Clinical Study Protocol

Study Title: The effects of sedatives on tobacco use disorder (SED-TUD)
Protocol Number: 229077
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Statement of Compliance

The trial will be carried out in accordance with all applicable regulations (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312). All research personnel have completed Human Subjects Protection Training and Good Clinical Practice Training.

I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Principal Investigator

Print/Type Name: _____

Signed: _____

Date: _____

1 Protocol Summary

1.1 Synopsis

Arkansas ranks third in the nation for cigarette smoking prevalence (25% of the population) and ranks second for smoking-attributed cancer mortality (33.5% mortality). There is an urgent need to reduce smoking rates in this state. However, even with counseling and pharmacotherapy, >70% of smokers relapse within 12 months of a quit attempt. More effective interventions for tobacco addiction are sorely needed. A sub-anesthetic dose of ketamine is a novel pharmaceutical agent that has shown promising effects in reducing craving and/or withdrawal symptoms to cocaine, alcohol, and opioids. However, its effects on tobacco use disorder have not yet been tested.

Ketamine is a glutamate N-methyl-D-aspartate (NMDA) receptor antagonist that enhances synaptic plasticity in the prefrontal cortex and subcortical brain areas. Glutamatergic function is altered in depressed patients and a single sub-anesthetic dose of ketamine (0.5 mg/kg) has also been shown to rapidly (within 24 hours) reduce depressive symptoms. Ketamine's enhancement of synaptic plasticity may underlie ketamine's antidepressant effects. Similar to depression, symptoms of substance use disorders may be related to reduced synaptic plasticity in the prefrontal cortex. Ketamine may be altering brain mechanisms common to both depression and drug use since the time course and pattern of ketamine's effects are similar to both disorders. Extensive research in animal models suggests that chronic drug use and the diminished ability to control drug seeking arises from a dysregulation in synaptic glutamate transmission by non-synaptic glial glutamate (i.e., a loss of glutamate homeostasis) at synapses connecting the prefrontal cortex to the nucleus accumbens. Blocking the NMDA receptor, which plays an important role in neuroplasticity, has been shown to disrupt cue-induced drug seeking behavior in rats. Among individuals with cocaine use disorder, ketamine has been shown to decrease craving and improve motivation to quit using cocaine. In particular, non-treatment seeking cocaine users demonstrated decreased craving and an increased preference for money over cocaine in a lab-based model of cocaine use administered 28-hours post-ketamine infusion; subjects also had reduced ad lib cocaine use over the next several days. Ketamine has also been associated with higher abstinence rates among treatment-seeking detoxified heroin users. Thus, ketamine holds potential to disrupt craving and motivation for drug use across different classes of drug use disorders. Given the broad nature of ketamine's effects in addiction, we hypothesize that it may prove to have effects in nicotine dependence.

This proposal will obtain preliminary data on the effect of a single sub-anesthetic ketamine infusion on cigarette craving and smoking behavior as well as measuring its tolerability, and acceptability. This single-blind, placebo-controlled, randomized clinical trial will test 12 non-treatment seeking smokers with a single intravenous infusion of ketamine (0.5 mg/kg) or placebo. Before and 24-hours after the infusion, smokers will undergo lab-based measures of cigarette craving and smoking latency and will also complete diaries of cigarettes smoked per day for 7 days before, and 7 days after, the infusion. Physical and subjective effects and adverse effects will be closely monitored throughout. Previous research suggests that ketamine will produce transient effects on craving and drug use behavior, with effects peaking 24-72 hours after infusion (Dakwar et al., 2017).

Aim 1. Determine the preliminary safety, tolerability, and acceptability of ketamine. Outcomes include physiology (pulse oximetry, vital signs), drug effects, side effects, and symptoms of depression. We hypothesize that relative to placebo, a ketamine infusion will be comparably safe, well tolerated, and acceptable to smokers.

Aim 2. Determine the effects of ketamine on cigarette craving, smoking latency, and smoking frequency. Outcomes include urge to smoke, nicotine withdrawal symptoms, mood,

latency to smoke in a smoking lapse analog task (pre- and post-infusion), and daily smoking frequency. We hypothesize that relative to placebo and baseline, ketamine will reduce craving, nicotine withdrawal, improve mood, increase the latency to smoke, and decrease the number of cigarettes smoked per day.

This pilot study is necessary to estimate the effect size to support future, in depth R01 research. Future research will compare ketamine to other psychoactive agents, including other NMDA receptor antagonists, determine optimal dosing strategies, estimate the duration of ketamine effects. Ultimately, this work could impact the field of tobacco addiction research by providing evidence of an innovative pharmacologic mechanism that promotes smoking cessation.

Study population: Up to 20 adult male and female otherwise healthy tobacco smokers from the Little Rock area will sign informed consent and be assessed for eligibility to participate until 12 (6 ketamine and 6 placebo) have been admitted and complete the study.

Phase: The overarching aim of this study is to assess its feasibility as a phase I/II study.

Description of sites/facilities enrolling participants: The study will be performed at the Psychiatric Research Institute (PRI) at the University of Arkansas for Medical Sciences (UAMS). PRI is a five-story, approximately 100,000 square foot state-of-the-art facility that incorporates inpatient and outpatient facilities, including 40 inpatient beds, research, clinical, educational and administrative space. It is connected to the main hospital at which emergency care can also be received. Two inpatient floors have 24-hr clinical coverage and research-certified nurses to provide back-up coverage for research protocols on the floor. The 4th floor where screening occurs includes two exam rooms, a nursing station and a clinical laboratory for processing samples and specimen storage. Medical backup is provided by the UAMS Psychiatric Research Institute, which has dedicated facilities for inpatient studies and the medical/psychiatric expertise to care for the subjects.

Health screenings will be conducted on the 4th floor of PRI. The drug infusion session will be completed in one of four bays in the UAMS PRI Procedures Suite on the 6th floor of PRI. The PRI Procedures Suite is the location for electroconvulsive therapy treatments and ketamine infusions. Medical staff members have access to both a MECTA and Thymatron machines. Philips vital sign machines incorporated with wireless technology to sync with the patient's electronic medical record. With over 1,300 sq ft, the Suite has a separate waiting area for patients and families, a prep area with four bays, a treatment room, and a separate recovery area with 5 bays. The infusion room has a physiologic monitor that will capture continuous pulse oximetry, heart rate, and electrocardiography, and intermittent non-invasive blood pressure measurements. Wall mounted oxygen, suction, and equipment to deliver positive pressure ventilation is available at the bedside. A crash cart and additional supplies are available.

Description of study intervention: This is a single-blind clinical trial and the study intervention (ketamine or placebo) will occur on 1 day. Participants will have previously completed eligibility screening. On the infusion day, they will report to the PRI, undergo pre-anesthesia physical evaluation, and receive a 20-minute infusion of ketamine (0.5 mg/kg) or placebo. Assessments of vital signs and dissociative state will be obtained every 15 min for 1 hour, then 1 hour later (hour 2). Self-reported drug effects, side effects, and subjective mood and tobacco withdrawal symptoms will be obtained at hour 2.

Study Duration: The duration of the study is anticipated to be approximately 2 years.

Participant Duration: The eligibility screening, study days, infusion day, and follow-up visit will be spread out across 4-6 weeks.

