PROTOCOL TITLE: Ketamine-assisted Motivational Enhancement Therapy for the Treatment of Tobacco Use Disorder

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1.0 BACKGROUND

1.1 Introduction and Context

Tobacco use causes more than 7 million deaths per year worldwide (WHO, 2022) and continues to be the leading modifiable risk factor for cancer globally (Tran et al., 2022). In the United States, it remains the single largest preventable cause of disease, disability, and premature death with an estimated life expectancy of 10 years shorter than that of a non-smoker. Unfortunately, in the year 2020, 12.5% of U.S. adults (30.8 million people) continue to smoke cigarettes (CDC, 2022 Aug) despite the multiple smoking cessation treatments available. While the forms of tobacco use are changing, such as the increasing use of e-cigarettes, a 2019 study showed cigarettes remain the most commonly used tobacco product (CDC, 2020).

Among individuals who currently smoke cigarettes, over 2/3 (68%) have reported a desire to quit (CDC, 2022 Mar). In 2018, 55.1% of smokers reported making at least one quit attempt in the past year, however, only 7.5% of people who tried to quit succeeded (CDC, 2022 Mar). Overall, those who use smoking cessation therapies, such as counseling and medications, had a higher success rate than those who did not. For example, abstinence rates were 15% in people who used assistance versus 7% in those who did not at 12 month follow up (Shu-Hong, 2000), however, the rate of sustained abstinence continues to be low (Babb et al., 2017). While the proven benefit of both non-pharmacological and pharmacological therapy in many patients is encouraging, there is a need for additional treatments.

1.2 Current treatment for smoking cessation

There have been many studies showing the benefit of pharmacologic treatment in the assistance of smoking cessation. While the proportion of smokers who benefit from smoking cessation medications decreases during the first year of use, a net benefit remains at 12 months. Specifically, a meta-analysis reported an abstinence rate of 20% in people who attempted smoking cessation with medications versus 11% without medications at 12 months (Rosen et al., 2018). Common medications studied include nicotine replacement therapy (NRT), varenicline, and certain antidepressants. These medications have a variety of mechanisms proposed to treat the associated nicotine dependence of cigarette smoking. Varenicline is classified as a selective nicotinic receptor partial agonist, a pathway thought to affect the release of dopamine in the midbrain. A meta-analysis showed varenicline having a two- to threefold increase chance of successful long-term smoking cessation compared with pharmacologically unassisted quit attempts (Cahill et al., 2012). The most common antidepressant studied for smoking cessation is bupropion. Nortriptyline has also shown to be efficacious, however, serotonin reuptake inhibitors have not been shown to be helpful (Hughes et al., 2004). Bupropion has dopaminergic and noradrenergic activity while nortriptyline has relatively weak dopaminergic but significant noradrenergic activity. A Cochrane review showed bupropion doubles the odds of quitting smoking (Hughes et al., 2004). NRT replaces the form of nicotine by acting on the same nicotinic receptors as cigarettes, showing to be helpful when compared to no treatment. A Cochrane review reported NRT helps to increase the rate of quitting by 50-70% (Stead et al., 2012). When comparing these medications, there have been studies showing more participants quitting successfully with varenicline than with bupropion but limited studies comparing varenicline to NRT. There have been a small number of studies directly comparing bupropion with NRT with some heterogeneity but tend to favor bupropion (Hughes et al., 2004). This may suggest that if varenicline is more efficacious than bupropion, it may also more efficacious than NRT.

Behavioral treatments have also been shown to increase quit rates at 6 months even in the abstinence of pharmacotherapy. Specific interventions include, but are not limited to, motivational interviewing, CBT, and mindfulness-based therapy. A Cochrane review showed motivational interviewing resulted in improved quit rates when compared to brief advice (Lindson-Hawley et al., 2015). When looking at mindfulness-based therapy, a meta-analysis concluded it did not have a significant improvement in abstinence over other behavioral interventions (Maglione et al., 2017). A Cochrane review looking at

various interventions showed benefit with any form of counseling (Hartmann-Boyce at al., 2021) and there has been no current consensus favoring one form of behavioral intervention. Additionally, when combining the results of studies in a meta-analysis, individual counseling compared to minimal intervention could increase the chance of quitting by 50-80% (Lancaster & Stead, 2017).

