paroxetine (Paxil), bupropion (Wellbutrin), and psychotherapies (talk therapies), such as cognitive-behavioral therapy (CBT). These treatment options also include Electroconvulsive therapy (ECT) and Transcranial Magnetic Stimulation (TMS).

2.3.2. Known Potential Benefits:

Possible gains for the subject are reduction in suicidal ideation and behavior with active treatment. All patients will receive one or more agents that have been shown to have anti-suicidal effects. Since there are two potential innovative treatments for suicidal behavior, considerable information will be generated as to the anti-suicide effects of opioid agents.

3. Objectives and Endpoints:

OBJECTIVES	MEASURE DESCRIPTION	TIMEFRAME
Primary		
Change in Scale for Suicide Ideation total scores will be analyzed as the primary outcome measure using analysis of variance model for repeated measures.	The model will include the difference in total scores on the suicidality measure from days 3 to 31 as a within subject effect, treatment, and time, as well as time x treatment interaction. The model will include Day 3 score as well. The total scores range from 0 to 38, with higher values indicating a greater risk of suicide. All effects will use $p<.05$ for simple effects and $p=0.1$ for interactions, using a sample size of 60, the hypothesis test will be fully powered (i.e., 80%) to detect effect sizes of 0.35 or greater.	Change from Day 3-31 and add to the model the Day 0 to 3 change in response to ketamine.
Secondary		
The secondary outcome will be change in depression measures (MADRS and HAMD) from day 1 to day 31.	The model will include the difference in total scores on the depression measures from days 3 to 31 as a within subject effect, treatment, and time, as well as time x treatment interaction. The model will include Day 3 score as well.	Change from Day 3-31 and add to the model the Day 0 to 3 change in response to ketamine.
Other		
Opioid activity of ketamine as well as buprenorphine	Peripherally by exploring opioid activity in subjects treated in the ketamine infusion and the sublingual buprenorphine vs. placebo phases by measuring serum metabolites of both ketamine and buprenorphine. The metabolites are measured in ng/mL with	Day 1 and 3-31.

	a reference interval of 1-10. Any presence of the drug will result in a number within the interval. If none detected, a not established level will be the result.	
Serum prolactin level	Levels of the hormone prolactin may be increased by opioids and ketamine in serum.	Change from Day 3-31.
Pupillometry	Moreover, we will apply pupillometry to estimate opioid activity. Levels of drug and opioid activity at specific time points will be correlated with response at that time point. In addition, regression analyses will be used to assess the relative contribution of opioid activity in blood, drug blood level, and pupil measure to improvement in suicidal behavior as well as mood, pain, and insomnia. This aim is exploratory.	

4. Study Design:

5. Study Population:

5.1. Inclusion criteria:

A subject will be eligible for inclusion only if all of the following criteria are met:

1. Male or female, 18 to 70 years of age, inclusive, at screen.
2. Able to read, understand, and provide written, dated informed consent prior to screening. Participants will be deemed likely to comply with study protocol and communicate with study personnel about adverse events and other clinically important information.
3. Diagnosed with Major Depressive Disorder (MDD), single or recurrent or Bipolar-II Disorder and currently experiencing a Major Depressive Episode (MDE) of at least eight weeks in duration, prior to screening, according to the criteria defined in the Diagnosis and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). The diagnosis of MDD will be made by a site psychiatrist and supported by the Structured Clinical Interview for DSM-5 (SCID-I/P).
4. Has a history of TRD during the current MDE, as assessed by the investigator. TRD is defined as failure to achieve a satisfactory response (e.g., less than 50% improvement of depression symptoms), as perceived by the participant, to at least one "treatment course" of a therapeutic dose of an antidepressant therapy of at least 8 weeks duration. The adequacy of dose and duration of the antidepressant therapy will be determined as per the MGH ATRQ criteria.

Participants must currently be on a stable (for at least 4 weeks) and adequate (according to the MGH ATRQ) dose of ongoing SSRI or SNRI antidepressant therapy, of which total duration must be at least 8 weeks. Participants may also have a history of intolerance to at least 2 antidepressant medications. These patients with the intolerance history will not be required to be currently taking an antidepressant medication.

