PROTOCOL TITLE: Ketamine-assisted psychotherapy for the treatment of persistent depression in abstinent opioid users

NCT Number: Pro00115696

Document date: August 18, 2022

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1.0 OBJECTIVES/SPECIFIC AIMS

1.1 Introduction and Context

Depression is common in patients with opioid use disorder (OUD). In patients seeking buprenorphine-naloxone treatment for OUD, about 1 in 4 have concurrent major depressive disorder (MDD) (Savant et al., 2013). Similarly, about one third to one half of patients enrolled in methadone maintenance treatment (MMT) are depressed (Peles, Schreiber, Naumovsky, & Adelson, 2007; Zhang et al., 2016). Unfortunately, depression occurs independent of MMT treatment duration suggesting that stabilization of OUD alone is not sufficient to improve mood symptoms (Peles et al., 2007).

The relationship between OUD and depression is complex and bidirectional. Depressed patients who initiate opioid therapy are more likely to transition to long-term high-dose therapy and are at higher risk of opioid abuse or non-medical use (Sullivan, 2018). Conversely, chronic opioid use can cause neurobiological changes increasing negative affective states leading to higher suicide risk and continued opioid use (Rizk, Herzog, Dugad, & Stanley, 2021). Given this interdependence, concurrent treatment of both mood and opioid use disorder symptoms is paramount to prevent destabilization of either disorder (Vekaria et al., 2021).

1.2 Current Treatment

Current literature is limited regarding the treatment of depressed patients with OUD despite desire for positive mood being the most commonly cited reason for relapse in patients with OUD (Kadam, Sinha, Nimkar, Matcheswalla, & De Sousa, 2017; Unnithan, Gossop, & Strang, 1992). A large, randomized placebo-controlled trial of imipramine in depressed patients receiving MMT showed promising results with 57% of imipramine-treated patients considered “responders” per clinical global impression compared with 7% of placebo-treated patients. Unfortunately, drop-out was common with only 84 of 137 patients completing an adequate 6 week trial (Nunes et al., 1998). Contrastingly, an RCT involving buprenorphine + desipramine vs buprenorphine + placebo vs methadone + desipramine vs methadone + placebo failed to show efficacy of desipramine over placebo in 164 opioid- and cocaine-dependent patients. Concerningly, patients receiving buprenorphine + desipramine more frequently had urine drug screens positive for opioids than those receiving buprenorphine + placebo (Kosten, Falcioni, Oliveto, & Feingold, 2004).

Selective serotonin reuptake inhibitors (SSRIs), the first line treatment in patients with moderate-to-severe MDD have a mixed-to-negative evidence base in co-occurring MDD and OUD (Carpenter, Brooks, Vosburg, & Nunes, 2004; Petrakis et al., 1998). Regarding the treatment of depression in patients on opioid agonist therapy, a 2010 Cochrane review found there is “low evidence supporting the clinical use of antidepressants to treat depression in opioid dependence”, while also noting that current literature is limited (Pani, Vacca, Trogu, Amato, & Davoli, 2010). This finding was further supported by a subsequent meta-analysis examining antidepressant use in patients engaged with MMT (Pedrelli et al., 2011). Given the prevalence of depression in patient with OUD regardless of stage of recovery and ineffectiveness of current interventions, more effective treatments for depression in OUD are critically needed.

1.3 Purpose and Objectives of the Study

The primary objective of the proposed study is to preliminarily explore the feasibility, efficacy, and tolerability of ketamine-assisted psychotherapy in treatment of MDD in patient with OUD currently in early or sustained remission by DSM-V criteria. We seek to enroll 10 individuals with current moderate-to-severe major depression despite ongoing abstinence from opioids.

1.4 Specific Aims

To achieve these objectives, the following Specific Aims are proposed:

Specific Aim 1: To preliminarily explore the efficacy of ketamine-assisted psychotherapy in reducing symptoms of depression using the Montgomery Asberg Depression Rating Scale (MADRS).

Specific Aim 2: To preliminarily explore the tolerability of ketamine-assisted psychotherapy in treatment of depression including adverse effects, cravings and relapse

2.0 BACKGROUND

2.1 Role of Depression in Maintaining Abstinence From Opioids

Negative affect has been found to be a key mediator in failure to achieve abstinence and depression is a frequently seen comorbidity in OUD in all stages of treatment and recovery. Nearly two out of three persons entering treatment for opioid detoxification screen positive for depression (Brienza et al., 2000; Stein, Santiago Rivera, Anderson, & Bailey, 2017; Volkow, 2004). In patients seeking buprenorphine-naloxone treatment for OUD, about 1 in 4 have concurrent major depressive disorder (MDD) (Savant et al., 2013). Similarly, about one third to one half of patients enrolled in methadone maintenance treatment (MMT) are depressed (Peles et al., 2007; Zhang et al., 2016). Unfortunately, depression occurs independent of MMT duration suggesting that stabilization of OUD alone is not sufficient to improve mood symptoms (Peles et al., 2007) and desire for improvement in mood is the most commonly cited reason for relapse in OUD following initial addictions treatment (Huhn et al., 2019; Kadam et al., 2017; Volkow, Jones, Einstein, & Wargo, 2019). In addition to contributing to relapse and being a risk for unintentional overdose, OUD is an independent risk factor for completed suicide. A national cohort study of veterans (n=4,863,086) found that after controlling for psychiatric and medical comorbidities, overall substance use was still associated with a 1.67 hazard ratio for suicide in men and 2.15 in women. Furthermore, in women, OUD was associated with the highest hazard ratio for suicide of any substance of abuse at 2.33 (Bohnert, Ilgen, Louzon, McCarthy, & Katz, 2017).