1.2 Schema:
Prior to enrollment: obtain informed consent, screen for inclusion/exclusion criteria, and physical exam. Eligible subjects then randomized to drug condition and complete 7-day smoking diary

Study Day 1: first smoking analogue task and subjective self-report measures

Study Day 2: drug infusion session and safety/tolerability assessments

Study Day 3: second smoking analogue task and subjective self-report measures, complete 7-day smoking diary

Follow-up lab visit (about 8-days post infusion)

1.3 Schedule of Activities:

Procedures	Screening (Day 1)	1st Study visit (Day 8 to 14)	2nd Study visit (Day 15 to 21) drug infusion	3rd Study visit (Day 16 to 22)	4th Study visit (Day 24 to 29)
Informed Consent	x				
Demographics	x				
Employment history	x				
MINI Psychiatric interview	x				
Drug use history questionnaire	x				
Smoking history questionnaire	x				
FTND	x				
Urinalysis	x				
Pregnancy test	x		x		
Vitals	x	x	x	x	x
Serum analysis	x				
ECG	x				
Height	x				
Weight	x				
Breath CO	x	x	x	x	x
BrAC	x	x	x	x	x
7-day smoking diary & CESD	x			x	
QSU		x	x	x	
PANAS		x	x	x	x
MNWS		x	x	x	
Smoking lapse analog task		x		x	
Drug infusion			x		
CADSS			x		
DEQ			x		
SEQ			x		x
Physiological monitoring			x		

2 Introduction

2.1 Study Rationale

This proposal will obtain preliminary data on the feasibility, safety and tolerability of sub-anesthetic ketamine infusion in cigarette smokers. In addition, the impact of ketamine on reducing the severity of withdrawal symptoms and smoking behavior will be explored. This innovative proposal is justified by a large body of preclinical and clinical data supporting ketamine's potential utility and the significance of the research is high due to the need for more effective interventions for tobacco use disorder.

2.2 Background and Significance

Arkansas ranks third in the nation for cigarette smoking prevalence (25% of the population) and ranks second for smoking-attributed cancer mortality (33.5% mortality) (Lortet-Tieulent et al., 2016; Nguyen and Ma, 2016). There is an urgent need to reduce smoking rates in this state. However, even with counseling and pharmacotherapy, >70% of smokers relapse within 12 months of a quit attempt (Ferguson et al., 2005). More effective interventions for tobacco addiction are sorely needed. A sub-anesthetic dose of ketamine is a novel pharmaceutical agent that has shown promising effects in cocaine, alcohol, and opioid use disorders (Jones et al., 2018). However, its effects on tobacco use disorder have not yet been tested.

Ketamine is a glutamate N-methyl-D-aspartate (NMDA) receptor antagonist primarily used as an anesthetic agent. Sub-anesthetic doses of ketamine (0.5 mg/kg) have shown effectiveness in alleviating treatment-resistant depression in clinically depressed populations (Mathew et al., 2012). The antidepressant effect peaks 24-72 hours post infusion (Iadarola et al., 2015) and has been attributed to the modulation of glutamate signaling and the promotion of synaptic plasticity in the prefrontal cortex (Mathew et al., 2012; Murrough et al., 2017). Similar to depression, substance use disorders are associated with increased affective stress and impaired motivation for change. These symptoms, in addition to heightened sensitivity to drug cues, may be related to disrupted synaptic plasticity in the prefrontal cortex (Goldstein and Volkow, 2002; Kalivas, 2008).

Extensive research in animal models suggests that chronic drug use and the diminished ability to control drug seeking arises from a dysregulation in synaptic glutamate transmission by non-synaptic glial glutamate (i.e., a loss of glutamate homeostasis) at synapses connecting the prefrontal cortex to the nucleus accumbens (Kalivas, 2009). This dysregulation contributes to lasting drug-induced changes in synaptic plasticity and dendritic spine morphology. For instance, during the development of drug addiction, long-term depression and long-term potentiation changes in glutamate-mediated synaptic communication between prefrontal and limbic brain regions may attenuate the salience of nondrug reinforcers (e.g., money) while enhancing drug-seeking and drug cue reactivity. Drugs that restore glutamate homeostasis may reset these drug-induced changes and interfere with drug-seeking behavior (Kalivas, 2009). Indeed, blocking the NMDA receptor, which plays an important role in neuroplasticity, has been shown to disrupt cue-induced drug seeking behavior in rats (Bespalov et al., 2000). Among individuals with cocaine use disorder, sub-anesthetic doses of ketamine have been shown to decrease craving and improve motivation to quit using cocaine (Dakwar et al., 2014). In particular, non-treatment seeking cocaine users demonstrated decreased craving and an increased preference for money over cocaine in a lab-based model of cocaine use administered 28-hours post-ketamine infusion; subjects also had reduced ad lib cocaine use over the next several days (Dakwar et al., 2017). Ketamine has also been associated with higher abstinence rates among treatment-seeking detoxified heroin users (Krupitsky et al., 2002). Thus, ketamine holds potential to disrupt craving and motivation for drug use across different classes of drug use disorders.

This project is innovative because ketamine has a distinctly different mechanism of

action than current FDA-approved medications for tobacco withdrawal. Current pharmacotherapies for tobacco addiction include nicotine replacement therapy (a full nAChR agonist), varenicline (a partial nAChR agonist), and bupropion (a norepinephrine-dopamine reuptake inhibitor and nAChR antagonist) (Slemmer et al., 2000). These drugs essentially "substitute" for nicotine, reducing symptoms of nicotine withdrawal and the reinforcing effects of nicotine. While they are about 2x as effective as placebo in promoting tobacco cessation, abstinence rates are typically below 25% among smokers in clinical trials of these medications (Eisenberg et al., 2008). Most problematically, these pharmacotherapies do not adequately diminish cravings and the urge to smoke. In contrast, ketamine blocks the NMDA receptor and has shown potential to disrupt or diminish cravings and the motivation for drug use across several drug classes, suggesting it may be altering the reinforcement process itself. This project will help guide future research on this and other agents that target these neural mechanisms and will have implications for new pharmacotherapies.

The goal of this proposal is to obtain preliminary data on the effects of sub-anesthetic ketamine infusion on cigarette craving and smoking behavior, as well as data on the tolerability and acceptability of the infusion. This small, exploratory phase I/II trial is necessary to justify a larger, more thorough R01 investigation. More research is needed on ketamine's mechanism of action and its effects on tobacco use. Future research will compare ketamine to other psychoactive agents, including other NMDA receptor antagonists, determine optimal dosing strategies, and estimate the duration of ketamine effects. Ultimately, this work could impact the field of tobacco addiction research by providing evidence of an innovative pharmacologic mechanism that promotes smoking cessation.

2.3 Risk/Benefit Assessment

2.3.1 Known Potential Risks

1. Loss of Confidentiality. There is a risk attendant to the confidentiality of medical records, psychological data, drug use history, and self-report data.

2. Ketamine. The dose of ketamine to be administered is below the threshold for anesthesia. Common side effects of ketamine include changes in respiration, heart rate and blood pressure, muscle tremors, diplopia and nystagmus, decreased hunger, nausea, vomiting, pleasant or unpleasant dream-like states, vivid imagery, hallucinations, confusion, excitement, irrational behavior, and anesthesia. Finally, ketamine may produce adverse psychotropic effects that could also exacerbate tobacco withdrawal symptoms. All participants will be clinically monitored according to the American Society of Anesthesiology Standards for Basic Anesthetic Monitoring during infusion of study drug, pulse oximetry, and electrocardiography, and intermittent non-invasive ocillometric blood pressure measurement. Body temperature will be recorded prior to infusion and prior to release. Following completion of the study drug infusion, study personnel will complete and document periodic assessment of oxygen saturation, and level of consciousness at least once every 15 minutes for the first hour of recovery, in addition to variables collected specifically for the purposes of the research protocol.

Although ketamine abuse is very context dependent, being almost entirely confined to clubs and large music parties (De Luca et al., 2012), risks associated with abuse liability of ketamine cannot be ruled out. The abuse liability of ketamine will be measured by assessing drug liking, perceived potency, and desire to take this drug again (Carter and Griffiths, 2009).