5. Meet the threshold on the total SSI score of >/=6 at both screening and baseline visits.
6. Participants must qualify as "Moderately Treatment Refractory" using the Maudsley staging method, which incorporates past treatments, severity of symptoms and duration of presenting episode.
7. In good general health, as ascertained by medical history, physical examination (PE) (including measurement of supine and standing vital signs), clinical laboratory evaluations, and 3-lead electrocardiogram (ECG) if no evaluation available from the last 6 months.
8. If female, a status of non-childbearing potential or use of an acceptable form of birth control per the following specific criteria:

a. Non-childbearing potential (e.g., physiologically incapable of becoming pregnant, i.e., permanently sterilized (status post hysterectomy, bilateral tubal ligation), or is post-menopausal with her last menses at least one year prior to screening); or b. Childbearing potential, and meets the following criteria: i. Childbearing potential, including women using any form of hormonal birth control, on hormone replacement therapy started prior to 12 months of amenorrhea, using an intrauterine device (IUD), having a monogamous relationship with a partner who has had a vasectomy, or is sexually abstinent.
ii. Negative urinary pregnancy test at screening, confirmed by a negative urinary pregnancy test at randomization prior to receiving study treatment.
iii. Willing and able to continuously use one of the following methods of birth control during the course of the study, defined as those which result in a low failure rate (i.e., less than 1% per year) when used consistently and correctly: implants, injectable or patch hormonal contraception, oral contraceptives, IUD, double-barrier contraception, sexual abstinence. The form of birth control will be documented at screening and baseline.

9. Body mass index between 17-40kg/m2.
10. Concurrent psychotherapy will be allowed if the type (e.g., supportive, cognitive behavioral, insight-oriented, et al) and frequency (e.g., weekly or monthly) of the therapy has been stable for at least three months prior to screening and if the type and frequency of the therapy is expected to remain stable during the course of the subject's participation in the study.
11. Concurrent hypnotic therapy (e.g., with zolpidem, zaleplon, melatonin, or trazodone) will be allowed if the therapy has been stable for at least 4 weeks prior to screening and if it is expected to remain stable during the course of the subject's participation in the study.

5.2. Exclusion Criteria:

A potential participant will NOT be eligible for participation in this study if any of the following criteria are met:

1. Female of childbearing potential who is not willing to use one of the specified forms of birth control during the study.
2. Female that is pregnant or breastfeeding.
3. Female with a positive pregnancy test at screening or baseline.
4. Total SSI score of <6 at the screen or baseline visits.
5. Lifetime history of opiate use disorder.
6. Current diagnosis of a Substance Use Disorder (as defined by DSM-5), with the exception of nicotine dependence, at screening or within six months prior to screening.