2.2 Glutamatergic Dysregulation Contributes to Both Depression and Addiction Pathology

Glutamatergic dysregulation in the prefrontal cortex and mesolimbic regions (including the amygdala and the nucleus accumbens) has been implicated in addiction pathology across multiple substances of abuse (Gass & Olive, 2008). Similarly, depression has been shown to have aberrant glutamate signaling (Murrough, Abdallah, & Mathew, 2017; Niciu et al., 2014). On a cellular level, astrocytes are responsible for maintaining glutamate homeostasis (Parpura & Verkhratsky, 2012) and both depression and addiction have been linked to impaired ability of astrocytes to upregulate glutamate (Rajkowska & Stockmeier, 2013; Scofield & Kalivas, 2014). Ketamine is a noncompetitive antagonist of NMDA glutamatergic receptors which has been widely used for pain control in conjunction with general anesthesia since it was FDA approved in 1970.

2.3 Clinical Trials for Depression Treatment

Results from several meta-analyses indicate that ketamine can induce ultra-rapid improvements in depression and suicidality (Han et al., 2016; Wilkinson et al., 2017). This remission is most enduring in individuals with a family history of substance use disorders (Niciu et al., 2014). It is widely accepted that all currently approved pharmacotherapy classes for depression (serotonin reuptake inhibitors, monoamine oxidase inhibitors, and tricyclic antidepressants) are associated with a delayed onset of anti-depressant activity of 2-4 weeks. A meta-analysis of nine high-quality studies showed that ketamine was significantly more effective than placebo in reducing symptoms of major depressive disorder at 24 hours, 72 hours, and 7 days post-infusion (Han et al., 2016). Additionally, results from a recent meta-analysis of ten clinical trials showed accumulating evidence that ketamine can significantly reduce suicidal ideation within 24 hours with moderate to large effect sizes (Wilkinson et al., 2017). The overall duration of anti-depressant response was found to last between 3-12 days (Andrade, 2017). However, in a subgroup analysis, positive family history of alcoholism was found to be associated with a significantly longer duration of anti-depressant efficacy, averaging 17 days for the family history positive group and 3.6 days for the family history negative group (Niciu et al., 2014). This suggests that the genetics underlying substance use confer a stronger response to the effects of ketamine.

2.4 Clinical Trials for Substance Use Disorder Treatment

Ketamine has shown early evidence of efficacy in the treatment of substance use disorders. One study evaluating the adjunctive use of ketamine in heroin use disorder showed that a single-session of high-

dose (2 mg/kg IM) ketamine demonstrated one-month abstinence rates of 85% compared to 55% abstinence in the low dose group (0.2 mg/kg IM), and one-year abstinence rates of 24% in the high dose group as compared to 6% in the low-dose control group (E. Krupitsky et al., 2002). In a follow-up study comparing three repeated sessions of ketamine infusions with concurrent psychotherapy to single-session treatment, abstinence rates were increased to 50% in the 3 session group as compared to the single session rate of 22% (Evgeny M Krupitsky et al., 2007). Related studies found that ketamine is useful as an adjunct to psychotherapy in the treatment of alcohol use disorder (E M Krupitsky & Grinenko, 1997) with one-year complete abstinence rates of 65.8% in the ketamine-assisted psychotherapy group compared to 24% in the control psychotherapy group. Intriguingly, the anti-depressant response to ketamine occurs primarily after the drug has been cleared from the body, suggesting that its primary effects are mediated through downstream processes. More recently, ketamine has been studied in cocaine use disorder and found to improve levels of motivation to quit using and to reduce cocaine craving (Elias Dakwar, Levin, Foltin, Nunes, & Hart, 2014) and reduce rates of cocaine self-administration by 67% relative to baseline (E Dakwar, Hart, Levin, Nunes, & Foltin, 2017; E Dakwar et al., 2018). Additionally, a single dose of ketamine combined with motivational enhancement therapy has been shown to increase abstinence and increase time to relapse in subjects with alcohol use disorder (Elias Dakwar et al., 2020) while a single dose of ketamine combined with mindfulness-based relapse prevention has yielded similar results in subjects with cocaine dependence (Elias Dakwar et al., 2019). Finally, ketamine combined with motivational enhancement therapy and mindfulness-based relapse prevention has shown promising open-label evidence for the treatment of cannabis use disorder (Azhari et al., 2021).

2.5 Novelty and Importance of the Current Study

Past studies have shown promising results for ketamine in the rapid treatment of MDD (Han et al., 2016) particularly in those with a family history of substance use (Niciu et al., 2014), however no prior studies have investigated the efficacy of ketamine-assisted psychotherapy in the treatment of depressed participants with OUD currently in early or sustained remission.

3.0 INTERVENTION TO BE STUDIED

3.1 Overview of Study Medication

Ketamine was originally FDA approved in 1970 for pain control in conjunction with general anesthesia (Ketalar, 2021). The drug has since been evaluated in academic settings for the treatment of pain and a multitude of psychiatric indications. Ketamine has been increasingly studied in academic settings and used off-label in private practice settings over the past 10 years (Wilkinson et al., 2017). Ketamine undergoes extensive hepatic first pass metabolism, with an oral bioavailability of approximately 16% ((Mathew et al., 2012). For induction of anesthesia, doses of 1 to 4.5 mg/kg IV or 6.5 to 13 mg/kg IM are recommended (Ketalar, 2021).