3. Intravenous (IV) line/Infusion Procedure. Angiocatheter insertion can cause pain and result in a hematoma. Intravenous line infiltration may cause pain. Participants will be offered comfort measures and observation for rare but serious consequences (e.g., compartment syndrome).

4. Blood Drawing. Subjects will have approximately 20 cubic centimeters (cc) of blood drawn during eligibility screening. Blood drawing can cause some pain and result in a hematoma.

5. Symptoms of Tobacco Withdrawal. Participants will be asked to refrain from smoking for up to 10 hours on 2 occasions during the study. They may begin to experience withdrawal symptoms in this amount of time. Symptoms may include tobacco craving, loss of concentration, negative mood, headache, drowsiness, trouble sleeping, increased appetite, and dry mouth.

6. Nonspecific Risks. Other risks from the rating scales are not beyond usual clinical procedures. Confidentiality of these results are specifically protected by Federal laws, and all records will be identified by code number only, with the master file kept under lock by the PI or data manager.

2.3.2 Known Potential Benefits
The information gained in this study can assist us in developing more effective strategies for treating tobacco use disorder, which ultimately would be of great benefit to society.

2.3.3 Assessment of Potential Risks and Benefits
2.3.3.1 Adequacy of Procedures to Minimize Risks
1. Subject Recruitment and Consent Procedures. Tobacco-dependent volunteers will be recruited via flyers, newspaper, word of mouth, internet, and ARresearch.org. A research staff member experienced in obtaining informed consent will interview subjects to determine interest in participating in this trial. Aspects of the study procedures, risks, and potential benefits will be explained, and any questions will be answered. The subject will be asked questions to ensure an adequate understanding of the study and encouraged to read through the consent form a second time. The subject is asked to read aloud a section of informed consent to ensure that s/he can read (if the person is illiterate, a witness will be found to be present for the entire informed-consent process). If the subject indicates any hesitation about signing the consent form, s/he will be encouraged to leave with the consent form to consider the matter at leisure. If a subject indicates a desire to sign the consent form, both the participant and staff member will sign the form. The staff member will document that the informed-consent process occurred and whether the person's questions were addressed to his/her satisfaction. If at any time the subject exhibits intoxication, sedation, over-agitation, or some form of inattentiveness, the consenting process will be stopped and the interview rescheduled. After obtaining written informed consent for participation in the study and completing all screening procedures, a study physician will review all medical and psychiatric data prior to admitting the subject and beginning medication.

2.3.3.2 Protections Against Risk
1. Our inclusion and exclusion criteria will be applied by experienced professionals, who will be carefully trained and monitored in order to accept only appropriate subjects into the study. Thus, effective screening will exclude subjects who would be placed at a greater risk. Risk level is determined by the medical and psychiatric history, drug use history, the physical examination, and the laboratory studies done prior to beginning this research protocol.

2. Although ketamine abuse is almost entirely confined to clubs and large music parties (De Luca et al., 2012), we will minimize risk of subsequent ketamine abuse after discharge by not informing participants of the actual drugs being studied. Study participants will receive a list of drugs that they could receive and their potential side effects (e.g., placebo, midazolam, ketamine) along with a statement that they will receive 1 of the drugs listed and no drug that is not on the list. Participants will be able to be informed of the actual drugs received once the

entire study has been completed, if they desire, to increase the time interval between having the drug-induced experience and knowing the actual drug. Not knowing exactly what drug they received minimizes the risk that participants will seek more ketamine immediately after the study. This also minimizes the risk that participants who have recently completed the study will share information about their ketamine experience with other prospective participants, who may desire to enter the study because they are seeking ketamine. This strategy has been used successfully in other studies to reduce risk of subsequent drug use following study participation. This study procedure has also been approved by the IRB in prior protocols that also had an IND, including IRB #29123, 57184, 104881, and 110528 (also #135883 that did not have an IND), with the FDA not having issues with this strategy for these protocols. Participants will also be asked about their drug use, including ketamine and other club drugs, at screening and follow up interviews to determine whether an increase in use of these kinds of agents occurred. Finally, data on drug liking and desire to use this drug again (Carter and Griffiths, 2009) will be obtained after the infusion.

Another justifications for the midazolam sham condition and the use of deception prior to drug administration is the problem of drug discrimination. Although participants are blinded to the drug condition, participants will easily discern whether they received active drug (ketamine) versus placebo, which can influence their subsequent mood and smoking behavior if they are under the belief that the active drug may affect these outcomes. Smoking behavior and mood are subjective and easily influenced by expectation. Many ketamine studies use an “active placebo”, such as midazolam, to avoid this limitation (in fact, the use of an active placebo during ketamine research is strongly recommended (Aan Het Rot et al., 2012). While an active placebo is not being used in this small pilot study, we may be able to minimize this confound by using the midazolam sham (an active placebo will be used in future studies).

3. All participants will be asked to not eat solid food for 7 hours prior to the infusion. Consumption of clear liquids will be permitted until the start of the infusion.

4. Participants will be monitored according to the American Society of Anesthesiology Standards for Basic Anesthetic Monitoring (American Society of Anesthesiologists Task Force on Sedation and Analgesia by Non-Anesthesiologists 2002, Standards and Practice Parameters Committee, 2011) with ketamine being administered by the study anesthesiologist. The anesthesiologist will perform a brief pre-anesthesia evaluation to ensure the person can safely undergo ketamine infusion, remain available to periodically evaluate the patient and intervene as needed to diagnose or treat any serious physiologic derangements during infusion, and be available by pager if any issues arise thereafter. The close monitoring of objective and subjective drug effects by direct observation, interviewing, and self-ratings will allow objective evaluation of the effects of ketamine. If at any point during the study adverse reactions are severe enough to warrant physician intervention, the subject will be removed from the study. If the subject drops out of the study, treatment referrals will be offered.

To ensure that participants return home safely after release, participants will be shuttled to and from the hospital by another driver on the ketamine infusion day. If the participant cannot arrange for their own transportation, a taxi will shuttle them to and from the hospital.

5. The experimental procedure will be completed in one of the ketamine infusion rooms in the UAMS PRI Ketamine Infusion Suite with at least an LPN-level research nurse present during the session. The infusion suite has a physiologic monitor that will capture continuous pulse oximetry, heart rate, and electrocardiography, and intermittent non-invasive blood pressure measurements. Wall mounted oxygen, suction, and equipment to deliver positive pressure ventilation are available at the bedside. A crash cart and additional supplies are also available.

The room contains full resuscitation equipment under the direct observation of an anesthesiologist certified by the American Board of Anesthesiology. Treatment of cardiac arrhythmia will depend on the particular dysrhythmia and physiologic response, and may range from continued observation by Dr. Lide to defibrillation. Management of respiratory depression will depend on the level of sedation, oxygenation, and ventilatory response, and may range from reminders to the patient to breathe, to supplemental oxygen, to facemask ventilation. Other adverse events will be treated in accordance with standard medical practice. See Miller's Anesthesia, 8th edition, for details. Participants will be discharged from the infusion suite based on criteria in the UAMS Practice Document: Interventional Service Line – Patient Discharge NR.CP.5.45 approved December 6, 2017.

6. We will follow use the following recommended criteria for ketamine discontinuation (Murrough et al., 2013):

1- In the event that three consecutive vital signs measurements (over 15 minutes) are consistently above the heart rate and BP limits (greater than 110 beats per minute and 170/100), then the study infusion will be discontinued.

2- In the event that the patient becomes sedated to the point that he/she is unresponsive to verbal commands or there is complete or partial airway obstruction, the study infusion will be discontinued. Should either of these problems occur, the anesthesiologist will treat the patient according to standard protocols. The patient would then be transferred to the post-anesthesia care unit or an intensive-care unit bed, as necessary for further observation and treatment.