7. Current diagnosis of Axis I disorders other than Dysthymic Disorder, Generalized Anxiety Disorder, Social Anxiety Disorder, Panic Disorder, Agoraphobia, or Specific Phobia (unless one of these is comorbid and clinically unstable, and/or the focus of the participant's treatment for the past six months or more).
8. History of schizophrenia or schizoaffective disorders, or any history of psychotic symptoms in the current or previous depressive episodes.
9. History of anorexia nervosa, bulimia nervosa, or eating disorder not otherwise specified with purging behavior in the past year.
10. Any Axis I or Axis II Disorder, which at screening is clinically predominant to their MDD or has been predominant to their MDD at any time within six months prior to screening. A diagnosis of borderline personality disorder is excluded.
11. In the judgment of the investigator, the subject is at significant risk for suicidal behavior during the course of his/her participation in the study.
12. Has dementia, delirium, amnestic, or any other cognitive disorder.
13. Has a clinically significant abnormality on the screening physical examination that might affect safety, study participation, or confound interpretation of study results.
14. Participation in any clinical trial with an investigational drug or device within the past month or concurrent to study participation.
15. Known history or current episode of:
    a. QTcF (Fridericia-corrected) ≥450 msec at screening (Visit 1) or randomization
    b. Syncopal event within the past year.
    c. Congestive heart failure (CHF) New York Heart Association Criteria >Stage 2
    d. Angina pectoris
    e. Heart rate <50 or >105 beats per minute at screening or randomization
16. Chronic lung disease.
17. Lifetime history of surgical procedures involving the brain or meninges, encephalitis, meningitis, degenerative central nervous system disorder (e.g., Alzheimer's or Parkinson's Disease), epilepsy, mental retardation, or any other disease/procedure/accident/intervention associated with significant injury to or malfunction of the central nervous system (CNS), or a history of significant head trauma within the past two years.
18. Presents with any of the following lab abnormalities w/in the past 6 months:
    a. Thyroid stimulating hormone (TSH) outside of the normal limits and clinically significant as determined by the study investigator. Free thyroxine (T4) levels may be measured if TSH level is high. Subject will be excluded if T4 level is deemed clinically significant by the study investigator.
    b. Any other clinically significant abnormal laboratory result at the time of the screening exam.
19. History of hypothyroidism and has been on a stable dosage of thyroid replacement medication for less than six months prior to screening. Subjects on a stable dosage of thyroid replacement medication for at least six months or more prior to screening are eligible for enrollment.
20. History of hypothyroidism and has been on a stable dosage of thyroid replacement medication without major changes in dosing (as determined by the PI) for six months prior to screening.
21. History of hyperthyroidism which was treated (medically or surgically) less than six months prior to screening.
22. Any current or past history of any physical condition which in the investigator's opinion might put the subject at risk or interfere with study results interpretation.
23. History of positive screening urine test for drugs of abuse at screening: cocaine, amphetamines, barbiturates, opiates.
24. Current (or chronic) use of opiates.
25. Current use of Lamictal and an inability to stop the medication prior to receiving ketamine.

5.3. Screen Failure:

Screen failures are defined as participants who consent to participate in the screening portion of the study (i.e., sign our screening ICF) but are not subsequently randomly assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this trial (screen failure) due to a specific modifiable factor may be rescreened at a later date once appropriate study criteria are met. Rescreened participants will be assigned the same participant number as for the initial screening.

In the case of screen failure, screening data of such patients will be electronically stored in our REDCap database.

6. Study Intervention:

Patients will receive an infusion of ketamine at 0.5mg per kg over 40 minutes. Ambient light will be lowered and patients are accompanied during and after the completion of the infusion until discharge. Patients will be assessed clinically at 3 hours and then at day 3. After the ratings are completed on Day 3, patients will be started on sublingual medication—buprenorphine or matched placebo beginning at 0.2 mg per day. Patients will be assessed weekly for 4 weeks. Doses will be adjusted at each session to a maximum of 0.8 mg after 3 weeks. Increases will be by 0.2mg increments. Participants will receive their study medication during weekly visits and will be instructed to self-administer it at home, ensuring the drug fully dissolves within 20 minutes before ingestion. As with our previous ketamine study, patients will be asked to maintain their other medications throughout the study as feasible. At the end of the active treatment phase, patients will discontinue the study drugs and will be followed up on Days 38 and 45 to monitor for any signs of withdrawal.

7. Participant discontinuation/withdrawal

7.1. Discontinuation of Study Intervention:

Subjects may be withdrawn from the study by the Principal Investigator if a subject:

- Is non-adherent with study procedures
- The randomization code is broken for the subject

The Principal Investigator may also withdraw a subject if he/she believes that for safety reasons it is in the best interest of the subject to be withdrawn.

Discontinuation information [e.g., date and the reason(s) for discontinuation] will be recorded in the subject's CRF (i.e., Study Completion Form) and relevant forms on REDCap.

Subjects withdrawn from the study due to an AE will be followed up for 30 days or until resolution. Subjects withdrawn from the study will be replaced if withdrawal occurs prior to the completion of the first treatment day (Visit 3). Should a participant fail to return for required visits or drops out of the study, an effort will be made to determine why. This information will subsequently be recorded on the subject's CRF and relevant forms on REDCap.

Subjects will be encouraged to remain adherent with all expected study visits. Non-adherence to expected study visits will be documented and may result in removal from the study. This will be clearly discussed during the informed consent process and reinforced throughout the study through regular screening for issues with compliance.