It is well established that pharmacotherapy and non-pharmacotherapy can both individually help with smoking cessation, however, combining pharmacotherapy and behavioral support has shown to further increase smoking cessation success (Patnode et al., 2021; Stead et al., 2016; Lancaster & Stead, 2017). Combined pharmacotherapy and behavioral intervention improved quit rates from an average of 8.6% in those receiving usual care to 15.2% (Patnode et al., 2021). While these interventions can have substantial clinical benefit, the rate of people who continue to smoke indicates a need for novel treatments.

1.3 Clinical trials for substance use and the rational for treatment with ketamine

Ketamine has shown early evidence of efficacy in the treatment of multiple types 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 (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% (Krupitsky et al., 2007). Related studies found that ketamine is useful as an adjunct to psychotherapy in the treatment of alcohol use disorder (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. Additionally, motivational enhancement therapy combined with just one ketamine infusion was shown to improve likelihood of abstinence from alcohol when compared to midazolam (Dakwar et al., 2020). Ketamine has also been studied in cocaine use disorder and found to improve levels of motivation to quit using and reduce cocaine craving (Dakwar et al., 2014) as well as reduce rates of cocaine self-administration by 67% relative to baseline (Dakwar et al., 2017). When ketamine was combined with mindfulness-based relapse prevention therapy for cocaine use disorder, it was shown that 48% of subjects who had the addition of one ketamine infusion were abstinent after 2 weeks compared to 10% of those who received a midazolam infusion (Dakwar et al., 2019). The benefit of ketamine treatment across several different substance use disorders as well as the synergistic effect of adding ketamine to various methods of psychotherapy suggests there may be an underlying mechanism and therefore a role for ketamine in the treatment of other substance use disorders such as tobacco dependence.

1.4 The neurobiology of tobacco use dependence

While there are about 9000 chemicals in cigarette smoke, nicotine is the major psychoactive ingredient and the component most associated with tobacco dependence. There are multiple proposed underlying mechanisms leading to nicotine dependence that current smoking cessation medications have targeted, including both the sensitization of nicotinic receptors in the ventral tegmentum area (VTA) after a period of abstinence as well as conditioned stimuli throughout the day after the nicotinic receptors have been desensitized (Fagerström & Balfour, 2006). The main areas of study have involved the mesocorticolimbic dopamine system, specifically the VTA projecting to the nucleus accumbens (NAc). Nicotine stimulates the mesocorticolimbic dopamine system via nicotinic acetylcholine receptors in the VTA causing increased firing of dopamine in the NAc (Mahajan et al., 2021). However, preclinical studies have also shown other critical interactions contributing to nicotine dependence with influences not only of dopamine and acetylcholine but also glutamate and GABA in the limbic system, prefrontal cortex, amygdala, and hippocampus (Markou, 2008). There is also another neurobiological pathway thought to be involved in aversive processing and nicotine withdrawal. This consists of the projection from the medial habenula to

the interpeduncular nucleus with major neurotransmitters being acetylcholine, glutamate, and substance P and could potentially have a role in limiting drug intake (Fowler et al., 2019). Furthermore, tobacco smokers have shown to have both structural and functional connectivity changes within the brain. For example, smoking can reduce gray matter volume in the orbitofrontal circuit (Li et al., 2015) and nicotine can temporarily increase fMRI signal in the striato-thalamo-orbitofrontal circuit (Bruijnzeel et al., 2015). The underlying mechanisms of these changes are multifactorial and likely involve multiple frontal-cortical inhibitory and excitatory balancing systems involved in nicotine dependence. While there has been past focus on the development of smoking cessation medications targeting the nicotinic system and dopaminergic system, the complexity of nicotine dependence shows there are other potential neurobiological targets for pharmacologic intervention.