3- In the event that the peripheral oxygen saturation is <95% over a 5-minute interval, the anesthesiologist has the option of supplementing oxygen. If oxygen saturation does not increase to 95% or greater with intervention, the infusion is discontinued, and further therapy is administered by the anesthesiologist.

7. Based on current recommendations by the manufacturer, pregnant women will be excluded by history and urine pregnancy test. Women capable of becoming pregnant will be asked to use effective birth control in order to participate and to inform the study physician if their birth control plans change after being accepted into the study.

8. Confidentiality will be protected by having all research records identified by code number only. A Certificate of Confidentiality will be obtained from the Department of Health and Human Services when the protocol is approved by the IRB and will be submitted to the IRB prior to subject enrollment.

9. If one participant experiences a study-related serious adverse event, the investigative team will review the data to determine whether the protocol needs to be modified or the trial stopped.

10. All personnel involved in this project will undergo triennial training in protection of human subjects and Good Clinical Practice.

2.3.3.3 Assessment of Potential Risks and Benefits

1. Potential Benefits. The risks associated with this study include the effects of the study medication, infusion, and tobacco withdrawal symptoms. In addition, subjects will have the inconvenience of participating in the study. Benefits offsetting these risks include that subjects will undergo a medical evaluation. The information gained in this study can assist us in developing more effective strategies for treating tobacco use disorder, which ultimately would be of great benefit to society. We believe that the benefits more than justify the risks of participating in this study.

2. Importance of Knowledge to be Gained. Despite several years of research on treating tobacco use disorder, prevalence is still high and current strategies are limited by high relapse rates. Moreover, effective strategies for treating tobacco use disorder still need to be identified. Thus, it is of vital importance to examine novel strategies for treating this condition. Examining ketamine infusion as a potential treatment strategy for reducing addiction is important because (1) the pharmacology of ketamine makes it a good candidate for reducing addiction, (2) ketamine infusion has been well tolerated and can be done on an outpatient basis, and (3) data from human and nonhuman studies support the use of ketamine. The findings of this study may support future studies that shed light on the efficacy of this medication as well as provide support for further development of ketamine as a pharmacotherapy for tobacco use.

3 Objectives and Endpoints

This proposal will obtain preliminary data on the effect of a single sub-anesthetic ketamine infusion on cigarette craving and smoking behavior as well as measuring its tolerability, and acceptability. This single-blind, placebo-controlled, randomized clinical trial will test 12 non-treatment seeking smokers with a single intravenous infusion of ketamine (0.5 mg/kg) or placebo. Before and 24-hours after the infusion, smokers will undergo lab-based measures of cigarette craving and smoking latency and will also complete diaries of cigarettes smoked per day for 7 days before, and 7 days after, the infusion. Physical and subjective effects and adverse effects will be closely monitored throughout.

Aim 1. Determine the preliminary safety, tolerability, and acceptability of ketamine. Outcomes include physiology (pulse oximetry, vital signs), drug effects, side effects, and symptoms of depression. We hypothesize that relative to placebo, a ketamine infusion will be comparably safe, well tolerated, and acceptable to smokers.

Aim 2. Determine the effects of ketamine on cigarette craving, smoking latency, and smoking frequency. Outcomes include urge to smoke, nicotine withdrawal symptoms, mood, latency to smoke in a smoking lapse analog task (pre- and post-infusion), and daily smoking frequency. We hypothesize that relative to placebo and baseline, ketamine will reduce craving, nicotine withdrawal, improve mood, increase the latency to smoke, and decrease the number of cigarettes smoked per day.

4 Study Design

4.1 Overall Design

This study has a mixed, within- and between-groups design. Non-treatment seeking smokers will be randomized into a ketamine or a placebo group. After the screening session, subjects will complete a 7-day smoking diary. Then complete the first study day in which a smoking analog task will be administered. On the second study day, the drug infusion will occur, followed by the third study day 24 hours after the infusion. Participants will complete a second 7-day smoking diary, then return to the lab for a follow-up visit.

4.2 Scientific Rationale for Study Design

The design of this study is modeled after Dakwar et al (Dakwar et al., 2017). In this previous study, non-treatment seeking cocaine dependent participants (aged 21-55) underwent lab-based measures of cocaine self-administration before and 24-hours after an intravenous ketamine infusion (0.71 mg/kg) or an active placebo, midazolam (0.025 mg/kg). The results showed ketamine decreased cocaine self-administration and craving in lab-based measures. There was also a slight reduction in cocaine use outside the lab that lasted for a few days. The goal of this study is to translate this work for tobacco use disorder.

4.3 Justification for Dose
Ketamine will be infused in order to control for variability in bioavailability of the agent. The 0.5 mg/kg dose of ketamine has been infused previously for opioid withdrawal (Jovaisa et al., 2006), is already being used clinically to treat depression at UAMS and is well-tolerated. If findings are positive, future studies will determine the optimal dosing and/or administration method.

4.4 End of Study Definition
A participant is considered to have completed the entire study if he or she has completed activities through the follow-up lab visit.

5 Study Population
5.1 Inclusion Criteria
Up to 20 male and female cigarette smokers will sign informed consent and be assessed for eligibility to participate until 12 have completed the study.

1) between the ages of 21 and 55
2) smoke ≥ 5 cigarettes/day of a brand delivering ≥ 0.5 mg nicotine
3) smoked ≥ 2 years
4) afternoon expired CO concentrations ≥ 10 ppm or morning urinary NicAlert ≥ 100 ng/ml (note: both will be measured at screening regardless of the time of day)
5) negative urine drug screen for illicit drugs (except for THC) and negative breath alcohol concentration
6) do not plan to change smoking behavior within the next 90 days

5.2 Exclusion Criteria
1) have an unstable medical condition or stable medical condition that would interact with study medications or participation, including chronic pulmonary disease, coronary artery disease, current brain tumor, current increased intracranial pressure or impaired consciousness
2) history of serious head trauma or neurological disorder (e.g., seizure disorder)
3) have any of the following: hypertension (i.e., systolic ≥140 mm Hg and/or diastolic ≥90 mm Hg on three separate measures; systolic >170 or diastolic > 110 on any occasion), liver function tests >3 times normal, Blood Urea Nitrogen and Creatinine outside normal range; ECG (electrocardiogram) abnormalities including but not limited to: bradycardia (<55 beats per minute); prolonged QTc interval (>450 msec); Wolff-Parkinson White syndrome; wide complex tachycardia; 2nd degree, Mobitz type II heart block; 3rd degree heart block; left or right bundle branch block; pre-existing severe gastrointestinal narrowing (pathologic or iatrogenic)
4) meet DSM-5 criteria for psychosis, schizophrenia, major depressive disorder, or bipolar disorder
5) current substance abuse/dependence other than nicotine
6) use of psychoactive medications or other drugs that would interact with study drug
7) use of cannabis/THC >4 days/week
8) current use of smokeless tobacco, nicotine replacement therapy, bupropion, or varenicline
9) history of regular use of ketamine for nonmedical purposes
10) among females, pregnancy or breastfeeding
11) Body Mass Index > 40

5.3 Lifestyle Considerations
NA

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently entered in the study. This refers to participants who have signed a consent form but do not meet eligibility criteria during the screening session. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this trial (screen failure) because of a questionable laboratory finding may be rescreened upon subsequent follow up and resolution of the issue as documented by a local physician. Rescreened participants will be assigned the same participant number as for the initial screening.

5.5 Strategies for Recruitment and Retention

Subjects will be recruited from the community via flyers, newspaper, word of mouth, and internet. Approximately 25% of Arkansas smoke tobacco. We should easily be able to recruit approximately 1-2 participants per month to stay on schedule.