7.2. Participant Discontinuation/Withdrawal from the Study

An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Pregnancy
- Significant study intervention non-compliance
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- Disease progression which requires discontinuation of the study intervention
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

The reason for participant discontinuation or withdrawal from the study will be recorded on the REDCap e-CRF.

Subjects may withdraw voluntarily from the study at any time.

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if he or she fails to return for one scheduled visit and is unable to be contacted by the study staff.

We will take the following actions if a participant fails to return for a required study visit:

- We will attempt to contact the participant and reschedule the missed visit within 24 hours and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or his designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). We will record these contact attempts in the participant's designated REDCap e-CRF.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with the primary reason of loss to follow-up.

8. Study Assessments and Procedures:

8.1. Efficacy Assessments:

Screening process:

Participants will be recruited through the Stanford Depression Research Clinic online recruitment pipeline (online portal for referrals). Potential participants will be prescreened through their medical records. Participants whose initial prescreening is consistent with study eligibility will then be invited to consent to and participate in screening with a study team member (over zoom) for further assessment of eligibility. In-depth screening will include demographics information; psychiatric and medical history; current and past medications with adequacy of trials assessed by the Massachusetts General Hospital (MGH) Antidepressant Treatment Response Questionnaire (ATRQ); psychiatric diagnoses via the Overview/History section of the Structured Clinical Interview for DSM-5 (SCID) and the Mini-International Neuropsychiatric Interview for DSM-5 (MINI); borderline personality disorder screener and diagnostic module from SCID for DSM-5 (if a participant meets the screening threshold on the self-reported pre-screening questions); suicidal ideations will be measured by the Scale for Suicidal ideation (SSI); depression assessment with the Hamilton Depression Rating Scale (17-item), and the Montgomery-Åsberg Depression Rating Scale (MADRS).

Participants will also be asked specifically about any significant neurologic disease, including dementia, Parkinson's or Huntington's disease, brain tumor, seizure disorder, subdural hematoma, multiple sclerosis, or history of significant head trauma; history of dementia or cognitive impairment; and whether they are receiving or planning to receive any other investigational treatments during this study. Screening will be performed by a consistent group of qualified study staff who have been trained and certified by the lab's Psychological Director to ensure fidelity to assessment procedures.
Screening must be completed within 2 weeks of formal study enrollment and baseline assessment, otherwise screening will need to be repeated prior to moving forward with enrollment and baseline assessment.

Efficacy assessments related to primary and secondary outcomes:

We will use the following clinical scales to quantify suicidal ideation: Scale for Suicide Ideation (SSI), Columbia-Suicide Severity Rating Scale (C-SSRS). General mood and anxiety will be quantified using the Montgomery Åsberg Depression Rating Scale (MADRS), and 21 items Hamilton Depression Scale (HAMD-21).

8.2. Safety and Other Assessments:

All patients will undergo a clinical study visit with the study psychiatrist (or their designee) as part of the assessment for suitability in the study. This visit will include assessment of current psychiatric symptoms, psychiatric history (including past diagnoses, hospitalization, suicide attempts, past medication trials), current medical concerns (if any), past medical history, current medications, allergies, family psychiatric history, and social history. A mental status exam will be performed. Vital signs and certain studies (e.g., EKG, basic labs) will be obtained. Follow up clinical study visits will be performed.

8.3. Adverse Events and Serious Adverse Events:

8.3.1. Definition of Adverse Events:

An adverse event (AE) is any untoward, undesired, or unplanned event in the form of signs, symptoms, disease, or laboratory or physiological observations occurring in a person who has received study interventions. The event need not be causally related to the ketamine infusion or buprenorphine/placebo treatment in order to be considered an AE.

An AE includes, but is not limited to:

- Any adverse finding including a sign, symptom, abnormal assessment (laboratory test value, vital signs, electrocardiogram finding, etc.), or any combination of these.
- Any clinically significant worsening of a pre-existing condition;
- An AE that has been associated with a preexisting condition is a clinical condition (including a condition being treated) that is diagnosed before an informed consent form is signed and is documented as part of the subject's medical history.