1.5 Innovation and Importance of the Current Study

There are promising results in past studies of ketamine in the treatment of other substance use disorders (Krupitsky et al., 2002; Krupitsky et al., 2007; Dakwar et al., 2014; Dakwar et al., 2017). Given these studies, the neurobiological similarity between various substance use disorders (Uhl et al., 2019), and the potential influences of ketamine on the underlying neurological circuitry (Ezquerra-Romano et al., 2018), it would be beneficial to assess the role of ketamine in nicotine dependence. There has been one animal study showing reduction of nicotine self-administration in rats given ketamine, suggesting there may be an underlying mechanism of ketamine helpful in reducing nicotine use (Rezvani et al., 2018), however, there are currently no past studies in humans studying the effects of ketamine on smoking cessation.

2.0 PURPOSE/SPECIFIC AIMS

2.2 Purpose and Objectives of the Study

The primary objective of the proposed study is to preliminarily explore the feasibility, efficacy, and tolerability of ketamine in the treatment of tobacco use disorder associated with cigarette use. We seek to enroll 8 individuals with tobacco use disorder who use cigarettes.

2.3 Specific Aims

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

- **Specific Aim 1:** To assess the feasibility of using ketamine-assisted brief motivational enhancement therapy in the treatment of cigarette smoking cessation
- **Specific Aim 2:** To preliminarily explore the efficacy, safety, and tolerability of ketamine-assisted brief motivational enhancement therapy for smoking cessation

3.0 STUDY DESIGN/METHODS

3.1 Study Overview

This is an open label trial of ketamine-assisted psychotherapy to assess the efficacy and safety of weekly intramuscular injections of ketamine in the assistance of smoking cessation. This will be determined by evaluating the severity of craving as well as the number of cigarettes smoked the week prior to each session and at each follow up.

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.

3.2 Duration of Intervention and Study

Participants will complete a total of 6 study visits (including baseline assessment and follow-up assessments) as shown in **Table 1**. Medication sessions with intramuscular ketamine will occur weekly for three weeks. Participants will meet virtually or in person for follow-up at 4 and 8 weeks following final medication session.

3.3 Description of Assessments

For full description of assessments, see exploratory outcomes (section 6.3).

3.4 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 1-3 (Wk 1-3)	Follow-up (Wk 4, 8)
Self-Reports and Consents				
Informed Consent	Obtain informed consent	X		
Demographics Form	Sample characterization	X		
General Anxiety Disorder (GAD-7)	Self-report of anxiety symptom severity	X	X	X
Insomnia Severity Index (ISI)	Measure of insomnia severity	X	X	X
Mystical Experiences Questionnaire (MEQ)	Measure of perceptual experiences	X	X	X
Five Facets of Mindfulness (FFMQ)	Assess aspects of mindfulness related	X	X	X
Fagerstrom Test of Nicotine Dependence (FTND)	Measure of nicotine dependence	X	X	X
Questionnaire on Smoking Urges (QSU)	Assessment of smoking cravings	X	X	X
Wisconsin Smoking Withdrawal Scale 2 (WSWS2)	Measures severity of smoking withdrawal	X	X	X
Timeline Follow-Back (TLFB)	Measure of substance use	X	X	X
Rhode Island Change Assessment (URICA)	Measure of stage of change	X	X	X
Beck Depression Inventory (BDI-II)	Self-report of depression symptom severity	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*	
Pre-screening Questionnaire	To assess for basic eligibility criteria before completing a full baseline visit.	X		

Urine Pregnancy Test (female subjects only)	Eligibility assessment	X	X	
Electrocardiogram (ECG; subjects with cardiac comorbidities or on QTc prolonging medications only)	Assessment of cardiac function	X		
Urine Drug Screen	Assess for use of psychoactive substances	X		
Salivary cotinine level	Assessment of smoking status	X	X	X

* Vital signs (blood pressure, pulse, respiratory rate, and pulse oximetry) will be obtained pre- and post-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.

3.5 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. 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 at the initial assessment and prior to each treatment session. Urine drug screens will be completed for all participants at the initial assessment to detect use of recreational psychoactive substances other than nicotine. Saliva cotinine levels will be measured at baseline, prior to each ketamine session and at 3 month follow up to detect smoking over approximately the previous 6 days. An ECG will be performed in participants with QTc interval of 450ms or longer in males or 460ms in females being exclusionary.