3.2 Safety and Toxicity

The acute toxicity of ketamine has been studied in multiple species. In mature mice and rats, the intraperitoneal LD50 values have been shown to be approximately 100 times the average human intravenous dose (Ketalar, 2021). Repeated, daily intravenous injections have been studied in rats, and dogs for as long as 6 weeks with excellent tolerability (Ketalar, 2021). Similarly, twice weekly treatments in monkeys over a four- to six-week period were well tolerated (Ketalar, 2021). At sub-anesthestic doses in human clinical trials for depression, the most clinically significant physical adverse event from ketamine is a transient increase in blood pressure, which was experienced by 29.8% of participants with a mean systolic blood pressure increase of 19.6 mmHg ($p<0.001$) and a mean diastolic blood pressure increase of 13.4 mmHg ($p<0.001$, (Wan et al., 2015)). Small, but statistically significant changes in perception (including derealization, depersonalization, distortion of time and space, and sense of illusion) were categorized as “feeling strange or unreal” and were experienced by 11.7% of participants. The average

peak score of 4.5 on the Brief Psychotic Rating Scale is consistent with very mild symptom severity (Wan et al., 2015).

3.3 Study Drug, Dose, Mode of Administration and Justification

Ketamine is concentrated at a dose of 100 mg/ ml and will be administered by intramuscular administration in the amount of 0.5 mg/kg with plan to flexibly titrate by 0.25 mg/kg each session based on tolerability to a maximum weight-based dose of 1.5 mg/kg. Total dose on a given day will be limited to 60 mg regardless of subject's weight. While formal dose response studies for depression are lacking, ketamine has been most widely studied for psychiatric indications at 0.5 to 1.0 mg/kg given intravenously. Recent studies have shown that intramuscular ketamine may be as effective as intravenous ketamine for depression and may be more practical clinically (Chilukuri et al., 2014; Xu et al., 2016). Although there are only a few studies evaluating the use of ketamine in the treatment of substance use disorders, doses in these trials have ranged from 0.5 to 0.8 mg/kg given intravenously or 2 mg/kg given intramuscularly (Jones, Mateus, Malcolm, Brady, & Back, 2018). When given intramuscularly, ketamine has a peak time of 5-30 minutes following injection and a bioavailability of 86-97% (Grant, Nimmo, & Clements, 1981). Of note, ketamine elimination clearance is high with a half-life of 2-3 hours and clearance in women that is up to 20% higher than men (Mion & Villevieille, 2013).

4.0 STUDY ENDPOINTS

4.1 Primary Outcome

Montgomery Asberg Depression Rating Scale (MADRS; (Montgomery & Asberg, 1979)). The MADRS is a clinician administered, 10-item questionnaire of depression severity. The total score ranges from 0-60, with scores of 0-6 considered normal (non-depressed), 7-19 indicative of mild depression, 20-34 indicative of moderate depression, and 35-60 indicative of severe depression. Individuals scoring 20 or higher on the MADRS will be included in the study. The MADRS evaluates the following symptoms of depression: 1) clinical appearance of sadness, 2) self-reported sadness, 3) inner tension, 4) reduced sleep, 5) reduced appetite, 6) concentration difficulties, 7) lassitude, 8) inability to feel, 9) pessimistic thought process, and 10) thoughts of suicide. The MADRS has a sensitivity of 94% and a specificity of 83%, has been shown to have high internal consistency, and correlates well with other measures of depression such as the Hamilton Depression Scale.

4.3 Exploratory Outcomes

Exploratory outcomes will include changes in characteristics related to opioid addiction including craving for opioids (Visual Analog Scale) and related areas of psychiatric functioning.

- Beck Depression Inventory (BDI-II; Beck, Steer, & Brown, 1996). A widely used 21-item self-report measure of depressive symptoms.
- Visual Analog Craving Scale (VAS; McMillan & Gilmore-Thomas, 1996). At baseline, during the interventional visits, and at each follow-up visit, subjects will be asked to report on the frequency, duration, and intensity of their opioid cravings on a 10 point (100 mm) VAS. This approach has been shown to yield a reliable and valid measure of craving in previous research.
- Timeline Follow-Back (TLFB; Linda C. Sobell, 1992): The TLFB obtains retrospective self-report of substance use by using a calendar and memory prompts to stimulate recall. Quantity and frequency assessments are made using this instrument (e.g., total amount of opioids used, percent of days using) as well as abstinence (yes/no). TLFB yields consistently high test-retest correlations and correlates well with other self-reports and collateral reports. The TLFB will assess consumption of opioids for 60 days prior to study

entry, during the interventional phase and the follow-up phase. Use of nicotine and other drugs of abuse, including prescription drugs, will also be assessed using the TLFB.

- Generalized Anxiety Disorder Screener (GAD-7; Spitzer, Kroenke, Williams, & Löwe, 2006)). The GAD-7 is a 7-item self report instrument that will assess generalized anxiety symptomology.
- Five Facets of Mindfulness Questionnaire (FFMQ; Baer, Smith, Hopkins, Krietemeyer, & Toney, 2006): The FFMQ assesses five components of mindfulness including observation, non-judgement of experience, non-reactivity to inner experience, acting with awareness, and description of experience.
- PTSD Checklist (PCL-5; Blevins, Weathers, Davis, Witte, & Domino, 2015): The PCL-5 is a 20-item self-report measure. The PCL-5 is similar in form to the PTSD Checklist (PCL) based on the DSM-5 (Weathers et al., 1993), which has excellent psychometric characteristics for screening and as a secondary indicator of PTSD symptom severity (McDonald & Calhoun, 2010).
- Insomnia Severity Index (ISI; Morin, Belleville, Bélanger, & Ivers, 2011). The ISI is a 7-item, self-report measure that assesses perceived severity of insomnia. The items sum to produce a total score (range 0–28). The ISI has an internal consistency alpha coefficient of 0.74, and has shown convergent validity with other measures such as the Pittsburgh Sleep Quality Index and sleep diaries).
- Brief Pain Inventory (BPI; (Cleeland & Ryan, 1994). This 9-item questionnaire uses a 10-point Likert scale to assess the severity of pain and its interference on difference aspects of quality of life and function.
- Mystical Experience Questionnaire (MEQ). This 30-item self-report questionnaire was developed and validated through factor analysis of retrospective accounts of profound experience with psilocybin-containing mushrooms. It includes four factors: transcendence of time and space, ineffability, positive mood and mystical (internal unity, external unity, noetic quality, and sacredness) (Barrett, Johnson, & Griffiths, 2015; Maclean, Leoutsakos, Johnson, & Griffiths, 2012).