The questions concerning whether the condition existed before the start of the active phase of the study and whether it has increased in severity and/or frequency will be used to determine whether an event is an intervention-emergent AE (IEAE).
An AE is considered to be intervention-emergent if [1] it was not present when the active phase of the study began and is not a chronic condition that is part of the subject's medical history, or [2] it was present at the start of the active phase of the study or as part of the subject's medical history, but the severity or frequency increased during the active phase.
For this study, the treatment follow-up period for adverse events is defined as 30 days following the last study visit.
Follow up will be documented in the subject's study file.

8.3.2. Definition of Serious Adverse Events:

A Serious Adverse Event (SAE) is defined as an AE that:

- Results in death
- Is life threatening (see below)
- Requires inpatient hospitalization or prolongation of an existing hospitalization (see below)
- Results in a substantial disruption of a person's ability to conduct normal life functions, i.e., the adverse event resulted in a significant, persistent or permanent change, impairment, damage or disruption in the patient's body function/structure, physical activities and/or quality of life
- Necessitates medical or surgical intervention to preclude such impairment
- Results in a congenital anomaly or birth defect

Additionally, important medical events that may not result in death, be life-threatening, or require hospitalization, may be considered SAEs, based upon appropriate medical judgment.

Life threatening refers to immediate risk of death as the event occurred or other medical intervention might have resulted in the death per the reporter. A life-threatening event does not include an event that,

had it occurred in a more severe form, might have caused death, but as it actually occurred, did not create an immediate risk of death.

Hospitalization is to be considered only as an admission. Hospitalization constitutes an AE to be classified as serious.

Note: Hospitalizations planned before the start of the study, for a preexisting condition that has not worsened, do not constitute an SAE (e.g., elective hospitalization for a total knee replacement due to a preexisting condition of osteoarthritis of the knee that has not worsened during the study).

If there is any doubt whether the information constitutes an SAE, the information will be treated as an SAE for the purpose of this study.

Timing for Reporting of Serious Adverse Events: Any SAE, regardless of causal relationship, will be reported to the Institutional Review Board (IRB), within 10 business days of the Principle Investigator learning of the event, by faxing or scanning a completed serious adverse event form to the assigned IRB panel. Follow-up information relating to an SAE will be reported to the IRB within 10 business days after the information is sent to the Principle Investigator. The subject should be observed and monitored carefully until the condition resolves or stabilizes or its cause is identified. All SAEs will be recorded in subject specific AE/SAE forms on REDCap and reviewed quarterly with the study DSMB.

8.3.3. Classification of an Adverse Event:

8.3.3.1. Severity:

All AEs will be assessed by the study clinician using the grading system defined below and recorded on designated REDCap subject-specific and study-wide AE logs.

- Mild – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- Moderate – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- Severe – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

8.3.3.2. Relationship to Study Intervention:

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

Causal relationship options and definitions are as follows:

- Definitely related: Event can be fully attributable to administration of ketamine or buprenorphine.
- Probably related: Event is most likely to be explained by administration of ketamine or buprenorphine, rather than the subject's clinical state or other agents/therapies.

- Possibly related: Event is as likely explained by administration of ketamine or buprenorphine, as by the subject's clinical state or other agents/therapies.
- Probably not related: Event is most likely to be explained by the subject's clinical state or other agents/therapies, rather than administration of ketamine or buprenorphine.
- Definitely not related: Event can be fully explained by the subject's clinical state or other agents/therapies, rather than the administration of ketamine or buprenorphine.

When assessing the relationship between an investigational product/protocol and an AE, the following parameters are considered:

- Temporal relationship between the administration of ketamine or buprenorphine and the AE
- Biologic plausibility of relationship
- Subjects' underlying clinical state or concomitant agents/therapies
- Where applicable, whether the AE abates on discontinuation of ketamine or buprenorphine (de-challenge)
- Where applicable, whether the AE reappears on repeat exposure to ketamine or buprenorphine (re-challenge)

SAEs that are not ketamine or buprenorphine related may nevertheless be considered by the Principal Investigator or the IMC to be related to the conduct of the study, i.e., to a subject's participation in the study.