6 Study Intervention

6.1 Study Intervention Administration

6.1.1 Study Intervention Description

Participants will be randomized to receive either ketamine or placebo on the drug infusion day.

6.1.2 Dosing and Administration

Ketamine is a schedule III anesthetic. The 0.5 mg/kg dose is already being used clinically to treat depression at UAMS and is well-tolerated. Sub-dissociative doses (<1 mg/kg) of ketamine have also been administered to pain patients in the ED with minimal adverse side effects and an efficacy similar to that of opioids (Pourmand et al., 2017). Participants with body mass index ≥ 30 may receive a dose using their calculated ideal body weight and not actual body weight, per the recommendation of the study physician and/or pharmacist.

On the infusion day, subjects will receive an infusion of ketamine (0.5 mg/kg). 100 mg of ketamine will be prepared in NS 100 ml IVPB (I mg/ml concentration). All study participants will receive a 22-gauge angiocatheter inserted intravenously by the study anesthesiologist and connected to standard intravenous tubing and a 1000 ml bag of crystalloid solution (Lactated Ringers or Plasma-Lyte). The infusion will be administered by infusion pump at a rate of 125 mL/hour. Study drug will be infused intravenously by pump over 20 minutes, the standard procedure for ketamine infusion for depressed patients at UAMS.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Acquisition and Accountability

The UAMS Research Pharmacy will purchase, store medication supplies, prepare all medications and be in charge of drug accountability and blinding. For purposes of ketamine dose preparation, the participant's body weight measured on the screening visit will be used. When dispensed from the pharmacy, medication will be stored in a separate container in the medication room cabinet behind the nurse's station on the inpatient floor until administration time. All medication administration will occur under observation by research/medical staff to ensure compliance with medication procedures. Unused medications will be returned to the research pharmacy typically within 24-48 hours for destruction.

6.2.2 Appearance, Packaging, and Labeling

Ketamine is formulated from the manufacturer as a slightly acidic sterile solution for intravenous infusion. We will prepare ketamine 100mg in NS 100ml IVPB (1mg/ml concentration).

6.2.3 Product Storage and Stability
See package inserts for relevant information.

6.2.4 Preparation
The appropriate doses of Ketamine will be compounded per protocol by the UAMS research pharmacy and provided to study staff based on physician's prescription in appropriately labeled sterile IVPB containers.

6.3 Measures to Minimize Bias: Randomization and Blinding.
Subjects will be blind to infusion medication. They will be given a list of drugs, including ketamine, and told that one of the drugs listed will be administered.

6.4 Study Intervention Compliance
The infusion will be administered by the study physician anesthesiologist to ensure medication is infused according to the protocol. Timing of medication administrations will be documented on a study checklist.

6.5 Concomitant Therapy
NA

7 Study Intervention Discontinuation and Participant Discontinuation/Withdrawal

7.1 Discontinuation of Study Intervention
NA

7.2 Participant Discontinuation/Withdrawal from the Study
Participants choosing not to take the study medication or not following study or unit procedures will be discharged from the study. Participants have a right to withdraw from the study at any time.

7.3 Study Retention and Lost to Follow-Up
In previous studies, we have implemented procedures to successfully recruit, enroll, and ensure the safety of subject populations.

Participants will receive no payment for the phone screening and in-person eligibility screening. Participants will be compensated $20 for completing the two 7-day smoking diaries ($10/diary), $178 for the smoking analog study days ($75 for participation, up to $14 for not smoking during the analog task), $100 for the drug infusion study day, and $10 for the follow-up lab visit. They will receive a $100 bonus for completing all aspects of the study. The maximum amount of compensation will be $408.

Staff will also obtain contact information from subjects and a reliable contact for sending up to three reminders of the appointment by phone and documenting these attempts in the participant's research record.

8 Study Assessments and Procedures
8.1.1 Efficacy Assessments

Assessment of Eligibility. Participants will undergo a comprehensive evaluation, including physical, psychiatric and routine laboratory studies (CBC, basic metabolic panel, urinalysis, ECG). These assessments must occur within 30 days of intake procedures. A physician will review laboratory data and ECG prior to study day 1. Women of childbearing potential will have a urine pregnancy test at initial assessment and prior to ketamine infusion.

Study Entry. Table 1 outlines the study timeline. Prospective participants will call the study telephone number and be given a brief description of the study and answer some questions regarding eligibility. Individuals who are interested in the study and meet basic inclusion criteria will be invited to a full screening session.

The screening interview will be conducted by a research staff member and take approximately 2-3 hours to explain the study, obtain informed consent, conduct informal interviews for mental health (i.e., to rule out major psychiatric illness) and other drug use disorders, collect vitals (blood pressure and heart rate), conduct drug urinalysis and urine pregnancy test for women, collect smoking history and medical history, review information in the phone screen. The research staff member will have a bachelor's degree and at least 2 years research experience or another equivalent combination of education and research. The ECG and blood draw will be performed by a research nurse. A blood evaluation will be performed (basic metabolic panel, CBC—these and any other laboratory test mentioned in this protocol will be outsourced to Quest Diagnostics and/or Redwood Laboratories). The study physician will review the results of the screening and determine eligibility.

Experimental Procedures. This study has a mixed, within- and between-groups design. Non-treatment seeking smokers will be consented, screened for eligibility, and randomized into a ketamine (n = 6) or placebo (n = 6) group (single-blind). Subjects will be told they may receive ketamine, midazolam, or placebo (to minimize drug expectations; only ketamine or placebo will actually be administered). After the screening session, eligible subjects will complete a 7-day smoking diary at home. Then, they will be asked to abstain from smoking for 10 hours (to induce withdrawal symptoms) and arrive for their first study day to complete the first smoking lapse analog task. After this study day, they may resume ad lib smoking before the second study day, when subjects will arrive and undergo a pre-anesthesia evaluation, followed by an intravenous administration of either ketamine or placebo. This procedure will last 2 hours. At the end of these 2 hours, they will complete self-report mood questionnaires and be released. They will be asked to abstain from smoking for 10 hours before the third study day visit, which begins on the following day- when the effects of ketamine on mood are thought to peak. Subjects will undergo a second smoking lapse analog task. They may resume ad lib smoking and they will be given a second 7-day smoking diary to begin the following day. This diary will be returned in 1 week at a follow-up lab visit, where participants' vitals will be measured, and any side effects and adverse events experienced since the drug infusion will be reported. See Table 1.

8.1.2 Dependent Measures

1 Self-report Measures of Tobacco Use. All subjects will complete a Smoking History Questionnaire and the Fagerström Test of Nicotine Dependence (FTND)(Heatherton et al., 1991) at screening. These measures will be used to screen subjects and characterize individual's smoking behavior.

2 Tobacco Use and Abstinence Biomarkers. Expired-air CO will be measured using a handheld monitor (Vitalograph, Lenexa, KS). Urinary cotinine concentrations will be measured with NicAlert™ strips (Nymox Pharmaceutical Corp, Canada). These biomarkers will verify smoking status at screening.

3 Smoking Diary. Subjects will be provided with a questionnaire to log the number of cigarettes smoked each day for 7 days. The first smoking diary will be recorded after the screening session and before the first study day. The second smoking diary will be recorded after the third study day.

4 Physiological Monitoring. All participants will be clinically monitored according to the American Society of Anesthesiology Standards for Basic Anesthetic Monitoring during infusion of study drug, including continuous assessment (i.e., every 5 min) of pulse oximetry, and electrocardiography, and intermittent non-invasive ocillometric blood pressure measurement. After infusion, these measures will be documented every 15 min for the first hour, then after 1 more hour.