3.6 Intervention Visit Procedures

Prior to administration of the study compounds, participants will complete self-report questionnaires and clinical assessments. Motivational enhancement therapy will be provided before and after ketamine administration, where the reduction of cigarettes and the subject's short and long term smoking-related goals will be discussed with the study physician. The study physician will then 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. Only individuals who are properly licensed will perform the injection of ketamine. Vital signs will be monitored prior to treatment and 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 a standard of care antihypertensive (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. Medications 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 be treated with standard of care antihypertensive agents and referred for further assessment and treatment. Subjects experiencing serious adverse effects related to study participation will not receive further administration of ketamine and will be withdrawn from the study. After completion of the injection, when participants return to their neurocognitive baseline per clinical

assessment, they will complete assessments of their perceptual experience of the intervention. We will evaluate the effects of the 3 weekly interventions in 2 follow up sessions. Participants will return for follow-up assessments 4 and 8 weeks following final medication session. Follow-up visits may be conducted by telehealth. If the follow up is done via telehealth, participants will be given their saliva cotinine tests in advance either at an in person visit or by mail and asked to return them by mail.

4.0 INTERVENTAL PRODUCTS

4.1 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).

4.2 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).

4.3 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 0.71mg/kg. The participants will be weight for proper injection dosage at each treatment visit. This dose of 0.71mg/kg is consistent with previous studies using intravenous ketamine showing improvement in substance use (Dakwar et al., 2020; Dakwar et al., 2019). Recent studies have also shown that intramuscular ketamine may be as effective as intravenous ketamine when studied for depression and may be more practical clinically (Chilukuri et al., 2014; Xu et al., 2016). When given intramuscularly, ketamine has a peak time of 5-30 minutes following injection and a bioavailability of 86-97% (Grant et al., 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).

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 self-reported current tobacco use will be eligible to complete informed consent and baseline evaluation.

5.2 Inclusion Criteria

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

1. 21 to 65 years old.
2. Able to provide informed consent.
3. Be a daily cigarette smoker with multiple unsuccessful previous quit attempts, and report a continued desire to quit smoking.
4. Agree to abstain from smoking for the ketamine session from 1 hour before ketamine administration
5. Agree to refrain from using any psychoactive drugs, including alcoholic beverages, within 24 hours of ketamine administration. Exceptions include caffeine and nicotine.
6. Subjects taking other psychotropic medications must be maintained on a stable dose for at least four weeks before study initiation.
7. Be healthy as determined by screening for medical problems via a personal interview, a medical questionnaire, a physical examination, an electrocardiogram (ECG) to verify normal QTc intervals.
8. Subjects with normal blood pressure not on antihypertensive medications or medication controlled hypertension as defined baseline visit systolic blood pressure (SBP) <140 mmHg or a diastolic blood pressure (DBP) <90 mmHg.

5.3 Exclusion Criteria

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

1. Women who are pregnant (positive pregnancy test) or nursing, or are not practicing an effective means of birth control which can include oral, implant, intrauterine device, or patch contraceptive methods as well as barrier contraceptive methods, history of surgery such as hysterectomy or tubal ligation, or abstinence
2. Subjects who meet DSM-5 criteria for current or history of psychotic spectrum disorders or current depression or bipolar disorder based on clinical interview.
3. Subjects meeting DSM-5 criteria for current substance use disorder other than tobacco use disorder.
4. Subjects with hypertension as defined by a baseline visit systolic blood pressure (SBP) >140 mmHg or a diastolic blood pressure (DBP) >90 mmHg.
5. A history of allergic or other adverse reaction to ketamine (or its excipients).
6. 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).
7. Cardiovascular conditions: uncontrolled hypertension, angina, a clinically significant ECG abnormality (e.g., atrial fibrillation), TIA in the last 6 months, stroke, peripheral or pulmonary vascular disease
8. Subjects who live greater than 20 miles from the study site and cannot arrange their own transportation will be excluded from the study.
9. Subjects with clinically significant kidney or liver impairment.
10. Have any current neurological illnesses including, but not limited to, seizure disorders, frequent migraines or on prophylaxis, multiple sclerosis, movement disorders, history of significant head trauma, or CNS tumor.
11. Morbidly obese (BMI >40), or severely underweight as determined by medical examination.

5.4 NUMBER OF SUBJECTS

Approximately 8 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, for example primary care clinics, relevant pulmonology clinics, smoking cessation clinic.