8.3.3.3. Expectedness:

The study psychiatrist, in accordance with the listed risks on the study ICF, will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

8.3.4. Time Period and Frequency for Event Assessment and Follow-Up:

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

Study psychiatrist will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.3.5. Adverse Event Reporting:

AEs will be monitored continuously by designated study staff, recorded in applicable subject-specific and study wide REDCap eCRFs, and reported to the Stanford IRB annually.

Research staff will be trained to attend to signs of AEs and to report any potential unrelated or unexpected AE immediately to the PI. If AEs occur, appropriate medical and/or psychiatric care will be facilitated for the research participant, and recorded in the appropriate electronic AE logs on REDCap. As per Stanford IRB requirements, AEs will be reported to the IRB annually.

All subjects will have telephone and email contact information to reach the Principal Investigator and the Stanford IRB, in case of any distress or adverse response to the hypnosis or other components of the study.

An AE or SAE can occur from the time that the subject signs the informed consent form to 7 and 30 days, respectively, from the subject's last study visit regardless of relationship to the protocol. All AEs and SAEs will be recorded on the subject-specific and study wide eCRFs, which will be provided to the DSMB on a quarterly basis. The DSMB will instruct the Principal Investigator to follow all AEs, SAEs, and other reportable events until the event has subsided or values have returned to baseline, or in case of permanent impairment, until the condition stabilizes.

In addition to the information obtained from those sources, the subject will be asked the following nonspecific question: "How have you been feeling since your last visit?" Signs and symptoms will be recorded using standard medical terminology.

The following AE information will be included (when applicable): the specific condition or event and direction of change; whether the condition was preexisting (i.e., an acute condition present at the start of the study or history of a chronic condition) and, if so, whether it has worsened (e.g., in severity and/or frequency); the dates and times of occurrence; severity; causal relationship to the study interventions; action taken; and outcome.

8.3.6. Serious Adverse Event Reporting:

The PI or his designee will immediately report to the sponsor any serious adverse event (SAE), whether or not considered study intervention related, including those listed in the protocol or investigator brochure and must include an assessment of whether there is a reasonable possibility that the study intervention caused the event. Study endpoints that are serious SAEs (e.g., all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the study intervention and the event (e.g., death from anaphylaxis). In that case, the investigator will immediately report the event to the sponsor.

All SAEs will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the participant is stable. Other supporting documentation of the event may be requested by the study sponsor and should be provided as soon as possible.

In case of SAEs, the study investigator will complete an Unanticipated Serious Adverse Event Form and submit to the study sponsor and to the reviewing Institutional Review Board (IRB) as soon as possible, but in no event later than 10 business days after the investigator first learns of the effect. The study sponsor will conduct an evaluation of an unanticipated adverse event and will report the results of such evaluation to the Food and Drug Administration (FDA) and to all reviewing IRBs and participating investigators within 10 business days after the sponsor first receives notice of the effect. Thereafter, the sponsor will submit such additional reports concerning the event as FDA requests. The Investigator will provide all relevant documentation pertaining to an SAE (e.g., additional laboratory tests, consultation reports, discharge summaries, postmortem reports, etc.) to the DSMB in a timely manner. Reports relative to the subject's subsequent course will be submitted to the DSMB until the event has subsided or, in case of permanent impairment, until the condition stabilizes.
Other reportable information, while not meeting the definition of an SAE, is reportable to the DSMB with the timeliness of an SAE.

This includes:

- Seizure
- Pregnancy occurring during the study period in which the subject was exposed to study intervention;
- Overdose (e.g., a dose higher than that prescribed by a healthcare professional for clinical reasons) with or without AEs;
- Abuse (e.g., use for non-clinical reasons) with or without an AE;
- Inadvertent or accidental exposure with or without an AE;

Designated study staff will be responsible for ensuring that unanticipated problems are reported to the IRB in compliance with their requirements for reporting serious and unexpected adverse events. Reporting will be conducted in compliance with guidelines specified by the Stanford University Research Compliance Office.

8.3.7. Reporting Events to Patients:

At enrollment, participants will be asked whether or not they would like to be informed about study outcomes. We will compile a list of those participants who would like to know about outcomes, and following study completion they will be individually emailed a copy of the study's primary outcome paper using individual, encrypted email.