5.0 INCLUSION AND EXCLUSION CRITERIA/STUDY POPULATION

5.1 Initial Screening Methodology

Initial screening eligibility will be conducted by the PI or trained research personnel. Subjects with a self-reported history of depression and opioid misuse or illicit opioid use for which they report being abstinent for at least 3 months (early remission) will be eligible to complete informed consent and baseline evaluation.

5.2 Inclusion Criteria

A subject may be eligible for enrollment if all the following inclusion criteria apply within the thirty days prior to first experimental session:

1. Between the ages of 18 to 64 years old.
2. Able to provide informed consent.
3. Meet DSM-5 criteria for Major Depressive Disorder, without psychotic features based on clinical interview.
4. Score at least 20 on the Montgomery-Asberg Depression Rating Scale (MADRS, moderate or severe depression).
5. Must meet criteria for opioid use disorder in early or sustained remission (3 months or great) by DSM-5 based on clinical interview.
6. Subjects taking other psychotropic medications (e.g. anti-depressants, anxiolytics, methadone, buprenorphine, naltrexone) must be maintained on a stable dose for at least four weeks before study initiation.

5.3 Exclusion Criteria

Subjects will be excluded from the study if any of the following criteria apply:

1. They are considered an immediate suicide risk by clinician assessment, self-report a suicide attempt within the past year or felt to be likely to require hospitalization during the study.
2. Subjects who meet DSM-5 criteria for current bipolar disorder based on clinical interview.
3. Subjects who meet DSM-5 criteria for current or history of psychotic spectrum disorders based on clinical interview.
4. Subjects meeting DSM-5 criteria for current substance use disorder (*i.e.,* not in early or sustained remission) other than tobacco use disorder.
5. Subjects who report use of ketamine >20 times in the past or who meet DSM-5 criteria for Other Hallucinogen Use Disorder due to ketamine use including subjects who are currently in early or sustained remission.
6. Women who are pregnant or nursing, and women who do not consent to use methods of highly effective birth control during the interventional phase of the study.
7. Subjects with hypertension as defined by a baseline visit systolic blood pressure (SBP) >140 mmHg or a diastolic blood pressure (DBP) >90 mmHg.
8. A history of allergic or other adverse reaction to ketamine (or its excipients).
9. Clinically significant physical exam findings or self-reported medical conditions for which a transient increase in blood pressure could be significantly detrimental (e.g. glaucoma, aneurysmal disease, cardiovascular disease, or end-stage renal disease).
10. QTc will be measured in subjects currently taking methadone and those with QTc 450ms or longer will be excluded.
11. Subjects who live greater than 20 miles from the study site and cannot arrange their own transportation will be excluded from the study.
12. Subjects with clinically significant kidney or liver impairment.

5.4 NUMBER OF SUBJECTS

Approximately 10 subjects are planned for enrollment in this study with no gender, race, or ethnicity exclusions.

5.5 SETTING

All procedures will be conducted in private research study rooms on MUSC campus.

5.6 RECRUITMENT METHODS

Recruitment will be conducted through online (i.e. Craigslist) and flyer advertisements throughout the hospital and outpatient clinics at MUSC and other local clinics providing OUD treatment.

Initial screening eligibility will be conducted by the PI or trained research personnel. Subjects with a self-reported history of depression and opioid misuse or illicit opioid use for which they report being abstinent for at least 3 months (early remission) will be eligible to complete informed consent and baseline evaluation.

6.0 CONSENT PROCESS

6.1 Qualifications of Study Personnel Obtaining Informed Consent and Capacity of Participants

The research team have completed (or will complete upon hiring) the Miami Collaborative IRB Training Initiative (CITI) course and its associated tests in research ethics. Only the PIs or Co-I's will obtain informed consent.

6.2 Location of Informed Consent

Informed consent will be obtained at the study research offices, in a private and interruption-free environment.

6.3 Method of Obtaining Consent

Study personnel will ensure that the participant is given full and adequate written and verbal information about the nature, purpose, possible risks and benefits of the study. There will be no mandatory waiting period prior to obtaining informed consent, however participants will not be required to make a decision at the time of initial contact. Participants will also be allowed to discuss the study with family or other individuals prior to giving their informed consent. After participants have reviewed the informed consent document, participants will be asked to relay their understanding of key elements related to the study procedures (i.e. voluntary nature of participation, basic study visit procedures, duration of study, anticipated risks and benefits) to ensure their understanding of the study prior to obtaining informed consent. Consent content will be reviewed as necessary to ensure that subjects have an adequate understanding to provide initial and ongoing consent. The participant's signed and dated informed consent will be obtained before conducting any study tests or procedures that are not related to their routine care. The Investigator will maintain the original, signed informed consent document. A copy of the signed informed consent document will be given to the participant.