Initial screening eligibility will be conducted by the PI or trained research personnel. Subjects with self-reported current tobacco use will be eligible to complete informed consent and baseline evaluation.

6.0 STUDY ENDPOINTS

6.1 PRIMARY OUTCOMES

- The primary outcome of this study will be the feasibility of using ketamine-assisted treatment for smoking cessation, which will assess the number of people selected for randomization that complete the full treatment. This will help determine if the treatment of ketamine in tobacco use would be beneficial for further study.

6.2 SECONDARY OUTCOMES

- Saliva cotinine levels will be collected prior to each ketamine session and at each follow up to detect smoking over approximately the past 6 days. Salivary cotinine levels of <15ng/mL have been considered as biological verification of non-smoking status (Benowitz et al., 2020)
- Time-line Follow Back (TLFB) (Sobell & Sobell, 1992) will be assessed at baseline, each treatment session, and at follow-ups. TLFB is a self-report calendar completed retrospectively by participants indicating the number of cigarettes smoked each day (Sobell and Sobell, 1992). The TLFB yields consistently high test-retest correlations and correlates well with other self-reports and collateral reports. Use of other drugs of abuse, including prescription drugs, will also be assessed using the TLFB.

6.3 EXPLORATORY OUTCOMES

Exploratory outcomes will include changes in characteristics related to cigarette use including craving for cigarettes (QSU, SASE, WSWS, FTND) and related areas of psychiatric functioning.

- Fagerstrom Test of Nicotine Dependence (FTND): a 6-item questionnaire used to measure the level of dependence of cigarette smokers (Fagerström et al., 2012).
- Questionnaire on Smoking Urges (QSU) is a multidimensional assessment of smoking craving with demonstrated sensitivity to smoking cessation (Tiffany & Drobes, 1991). It will be assessed at baseline, during interventional visits, and at each follow-up visit.
- Wisconsin Smoking Withdrawal Scale 2 (WSWS2): measures severity of smoking withdrawal and exhibits good validity and reliability in smoking cessation studies (Shiffman et al., 2004; Welsch et al., 1999; Smith et al., 2021). It will be assessed at baseline, during interventional visits, and at each follow-up visit.
- Generalized Anxiety Disorder Screener (GAD-7) (Spitzer et al., 2006)): The GAD-7 is a 7-item self-report instrument that will assess generalized anxiety symptomology. It will be assessed at baseline, during interventional visits, and at each follow-up visit.
- Insomnia Severity Index (ISI): found to be a reliable and valid tool to quantify perceived insomnia severity and can be useful as an outcome measure in research studies (Bastien, 2001).
- 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 et al., 2015; Maclean et al., 2012). It will be assessed at baseline, during interventional visits, and at each follow-up visit.

- Five Facets of Mindfulness Questionnaire (FFMQ) (Baer et al., 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. It will be assessed at baseline, during interventional visits, and at each follow-up visit.
- Rhode Island Change Assessment (URICA) (Stephens et al., 2004): The URICA is a questionnaire designed to measure stage of change in psychotherapy with four scale scores derived corresponding to the precontemplation, contemplation, action and maintenance stages. It will be assessed at baseline, during interventional visits, and at each follow-up visit.
- Beck Depression Inventory (BDI-II; Beck, Steer, & Brown, 1996). A widely used 21-item self-report measure of depressive symptoms.

7.0 CONSENT PROCESS

7.1 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.

7.2 Location of Informed Consent

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

7.3 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.

7.4 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.

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 her 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, her mentors, and approved study personnel. All data will be confidentially stored (i.e., in locked files or on encrypted servers) 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 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. Amador) 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 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) 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 her 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. 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 be 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. Serious adverse effects (SAE) 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 to detect any worsening symptoms. Additionally, participants will be advised to observe any signs of worsening substance use or psychiatric 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. Amador 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 anxiety severity. 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 post-dose by trained healthcare professionals (*e.g.* 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.

Other rare risks of ketamine include cystitis which are likely due to repeated use of ketamine. There is also a small risk of anaphylaxis.

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. 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.

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 tobacco use. 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 tobacco use disorder 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 165744 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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