We will closely monitor AE's on a continuous basis, and involve the DSMB in assessing whether any AE is unexpected, or more severe than expected (at a rate greater than what would be expected by chance). Should we identify any AE that meets one of those two criteria or should we have any unexpected SAE's we will notify currently enrolled participants, and change our consent to include the pertinent information.

8.3.8. Reporting Pregnancy:

We will not include pregnant women in this study. If the participant is of childbearing potential and not already pregnant, the participant must agree to use adequate contraception (hormonal / barrier method

of birth control or abstinence) prior to study and for the duration of the study participation. During the screening phase of this study, participants of childbearing potential will be administered a pregnancy test; a negative pregnancy test will be required to confirm eligibility for study participation and will be done prior to receiving ketamine. If a participant becomes pregnant or suspects she is pregnant while participating in the buprenorphine/placebo phase of the study, she should inform the research staff immediately via in-person meeting, telephone call, or email. If a participant reports pregnancy occurring during the study period in which the participant was exposed to buprenorphine/placebo, research staff will stop the study visit and then notify the principal investigator.

9. Statistical Considerations:

Null hypothesis statistical testing (NHST) and p-values were planned only for the pre-specified primary (SSI suicidality scores) and secondary efficacy measure (MADRS and HDRS depression scores) to minimize type 1 error risk. For any supplemental analyses (e.g, clinical endpoints), NHST is only employed if the prespecified efficacy analyses are statistically significant. For all research questions, effect sizes rather than p-values are emphasized. Effect size for the prespecified efficacy endpoints will use Glass's delta estimate, a variant of Cohen's d that corrects for the unequal variances often observed in intervention studies. Effect size for clinical analyses with a dichotomous outcome will be expressed as Number Needed to Treat (NNT).

Analysis of baseline characteristics: Demographic data including age, gender, ethnicity, diagnosis, treatment history, and previous suicide attempts will be summarized using descriptive statistics (means, standard deviation, range for continuous variables and frequency counts for categorical variables). Mean baseline scores on primary and secondary symptom measures (e.g., SSI, MADRS) as well as other related measures will be presented in a table. These demographics will be provided for the ITT all patients randomized and for the mITT efficacy evaluation sample.

Analysis of primary endpoint: The primary endpoint of this RCT, submitted a priori in clinical trials.gov, is reduction in SSI suicidality score from baseline to day 31. All randomized participants received a standard ketamine infusion, and SSI will be assessed at day 1 prior to the infusion and at day 3. Subsequently, patients will receive 4 weeks of either daily low-dose buprenorphine or placebo with doses increased weekly accompanied by weekly clinical assessments. H0, the null hypothesis, is that mean SSI suicidality ratings will not differ between patients randomized to low-dose buprenorphine and patients randomized to placebo. The research hypothesis H1 is patients randomized to the buprenorphine condition will have significantly lower SSI scores by the end of treatment (day 31). Null hypothesis testing and p-values were planned only for the primary and secondary hypotheses with consideration of type 1 error risk. For all analyses, effect sizes will be emphasized using Glass's estimate, a variant of Cohen's d that corrects for the unequal variances often observed in intervention studies or Number Needed to Treat.

Statistical analysis of the primary outcome will be based on the modified intention to treatment (mITT) population, defined as participants who received at least one SSI assessment during the active

treatment phase. Although ITT estimates theoretically have less bias, the mITT is a conservative decision for the current design in which all patients will first receive ketamine. Including patients who only received ketamine and completed no assessments past the ketamine phase (days 1 to 3) would provide no information regarding response to follow-on buprenorphine or placebo. Moreover, given the known antidepressant effect of ketamine on suicide, their inclusion would likely underestimate the projected means at time points during the post-ketamine evaluation of 4 weeks of follow-on buprenorphine vs placebo.