6.4 Capacity of Participants to Give Informed Consent

No vulnerable populations (e.g. children, cognitively impaired individuals, incarcerated individuals, or pregnant women) will be included in the study, and informed consent must be obtained directly from the participants.

7.0 STUDY DESIGN/METHODS

7.1 Study Overview

This is an open label trial of ketamine-assisted psychotherapy to assess the efficacy and safety of weekly intramuscular injections of ketamine along with multimodal psychotherapy, including supportive, non-directive and insight-oriented components, for decreasing symptoms of MDD in subjects with OUD in early or sustained remission. Psychotherapy will include setting goals for treatment of subject's depression as well as setting an intention or focus for each medication session. After medication administration, therapy will include supportive talk and guidance during acute medication effects. At the end of each session, the subject will be encouraged to reflect on his or her experience as it relates to their intention and broader goals. Finally, the subject will be encouraged to build insight into their depression and develop behavioral goals to enact their insights and reach their goals.

Subjects will participate in a baseline visit to complete informed consent as well as complete assessments to evaluate study eligibility and collect baseline data. Eligible participants will return for the initial ketamine intervention procedure. Participants will be subsequently monitored until they have returned to baseline based on clinical assessment during which time they will complete measures assessing their perception of the interventional experience

7.2 Duration of Intervention and Study

Participants will complete a total of 12 study visits (including baseline assessment and follow-up assessments) as shown in **Figure 1**. Medication sessions with intramuscular ketamine will occur weekly for eight weeks. Participants will meet virtually or in person for follow-up 1, 2, 4, and 8 weeks following final medication session.

7.3 Schedule of Assessments

The instruments to be used are standardized, have good psychometric properties, and are widely used. The schedule of study assessments is provided in **Table 1**.

Table 1: Schedule of Assessments

Instrument Name	Purpose	TIME POINT		
		BL (Wk 0)	Tx 1-8 (Wk 1-8)	Follow-up (Wk 9, 10, 12, 16)
Self-Reports and Consents				
Informed Consent	Obtain informed consent	X		
Demographics Form	Sample characterization	X		
Beck Depression Inventory-II	Self-reported assessment of depression symptom severity	X	X	X
Visual Analog Scale (VAS)	Measure subjective levels of opioid craving	X	X	X
General Anxiety Disorder (GAD-7)	Self-report of anxiety symptom severity	X	X	X
Mystical Experiences Questionnaire (MEQ)	Measure of perceptual experiences		X	
Brief Pain Inventory	Measure of pain and quality of life	X	X	X
Insomnia Severity Index (ISI)	Assess insomnia and sleep quality	X	X	X
Five Facets of Mindfulness (FFMQ)	Assess aspects of mindfulness related	X	X	X
PTSD Checklist (PCL-5)	Measure of PTSD symptoms	X	X	X
Fagerstrom Test of Nicotine Dependence (FTND)	Measure of nicotine dependence	X	X	X
Timeline Follow-Back (TLFB)	Measure of substance use	X	X	X
Clinician Assessments				
History and Physical Exam	Eligibility assessment	X		
Vital Signs Measurement	Obtain readings of blood pressure, pulse, temperature, respirations and pulse oximetry	X	X*	
Montgomery-Asberg Depression Rating Scale (MADRS)	**Primary Outcome:** Clinician assessed measure of depression symptom severity	X	X	X
Pre-screening Questionnaire	To assess for basic eligibility criteria before completing a full baseline visit.	X		
Laboratory and Procedural Tests				
Urine Pregnancy Test (female subjects only)	Eligibility assessment	X	X	
Urine Drug Screen	Assessment of illicit drug use	X	X	
Electrocardiogram (ECG; subjects on methadone only)	Assessment of cardiac function	X		

* Vital signs (blood pressure, pulse, respiratory rate, and pulse oximetry) will be obtained prior to treatment sessions and at 60 minutes post-treatment. Temperature will be monitored immediately prior to treatment. If there is an increase in systolic or diastolic blood pressure >30 mm Hg from baseline, or an increase in pulse rate >30 bpm from baseline, subjects will be treated with standard of care antihypertensive medications (i.e. clonidine) and the measurements will be repeated every 20 minutes until BP and pulse are within 30 points of the baseline values.

7.4 Baseline Assessment Procedures

After completing study informed consent, participants will undergo a comprehensive evaluation to assess for inclusion and exclusion criteria. This will include self-reports and clinician assessments as shown in Table 1. This will also include assessment of depression severity and participants at highest risk for suicidality based on clinician assessment, those with a self-reported suicide attempt within the past year, and those felt likely to require hospitalization during the course of the study will be excluded. The comprehensive exam will also include a history and physical exam by the study PI (pulse oximetry measurements will be a component of the respiratory evaluation) and baseline medication evaluation for potential harmful interactions. Urine pregnancy tests will be completed for every woman of childbearing potential. Urine drug screening will be collected at baseline and prior to each ketamine session to monitor

for opioid and other illicit substance use. For patients currently taking methadone, ECG will be performed to assess for cardiac function with QTc interval of 450ms or longer being exclusionary. Assessments may be conducted by telehealth with vital signs to be provided by participant's home or pharmacy measurement.