5 Study Drug. Ketamine is a schedule III anesthetic. Participants will undergo pre-infusion assessments including a medical history and physical examination, application of physiologic monitors (including pulse oximetry, non-invasive ocillometric blood pressure measurement) and insertion of the IV line. Normal saline infusion at 125 mL/min will begin and pre-session research assessments will be completed. 100 mg of ketamine will be prepared in NS 100 ml IVPB (I mg/ml concentration). All study participants will receive a 20-gauge angiocatheter inserted intravenously and connected to a 1000 mL bag of crystalloid solution. The infusion will be administered by infusion pump at a rate of 125 mL/hour. Study drug will be infused intravenously by pump over 20 minutes, the standard procedure for ketamine infusion for depressed patients at UAMS. The placebo will be the crystalloid solution alone. Subjects will be blind to the contents of the infusion. Participants will remain in the Ketamine Infusion Suite for at least 2 hours under observation of a nurse before being released.

6 Safety and Tolerability Measures. Clinician Administered Dissociated States Scale (CADSS) measures perceptual alterations that the subject may experience during the infusion session (Bremner et al., 1998). Drug Effects Questionnaire (DEQ) consists of scales rated from 0 (not at all) to 10 (extremely) e.g., "do you feel a drug effect?". Side Effects Questionnaire (SEQ) consists of scales rated from 0 (not at all) to 10 (extremely) of aversive side effects associated with ketamine and other drugs (e.g., nausea, headache, feeling faint, blurred vision). The CADSS will be administered throughout the drug infusion. The DEQ and SEQ will be administered at the end of the 2-hour study medication session.

7 Subjective Mood Measures. The 10-item Tiffany Questionnaire of Smoking Urges-Brief (QSU (Cox et al., 2001)) measures urges to smoke in response to positive or negative reinforcement (visual analog scale, range 1–100). The 21-item Positive and Negative Affect Schedule (PANAS (Watson et al., 1988)) measures current emotional state for positive and negative moods (Likert scale, range 1-5). The 8-item Minnesota Nicotine Withdrawal Scale (MNWS (Hughes and Hatsukami, 1986)) measures symptoms of nicotine withdrawal. The QSU, PANAS, and MNWS will be administered at screening, before and after the drug infusion, and before and after the smoking lapse analog tasks. Since ketamine may affect symptoms of depression, the 20-item Center for Epidemiologic Studies Depression Scale (CESD (Beekman et al., 1997)) will be included on day 7 of the smoking diary to assess depression symptoms over the previous week.

8 Smoking Lapse Analog Task. The smoking lapse analog task is a lab-based model of real-world lapse during a quit attempt (McKee, 2009). This task measures the relative value of a drug (cigarette) vs a nondrug (money) reward, and it is appropriate for testing the effects of

ketamine on drug craving and drug-taking behavior. Participants will be seated in a smoking-permitted room. Set on a table in front of them will be a pack of their preferred brand of cigarettes, a lighter, and an ashtray. Participants are instructed they can initiate smoking at any time over the next 50 min, but for each 5 min they delay smoking, they would earn $1 (total of $0 to $10 based on how long they delay). They will be instructed that the session will end in 50 min regardless of whether they choose to smoke, but they can smoke 1 cigarette within this time. Immediately following the 50 min session is a 60 min period of ad lib smoking, where participants will be provided with a $4 “tab” which they can save or use to smoke additional cigarettes (up to 8 cigarettes) at $0.50 each. The time at which participants choose to smoke is the primary dependent variable (range 0–50min).

Table 1

- Consent and eligibility screening
  - 7-day smoking diary (CESD on day 7)
- First Study Day (10 hours abstinent)
  - Subjective mood (QSU, PANAS, & MNWS)
  - 2hr - Smoking lapse analog task
  - Subjective mood (QSU, PANAS, & MNWS)
- Second Study Day
  - Subjective mood (QSU, PANAS, & MNWS)
  - Pre-anesthesia evaluation
    - 0hr – Ketamine or Placebo infusion
    - .25hr – Physiological monitoring & CADSS
    - .5hr – Physiological monitoring & CADSS
    - .75hr – Physiological monitoring & CADSS
    - 1hr – Physiological monitoring & CADSS
    - 2hr– Physiological monitoring & CADSS
  - Drug side-effects (DEQ & SEQ)
  - Subjective mood (QSU, PANAS, & MNWS)
- Third Study Day (10 hours abstinent)
  - Subjective mood (QSU, PANAS, & MNWS)
  - 2hr - Smoking lapse analog task
  - Subjective mood (QSU, PANAS, & MNWS)
- 7-day smoking diary (CESD on day 7)
- Follow-up lab visit (SEQ & PANAS)

8.1.3 Milestones.

We will train staff and develop procedures during month 1, enroll 1-2 subject/month into the study proper during months 2—12, allowing for holidays and staff vacations. All study procedures and follow-up visits will be completed by month 12. Data analyses, manuscript preparation and final report will be completed by Month 15. These data, if positive, will be used to support an R21 or R01 submission to comprehensively test the effects of ketamine infusion on tobacco use disorder.

8.2 Safety Assessments

Participants will be encouraged to report the occurrence of untoward effects. Participants will be asked whether they are experiencing any symptoms and, if so, a symptoms form will be completed. All symptoms will be monitored until resolution.

8.3 Adverse Events and Serious Adverse Events

8.3.1 Definition of an Adverse Event

Adverse event means any untoward occurrence associated with the use of an intervention in humans, whether or not considered intervention-related. Specifically, adverse event refers to any new untoward occurrence that had not been experienced previously by a participant OR an occurrence that has been experienced previously be the participant (e.g., pre-existing condition) that is greater in severity and/or duration than previously.

8.3.2 Definition of a Serious Adverse Event

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

8.3.3 Classification of an Adverse Event

8.3.3.1 Severity of Event

All AEs will be assessed by the study physician and Principal Investigator using the following guidelines to describe severity:

- Mild — Events require minimal or no treatment and do not interfere with the participant's daily activities.
- Moderate — Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- Severe — Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.

8.3.3.2 Relationship to Study Intervention

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

- Definitely Related — There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.

- Probably Related — There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention,

is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.

- Potentially Related — There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.

- Unlikely to be related — A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).

- Not Related — The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

8.3.3.3 Expectedness

The study physicians will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

8.3.4 Time Period and Frequency for Event Assessment and Follow-up

An LPN or RN-level nurse will ask whether a participant is experiencing any symptoms during the infusion day and will record any occurrences on a symptoms form. Symptoms are reviewed by the study physician to determine whether the symptom meets the criteria for an AE or SAE.

All AEs including local and systemic reactions will be captured on the appropriate case reporting form. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product, and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

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

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

Study staff will record all reportable events with start dates occurring any time after informed consent is obtained until the follow-up visit (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization. At least 3 attempts will be made to follow up with the participant and these attempts will be documented.

8.3.5 Adverse Event Reporting

Institutional Review Board Reporting
All AEs not meeting the criteria for an unanticipated problem involving risks to subjects or others (UPIRTSO: unanticipated problem involving risks to subjects or other) will be recorded and reported to the UAMS IRB at continuing review.

Copies of each report and documentation of IRB notification and receipt will be kept in the Clinical Investigator's binder.

Sponsor Reporting for Drug Studies under an IND
The Sponsor will be promptly notified of all SAEs that are related to the study intervention and unanticipated/unexpected. These SAEs will be reported to the Sponsor using the FDA MedWatch 3500A.

The Sponsor will report events to FDA in accordance with 21CFR312.

All other AEs and SAEs will be reported to the Sponsor and FDA in the Annual Progress Report.