Repeated measurements of the SSI will be compared across treatment groups using a linear mixed-effects model. The mixed model makes use of all available SSI scores across the study timepoints to estimate group differences in means. The model will include fixed effects of treatment group, time, time by treatment group interaction, and a random effect of participant intercept. An unstructured covariance matrix, or a first order auto-regressive structure, will be used based on relative model fit according to the information criterion index. This model parameterization is suited for testing of between-group differences over repeated measurements, consistent with the primary study hypothesis. The SPSS syntax is:

MIXED SSI with time treatment

/Criteria=CIN(95) MXITER(100) MXSTEP(10) SCORING(1)

SINGULAR (0.0000000001) HCONVERGE(0, ABSOLUTE) LCONVERGE(0, ABSOLUTE), PCONVERGE(0.00000001, ABSOLUTE)

/FIXED time time*treatment | SSTYPE(3)

/METHOD=ML

/RANDOM=INTERCEPT time | PARTICIPANT COVTYPE(UN).

The result of the hypothesis test for efficacy of Ketamine followed by Buprenorphine will be determined by the statistical significance of the treatment by time interaction (two-sided alpha=.05). Only if group differences are deemed statistically significant on the prespecified primary outcome, a supplemental analysis of clinical significance will be conducted by calculating the proportion of responders, defined as a 50% or greater reduction in SSI suicidality ratings from baseline to day 31, in each of the two treatment groups. These proportions will be compared with a 2x2 chi-squared test.

Analysis of secondary endpoints: The secondary outcome will compare treatment groups on the change in depression symptoms from baseline to day 31 using weekly scores from the MADRS and HDRS. A similar mixed-effects model used for the primary endpoint will be applied. The trajectories of MADRS and HDRS mean scores will be compared between the two groups in the mixed model with statistical significance determined by the p-value for the treatment group by time interaction term. If the groups differ significantly on the MADRS scores, the proportion of responders (i.e., >50% or greater reduction from

baseline to day 31) will be statistically with a 2x2 chi-squared test. The MADRS depression assessment includes one item that assesses suicidal thoughts. Mean scores and standard deviations on this item will be calculated for the K+Buprenorphine and K+Placebo groups, and effect sizes will be calculated using Glass's formula.

***Analysis of safety endpoints*:** Frequencies of side effects, adverse events, and serious adverse events observed during the active treatment phase will be summarized by group, and the most commonly reported adverse events will be tabulated. Changes in suicidality and withdrawal symptoms during the 2-week post intervention phase (days 38 and 45) will be described with means, standard deviations, and ranges for the SSI and MADRS, as well as for clinician and patient ratings of withdrawal (COWS and SOWS). These measures will be compared across groups using independent measures t- tests. No type 1 error correction is planned for safety analyses.

Evaluation of treatment blind: Two-weeks post-intervention (day 45), patients will be asked to endorse one of the following: I think I was taking active medication; I think I was taking placebo; I am unsure if I was taking an active medication or a placebo. Frequency counts and percentages will describe the correct and incorrect guesses.

Missing data: For both primary and secondary endpoints, the mixed-effects models implicitly assume data missing at random. Sensitivity analyses will only be conducted if necessary (e.g., if the missingness is non-ignorable due to high frequency of missingness or if data are not missing at random).

Sample size justification: The only RCT evaluating buprenorphine for reducing suicidality was that of Yovell and colleagues. They calculated that a sample of 75 participants with a 2:1 randomization ratio would provide 80% power at a 5% significance level to detect a 6.3-point difference between groups in scores on the Scale for Suicide Ideation, assuming a standard deviation of 9.0. They observed that patients in the buprenorphine group had a greater reduction in Suicide Ideation Scale score than patients in the placebo group, (mean difference= -4.3, 95% CI=-8.5, -0.2; p=0.04) at week 2 and at the end of week 4 (mean difference=-7.1, 95% CI=-12.0, -2.3; p=0.004). Sensitivity analysis revealed similar results (mean difference=-5.7, 95% CI=-10.1, 21.4; p=0.01).

Based on effect sizes observed by Yovell et al on the same endpoint measure of SSI, the a priori power calculation for the current study indicated n=60 patients would have 80% power to detect medium effect sizes of .35 or greater on the primary outcome of the group differences in SSI. (We did not power the study to test the differences between groups on secondary measures).

10. References:

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