7.5 Intervention Visit Procedures

Prior to administration of the study compounds, participants will complete self-report questionnaires and clinical assessments. The study physician will disinfect the subject's shoulder using an alcohol wipe, and the study physician will then administer the medication by intramuscular administration into the participant's deltoid muscle. Vital signs will be monitored prior to treatment, and at 60 minutes post-treatment. If during the post-administration observation period, ketamine administration causes an increase in systolic or diastolic blood pressure >30 mm Hg from baseline, or an increase in pulse rate >30 bpm from baseline, the subject will be treated with standard of care antihypertensives (i.e. clonidine), and repeat vital sign measurements will be taken approximately every 20 minutes until blood pressure and pulse are within 30 points of baseline values. Standard of care antihypertensive medications will be procured via intrainstitutional transfer from MUSC investigational drug services pharmacy distribution center. They will be stored in a DHEC compliant locked box within a locked room accessible only to study team members. If the subject experiences symptoms of hypertensive emergency, the subject will not receive further administration of ketamine and will be withdrawn from the study. After completion of the injection, participants until returned to baseline per clinical assessment which time they will undergo debriefing and complete assessments of their perceptual experience of the intervention. We will evaluate the effects of a weekly interventions for 8 sessions. Participants will return for follow-up assessment 1, 2, 4 and 8 weeks following final medication session. Follow-up visits may be conducted by telehealth.

8.0 DATA MANAGEMENT

8.1 Data Analysis Plan

Baseline demographic characteristics will be collected, and descriptive statistics will be used to characterize participants. Data will be collected and managed using the secure REDCap (Research Electronic Data Capture) database.

8.2 Data Confidentiality Procedures

We will take rigorous precautions to maintain confidentiality for all participants, using procedures that the PI and his mentors have successfully employed in similar previous, as well as ongoing related studies. All study data related to mental health outcomes (i.e., the participant responses to questionnaires) and demographics will not have any unique identifying data attached. There will be only one master list of participants (not linked to participant responses). This list will be kept locked separate from other data and will be available only to the PI, his mentors, and approved study personnel. All data will be confidentially stored (i.e., in locked files or on encrypted servers) so as to protect the confidentiality of participant information. Access to research records (paper and computerized) will be restricted to the project staff, and to sponsor audit personnel and MUSC IRB auditors when indicated. All study personnel have completed (or will complete upon hiring) a certified program of instruction in the protection of human subjects in research, such as the University of Miami CITI course. These courses in the responsible conduct of research and the protection of human subjects will be completed on an annual basis, in compliance with MUSC regulations.

8.3 Data Quality Control Procedures

Data quality will be monitored by random inspection of the completed forms by the study team and any irregularities or problems detected will be discussed with the PI.

8.4 Study Documentation and Data Handling

Any clinical study event that is judged to be an AE will be recorded on the AE form during the course of the study. The PI and/or trained Research Assistant will ensure this information is captured during every study visit. Whenever a study participant has reported an AE, the study coordinator will discuss the event immediately with the PI (if possible while the study participant is there) who will evaluate the event. If the AE is not serious, the information will be recorded, managed medically as appropriate, and the event will be followed until resolution. SAEs will also be recorded on the AE Form, managed medically as appropriate, and the event is followed until resolution. In addition, the PI will review all completed AE forms for determination of SAE. All SAE reports will be sent to the MUSC IRB within 24 hours of learning of event occurrence.

AEs/SAEs will be documented and reported as per IRB requirements. Research staff will identify AEs and obtain all available information to assess severity, seriousness, study relatedness, expectedness, outcome and the need for change or discontinuation in the study intervention. Adverse events will be documented on AE Logs and additional relevant AE information, if available, will be documented in a progress note in the research record as appropriate to allow monitoring and evaluating of the AE. If the AE meets the definition for Serious, appropriate SAE protocol specific reporting forms will be completed and disseminated to the appropriate persons and within the designated timeframes as indicated above. For each AE/SAE recorded, the research staff will follow the AE/SAE until resolution, stabilization or until the participant is no longer in the study. When a reportable SAE is identified, the research assistant will initiate an SAE form, and the following individuals will be notified within 24 hours of the site's initial notification of the SAE:

1. The PI (Dr. Dobson) will provide oversight, consultation, assessment, and documentation as appropriate of the SAE.
2. The research staff will notify the MUSC IRB, and complete the AE report form in conjunction with the PI. Communication with the MUSC IRB is through email, memos, official IRB forms, and online reporting.

If complete information is not available when the initial 24-hour SAE report is disseminated, follow-up information will be gathered to enable a complete assessment and outcome of the event. This information may include hospital discharge records, autopsy reports, clinic records, etc. The research staff will attach copies of source documents to the SAE report for the PI and for forwarding to the sponsor as appropriate. All deaths that occur during the study or 30 days post termination from the study are required to be reported as adverse events even if they are expected or unrelated. Other adverse events are reportable to the MUSC IRB if the AE is unexpected AND related or possibly related AND serious or more prevalent than expected. All three criteria must be met for an AE to be reported to the MUSC IRB. The IRB definition of unexpected is that the AE is not identified in nature, severity or frequency in the current protocol, informed consent, investigator brochure or with other current risk information. The definition of related is that there is a reasonable possibility that the adverse event may have been caused by the drug, device or intervention.

8.5 Privacy Protection and Confidentiality Assurances

While absolute confidentiality cannot be guaranteed, every possible effort will be made to protect the privacy of study participants, and all of the investigators have an excellent history of maintaining subject privacy and data security. Participants will be provided with a written informed consent document which specifies the risks and confidentiality protections and limits of study procedures. Subject names will remain confidential and all study data related to outcomes (i.e., the participant responses to questionnaires) and demographics will not have any unique identifying data attached in any way. There

will be only one master list of participants (again, not linked to any participant responses) which will be kept locked separate from all data and will be available only to the PI, Co-Is and approved study personnel. All data will be stored in a confidential manner (i.e., in locked files or on encrypted computers) so as to protect the confidentiality of participant information. Access to research records (paper and computerized) will be restricted to the project staff. Access to de-identified study data will be limited to named PI, co-Is and MUSC IRB auditors.