Deaths that are related to research will be reported to the Sponsor immediately upon Investigator notification. A death due to a terminal condition of the research participant would be considered anticipated and not related to the research.

THE SPONSOR WILL REPORT DEATHS TO FDA IN ACCORDANCE WITH 21CFR312.

8.3.6 Serious Adverse Event Reporting
Institutional Review Board Reporting
Only adverse events meeting the UPIRTSO (Unanticipated Problem Involving Risks to Subjects or Others) will need to be reported to the UAMS IRB within the required 10 day allotment of being notified of the event. UPIRTSO requires that an unanticipated problem meet the following qualifications: a) unanticipated or unexpected; b) related to the research; and c) involves new or increased risk to the subject(s). All other AEs, including expected SAEs, will be recorded and reported to the UAMS IRB at continuing review.

Copies of each report and documentation of IRB notification and receipt will be kept in the Study binders.

Sponsor Reporting for Drug Studies under an IND
The Sponsor will be promptly notified of all SAEs that are related to the study intervention and unanticipated/unexpected. These SAEs will be reported to the Sponsor using the FDA MedWatch 3500A.

The Sponsor will report events to FDA in accordance with 21CFR312.

All other SAEs will be reported to the Sponsor and FDA in the Annual Progress Report. Deaths that are related to research will be reported to the Sponsor immediately upon Investigator notification. A death due to a terminal condition of the research participant would be considered anticipated and not related to the research.

THE SPONSOR WILL REPORT DEATHS TO FDA IN ACCORDANCE WITH 21CFR312.

8.3.7 Reporting Events to Participants
Subjects will be informed of any new findings that might influence their decision to continue their participation in the study.

8.3.8 Events of Special Interest
NA

8.3.9 Reporting of Pregnancy
NA

8.4 Unanticipated Problems
8.4.1 Definition of Unanticipated Problems
The Office for Human Research Protections considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

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

8.4.2 Unanticipated Problem Reporting
IRB Reporting

AEs meeting the UPIRTSO criteria will be reported to the UAMS IRB within the required 10 day allotment of being notified of the event.

Sponsor Reporting for Drug Studies Under an IND

The Sponsor will be promptly notified of all SAEs that are related to the study intervention and unanticipated/unexpected. These SAEs will be reported to the Sponsor using the FDA MedWatch 3500A.

The Sponsor will report events to FDA in accordance with 21CFR312.

Deaths that are related to research will be reported to the Sponsor immediately upon Investigator notification. A death due to a terminal condition of the research participant would be considered anticipated and not related to the research.

THE SPONSOR WILL REPORT DEATHS TO FDA IN ACCORDANCE WITH 21CFR312.

8.4.3 Reporting Unanticipated Problems to Participants
Active participants will be notified at their next study visit of any changes to study procedures or drug information deemed necessary by the investigators upon review of the UPIRTSO. This notification will be documented in their study records. Once the IRB has approved the changes, including those to the consent form, participants will be invited to consider the changes and sign the consent if they choose to continue their participation.

9 Statistical Considerations
9.1 Statistical Hypotheses
This is a feasibility study so no hypotheses have been generated at this time.

9.2 Sample Size Determination
This is a feasibility/pilot study, so sample size was not determined.

9.3 Populations for Analyses

Population for analysis under Specific Aim 1: Those completing all aspects of the study.

Population for analysis under Specific Aim 2: Those completing all aspects of the study.

9.4 Statistical Analyses

9.4.1 General Approach

We will use descriptive statistics to characterize baseline characteristics of participants using the intent-to-treat sample.

Specific Aim 1. Determine the preliminary safety, tolerability, and acceptability of ketamine. Outcomes include physiology measures (pulse oximetry, vital signs), self-report questionnaire scores for dissociative state (CADSS), drug effects (DEQ), side effects (SEQ), depressive symptoms (CESD), as well as the number, type and severity of adverse events. Physiology measures and CADSS will be entered into separate 2 (group) x 6 (time: up to 4hr post infusion) repeated-measures ANOVAs. CESD scores will be entered into a 2 (group) x 2 (time: pre/post drug infusion). DEQ and SEQ scores will be compared using linear regression, using group as a predictor. These analyses are exploratory for the purposes of deriving effect size estimates for future grant applications.

Expected Results: While ketamine is expected to increase dissociative state, *we hypothesize that relative to placebo, a ketamine infusion will be comparably safe, well tolerated, and acceptable to smokers*.

Specific Aim 2. Determine the effects of ketamine on cigarette craving, smoking latency and smoking frequency. Outcomes include self-report urge to smoke (QSU), symptoms of nicotine withdrawal (MNWS), mood (PANAS), delay to smoke measured in the analog task, and cigarettes smoked each day across 7 days pre- and post-study days. Self-report measures will be entered into separate 2 (group) x 2 (time: pre/post drug infusion) x 2 (time: pre/post smoking lapse analog task) repeated-measures ANOVAs. The time (in min) to smoking the first cigarette will be analyzed with a 2 (group) x 2 (time: pre/post drug infusion) repeated-measures ANOVA. The number of cigarettes per day will be entered into a 2 (group) x 2 (time: pre/post drug infusion) x 7 (time: days) repeated-measures ANOVA. These analyses are exploratory for the purposes of deriving effect size estimates for future grant applications. Expected Results: *We hypothesize that relative to placebo and baseline, ketamine will reduce craving, nicotine withdrawal, improve mood, increase the latency to smoke, and decrease the number of cigarettes smoked per day.*

9.4.2 Analysis of the Primary Efficacy Endpoints

NA

9.4.3 Analysis of the Secondary Endpoints

NA

9.4.4 Safety Analysis

NA

9.4.5 Baseline Descriptive Statistics

Groups will be assigned to a drug condition based on their age, sex, race, cigarettes/day and nicotine dependence severity in order to balance these demographic variables as much as possible between groups. We will compare baseline mood symptoms between the two groups.

Any differences that relate to outcomes maybe be included as covariates of no interest in the relevant analyses. Exploratory analyses will be conducted using SPSS v24.

9.4.6 Planned Interim Analyses
No interim analyses are planned.

9.4.7 Sub-group Analyses
NA

9.4.8 Tabulation of Individual Participant Data
NA

9.4.9 Exploratory Analyses
NA

10 Supporting Documentation and Operational Considerations
10.1 Regulatory, Ethical, and Study Oversight Considerations
10.1.1 Informed Consent Process
10.1.1.1 Consent/Assent and Other Informational Documents Provided to Participants
A consent form describing in detail the study intervention, study procedures, and risks is given to the participant and written documentation of informed consent is required prior to starting intervention/administering study intervention. Consent materials include the IRB-approved version of the consent form and HIPAA.

10.1.1.2 Consent Procedures and Documentation
Participants will be recruited via flyers, newspaper, word of mouth, and internet. A research staff member experienced in obtaining informed consent will interview subjects to determine interest in participating in this trial. Aspects of the study procedures, risks, and potential benefits will be explained, and any questions will be answered. The subject will be asked questions to ensure an adequate understanding of the study and encouraged to read through the consent form a second time. The subject is asked to read aloud a section of informed consent to ensure that s/he can read (if the person is illiterate, a witness will be found to be present for the entire informed-consent process). If the subject indicates any hesitation about signing the consent form, s/he will be encouraged to leave with the consent form to consider the matter at leisure. If a subject indicates a desire to sign the consent form, both the participant and staff member will sign the form. The staff member will document that the informed-consent process occurred and whether the person's questions were addressed to his/her satisfaction. If at any time the subject exhibits intoxication, sedation, over-agitation, or some form of inattentiveness, the consenting process will be stopped and the interview rescheduled. After obtaining written informed consent for participation in the study and completing all screening procedures, a study physician will interview the subject and review all medical and psychiatric data prior to admitting the subject and beginning medication.