8.6 Data Sharing

The data collected from study participants, including PHI, will be entered into and securely stored in the database on a secure server by a member of the research study team. Electronic data will be stored, managed, and analyzed by the study PI and his statistical advisor.

9.0 PROVISIONS TO MONITOR THE DATA TO ENSURE THE SAFETY OF SUBJECTS

Ongoing Clinical Monitoring: The research team will closely monitor for any increase in substance use or psychiatric distress at every study intervention visit. Subjects with clinically significant worsening of depression (i.e. development of suicidal ideation) or worsening of opioid use will be immediately referred for a higher level of treatment, and the PI will review trial safety. The PI will be responsible for assessing potential participants for inclusion and exclusion criteria, and for assessing for adverse effects (AE's) throughout the trial. AE's will collected, documented, and reported. If the AE is not serious, the information will be recorded, managed medically as appropriate, and the event will be followed until resolution. SAEs will also be recorded on the AE Form, managed medically as appropriate, and the event is followed until resolution. In addition, the PI will review all completed AE forms for determination of SAE. All SAE reports will be sent to the MUSC IRB within 24 hours of learning of event occurrence. The PI will be responsible for withdrawal of a study participant if they become pregnant or feel that participation is no longer in a subject's best interests. Mental health symptoms will be monitored using standardized measures at each visit in order to detect any worsening symptoms. Additionally, participants will be advised to observe any signs of worsening substance use or depression symptoms, and to discuss these with the research team. All participants will be informed at the initial visit that they may terminate participation at any point. If a participant experiences distress or other problems between visits, he or she will be encouraged to contact Dr. Dobson or his/her outpatient mental health provider. If a participant needs or desires immediate attention, arrangements will be made for an appointment with an experienced mental health provider. The informed consent document will provide direction to contact the study staff during office hours and/or go to the Emergency Room at any time for worsening of symptoms. In addition, participants will have access to urgent care services at MUSC. If any of the research personnel believes that a participant is medically or psychiatrically compromised by participation, the PI will be notified and will contact the participant immediately to assess concerns and assure participant safety. The PI will attempt to address all participant concerns and will set up an alternate referral for counseling for those who desire it from outside the project. All participants will review, at the initiation of participation, an informed consent document which specifically reviews potential psychological distress as a potential outcome of participation. If necessary, the participant will be asked to complete a safety plan and to call the project staff, a national hotline, or 911. The Mobile Crisis unit of Charleston County, which involves a team of police and psychiatric workers, or the EMS unit may be dispatched to the participant's home to assure safety. The investigative team has a long history of ensuring participant safety using similar methods in these populations.

Pre-Intervention Assessment: A comprehensive exam will be conducted as part of the baseline assessment to minimize risks from study participation. This will include assessment of depression severity, and participants at highest risk for suicidality will be excluded. The comprehensive exam will also include a history and physical exam by the study PI (pulse oximetry measurements will be a component of the respiratory evaluation), baseline medication evaluation for potential harmful interactions, and electrocardiogram to ensure safe study participation.

Peri-Intervention Monitoring: Subjects will be continuously medically and psychiatrically monitored throughout the course of the intervention and until return to medical and psychiatric baseline. Subjects will be instructed not to eat for at least 2 hours before taking the intervention sessions to reduce the risk of nausea and vomiting. Emergency services will be contacted in the event of any medical complications. Subjects will not be allowed to drive themselves after the interventional visits, and alternative transportation will be arranged if needed.

10.0 WITHDRAWAL OF SUBJECTS

All potential participants will be thoroughly screened for eligibility after completing informed consent. The PI may withdraw subjects from participation at any time if the participant demonstrates or reports significant distress, is felt to be at risk of harm to themselves or to others, or is otherwise unable to complete the study protocol. Referrals to university and community resources will be made as indicated for all participants withdrawn from the study. The trial will be stopped under any of the following conditions: 1) there is clear evidence of harm; 2) there is no likelihood of the intervention demonstrating benefit, or 3) there is overwhelming evidence of the benefit of the intervention.

11.0 RISKS TO SUBJECTS

11.1 Overview

All medications have potential side effects. Ketamine has been well studied since its FDA approval in 1970. Based on extensive prior research with intravenous ketamine in the treatment of depression, the prevalence of the most commonly observed adverse reactions are estimated below by category. Participants will be informed of potential side effects associated with ketamine before study participation, and will be closely monitored both during the treatment and at each follow-up visit.

11.2 Physical Risks

The most significant physical adverse event from ketamine is a transient increase in blood pressure, which in previous studies was experienced by 29.8% of subjects with a mean systolic blood pressure increase of 19.6 mmHg +/- 12.8 mmHg and a mean diastolic blood pressure increase of 13.4 mmHg +/- 9.8 mmHg. Peak levels are reached on average 40 minutes post-treatment and resolve by 240 minutes post-treatment (Wan et al., 2015). Participants experiencing clinically significant hypertension (greater than 180 mmHg SBP or greater than 105 mmHg DBP, or greater than 30 mmHg SBP or DBP from baseline values) will be treated with standard of care hypertensives (e.g. clonidine) and monitored until symptom resolution.