10.1.2 Study Discontinuation and Closure
This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to investigators, and applicable regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator will promptly inform study participants, the IRB, and sponsor and will

provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and/or FDA.

10.1.3 Confidentiality and Privacy

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. This confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without written consent by the participant.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), regulatory agencies or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at the clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Self-report and observer-report data will be collected using both standardized paper forms and forms presented on a computer that will be identified with the participant's study ID. The codes that link the name of the participant and study ID will be kept confidential in secured cabinets. Paper data will be entered into the computer independently by two different research staff trained to perform data entry, and the Principal Investigator or data manager will use a verification program to determine and correct any discrepancies based on source data. The computer data will be stored on a secure server and downloaded by the Principal Investigator, who will then transfer the data from Access to SPSS and check for missing data. The computer(s) used to collect data will be kept in a locked office or locked cabinet when not in use.

Blood samples, urine samples and laboratory results will be identified only with subject ID. Data will be identified by subject's study ID and entered into the computer independently by two different research staff trained to perform data entry, and the PI will employ a verification program to determine and correct any discrepancies based on source data.

<u>Certificate of Confidentiality</u>

To further protect the privacy of study participants, a Certificate of Confidentiality will be issued by the National Institutes of Health (NIH). This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any

civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants

10.1.4 Future Use of Stored Specimens and Data
Data collected for this study will be analyzed and stored at PRI. No unauthorized individuals will have access. No specimens will be obtained for future use.

10.1.5 Key Roles and Study Governance
Principal Investigator
Merideth Addicott PhD
University of Arkansas for Medical Sciences
Psychiatry Department
Telephone: 501-526-2436
maddicott@uams.edu

Study Monitor
Riley Lide, MD
University of Arkansas for Medical Sciences
Department of Anesthesiology
rlide@uams.edu

10.1.6 Safety Oversight
Safety oversight of this feasibility study will be by the study investigators.

10.1.7 Clinical Monitoring
If conducted under an IND, clinical site monitoring will be conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), and with applicable regulatory requirement(s).

10.1.8 Quality Assurance and Quality Control
The study team will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion. An individualized quality management plan will be developed to describe a site's quality management.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated for clarification/resolution.

Following written Standard Operating Procedures, if the study is conducted under an IND, the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, recorded, and reported in compliance with the protocol, and applicable regulatory requirements.

The investigational team will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

10.1.9 Data Handling and Record Keeping
10.1.9.1 Data Collection and Management Responsibilities

Data Acquisition, Collection, Transmission, and Entry

Self-report and observer-report data will be collected using both standardized paper forms and forms presented on a computer that will be identified with the participant's study ID. The codes that link the name of the participant and study ID will be kept confidential in secured cabinets. Paper data will be entered into the computer independently by two different research staff trained to perform data entry, and the Principal Investigator (PI) or data manager will use a verification program to determine and correct any discrepancies based on source data. The computer data will be stored on a secure server and downloaded by the PI or data manager, who will then transfer the data from Access to SPSS and check for missing data. The computer(s) used to collect data will be kept in a locked office or locked cabinet when not in use.

Blood samples, urine samples and laboratory results will be identified only with subject ID. Data will be identified by subject's study ID and entered into the computer independently by two different research staff trained to perform data entry, and the PI or data manager will employ a verification program to determine and correct any discrepancies based on source data.

Procedures in Place to Ensure the Validity and Integrity of the Data

The research assistant will have at least a bachelor's level education or commensurate experience, and the research nurse will be a Registered Nurse, both with previous experience in clinical rating and/or interviewing.

As for training on the scales and tasks, the PI and/or data manager first will give a training session on the background of the particular scale and how it is to be completed. Then the staff member will observe completion of the assessment by an experienced rater on at least three occasions. Afterward, the staff member will complete the assessment in the presence of an experienced rater on at least three occasions, with feedback given each time, until the supervisor is confident that the person understands the assessment and completes it properly. Thereafter, assessments will be checked on a continuous basis for appropriate completion, and constructive criticism will be given as necessary.

Each research staff member will be instructed on the timing of assessments for each individual. Checklists will be used to ensure that assessments are obtained at the time indicated. The research staff and PI also will review assessments.

For the computerized assessments, the programs were created in such a way that (1) each subject has his/her own template of questionnaires that are prescheduled based on the timing of assessments outlined in the protocol, (2) each question must be answered in order to go to the next task or question, (3) each answer has a "built in" range of appropriate values such that out-of-range answers will not be accepted. The PI will create each subject's template, will train research assistants in computer use, and will periodically spot-check to ensure research assistants are completing assessments according to proper procedures. The computer data will be stored on a secure server and downloaded by the PI, who will then transfer the data from Access to SPSS and check for missing data. The computer(s) used to collect data will be kept in a locked office when not in use.

For paper assessments, the research assistant will review the assessments for missing/out-of-range values. Paper data will be entered into the computer independently by two different research staff trained to perform data entry, and the PI will employ a verification program to determine and correct any discrepancies based on source data. If the PI notices recurring data entry errors, she will inform the person(s) responsible and retrain them as necessary.

Prior to statistical analyses, the PI or data manager will check the data for mislabeling, missing data, out-of-range data, etc., and will change/correct as appropriate based on source data. A master data set will be created with at least two backups.

10.1.9.2 Study Records Retention
Study documents will be retained for a minimum of 3 years after the study has closed or the findings published, whichever is longer.

10.1.10 Protocol Deviations
A protocol deviation is any noncompliance with the clinical trial protocol, or Standard Operating Procedures requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions may be developed by the study team and implemented promptly.

It is the responsibility of the PI to use continuous vigilance to identify and record deviations. All deviations will be addressed in study source documents and sent to the UAMS IRB per their policies. The PI is responsible for knowing and adhering to the reviewing IRB requirements.

10.1.11 Publication and Data Sharing Policy
This study will be conducted in accordance with the following publication and data sharing policies and regulations: NIH Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

10.1.12 Conflict of Interest Policy
Investigators have no conflicts of interest to disclose.

10.2 Additional Considerations
N/A

10.3 Abbreviations

AE	Adverse event
BrAC	Breath Alcohol Content
BUN	blood urea nitrogen
CADSS	Clinician Administered Dissociated States Scale
CBC	complete blood count
cc	cubic centimeters
CESD	Center for Epidemiologic Studies Depression Scale
CO	carbon monoxide
CONSORT	Consolidated Standards of Reporting Trials
DEQ	Drug Effects Questionnaire
DSM-5	Diagnostic and Statistical Manual version 5
ECG	electrocardiogram
FDA	Food and Drug Administration
FTND	Fagerström Test of Nicotine Dependence
HIPAA	Health Insurance Portability and Accountability Act
hr	hour
ID	identification
IND	investigational new drug

IV	intravenous
IVPB	intravenous piggyback
LPN	licensed practical nurse
mg/kg	milligrams per kilogram
mg/ml	milligram per milliliter
mm Hg	millimeters mercury
MNWS	Minnesota Nicotine Withdrawal Scale
NIH	National Institutes of Health
NMDA	N-methyl-D-aspartate
NS	normal saline
PANAS	Positive and Negative Affect Schedule
PI	Principle Investigator
PRI	Psychiatric Research Institute
QC	quality control
QSU	Questionnaire of Smoking Urges
SAE	serious adverse event
SED-TUD	The effects of sedatives on tobacco use disorder
SEQ	Side Effects Questionnaire
SPSS	Data analysis software
UAMS	University of Arkansas for Medical Sciences
UPIRTSO	Unanticipated Problem Involving Risks to Subjects or Others

10.4 Protocol Amendment History

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