The most prevalent physical adverse effect was transient sedation and occurs in approximately 16% of patients receiving ketamine. Sedation will be monitored via continuous clinical observation during interventional sessions. A medical emergency team will be called for participants that are unable to be aroused with painful trapezius squeeze or that experience hypoxia (i.e. a pulse oximeter reading of 92% or less), although in the investigative team's extensive experience using ketamine clinically for depression at these doses, such serious events have never occurred. Vital signs will be routinely monitored during treatment and emergency airway equipment will be immediately available. Subjects will be monitored for 2 hours post-dose by trained healthcare professionals (*eg* PI, co-I, or study nurse). Due to transient cognitive impairment associated with sedation, participants will not be allowed to drive themselves following the interventions. Subjects who do not have transportation and live within 20 miles will receive compensation for taxi, Uber or Lyft transportation to and from medication sessions up to $100 each way. Subjects who live greater than 20 miles from the study site and cannot arrange their own transportation will be excluded from the study. Participants will be advised not to operate heavy machinery for at least 24 hours after the interventions.

There are also the standard risks associated with intramuscular injections including temporary local pain, irritation, or redness at the site of the injection. There is a very small (<1%) risk of infection, muscle fibrosis, or persistent muscle or nerve damage at the site of injection.

11.3 Psychological Risks
Ketamine commonly causes transient dissociation (including derealization and depersonalization) and perceptual changes (e.g. distortion of time and space, sense of illusions). Based on prior studies these effects occur in 42% of subjects receiving ketamine. Anxiety occurs in 15% of subjects receiving ketamine. Psychological distress will be minimized with pre-treatment relaxation exercises and psychological reassurance as needed. Psychological distress will be minimized with pre-intervention relaxation exercises and reassurance as needed. In prior trials with ketamine for depression, these measures are sufficient to manage dissociation and anxiety in the overwhelming majority of participants. However, standard of care medications for agitation (e.g. benzodiazepines) will be available in the event that participants develop severe anxiety psychological distress unmitigated by reassurance and relaxation exercises. Psychiatric hospitalization will be arranged if needed, in the unlikely event of severe or prolonged psychiatric symptoms (e.g. lasting greater than four hours or the business day). Participants may also have emotional distress from answering the questionnaires, although this is mild in the investigators' experience with these instruments.

11.4 Abuse Liability
Ketamine is a psychoactive substance and is considered to have abuse liability. Ketamine is classified as Schedule III controlled substances (CIII). While there have been no randomized controlled trials evaluating the risk of subsequent illicit or recreational use of ketamine following medical administration (either for induction of sedation in conjunction with general anesthesia or in monitored off-label use for depression or pain management), in the extensive sub-anesthetic trials of ketamine for depression, there have been no published reports of illicit use developing after initial medical treatment with ketamine. None of the previous studies using ketamine in the treatment of substance use disorders reported illicit ketamine use following the ketamine interventions (Jones et al., 2018). Animal models using intracranial self-stimulation have demonstrated that ketamine fails to progress to self-administration, also suggesting a lack of abuse liability. Globally, the World Health Organization (WHO) evaluates the overall risks and abuse liability of ketamine; in their most recent report, the WHO affirmed that ketamine does not pose a global health risk, and again recommended its continued use (WHO, 2016). Substance use will be assessed at each visit throughout the study, and participants will be referred for ongoing care if they develop new or worsening substance use. If participants report illicit use of ketamine between intervention sessions, they will be withdrawn and referred for substance abuse treatment.

11.5 Social Risks: Adverse social consequences may arise if the participants' medical history or psychiatric history (including substance use history as well as psychiatric comorbidities) are inadvertently communicated to others.

11.6 Legal Risks: Legal risks may arise if individuals are homicidal or suicidal and make these intentions known to the PI project staff, who may then be required to notify authorities and the target of homicidal intent. There is also a legal and physical risk if participants were to drive or operate heavy machinery while cognitively impaired. Subject will be advised against operating heavy machinery following treatment.

11.7 Economic Risks: Subjects will be reimbursed for travel expenses including taxi, Uber or Lyft fare within 20 miles of study site as well as for any medical care related to study-related injuries. Subjects will not be compensated for medications sessions but will receive $15 for each follow-up session completed.

11.8 Other Risks: While every possible effort will be made to protect the privacy of study participants, there is a risk of loss of confidentiality. There may also be unknown risks associated with the study procedure or intervention.

12.0 POTENTIAL BENEFITS TO SUBJECTS OR OTHERS

12.1 Potential Benefits to Subjects
Potential benefits of participation in this study may include a reduction in depression symptoms. Participants may also gain diagnostic information about their medical or psychiatric comorbidities,

although this is not guaranteed. Overall, there is no guarantee or promise that participants will receive any benefit from participation in this study.

12.2 Justification of Risks

The potential benefits of the knowledge to be gained from the proposed study are considerable. This study proposes to test intramuscular ketamine in the treatment of co-occurring OUD in early or sustained remission and MDD among participants. The plans for monitoring risk as described above warrant the conduct of this study for the knowledge that may reasonably be expected to result.

13.0 SHARING OF RESULTS WITH SUBJECTS

The data collected from study participants, including PHI, will be entered into and securely stored in the database on a secure server by a member of the research study team. Electronic data will be stored, managed, and analyzed by the study PI and a statistical mentor advisor. Individual baseline data may be released to participants on request for their subsequent medical use or disclosure.

14.0 DRUGS OR DEVICES

The IND application for ketamine's use in this study has been submitted by PI for FDA review. IND number 159117 has been issued by the FDA. Study will not begin until a Study May Proceed letter is received from the FDA. Medication and placebo will be stored in lock boxes on the MUSC campus and be administered by the PI or co-I.

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