Ketamine for Treatment of Multiple Sclerosis-related Fatigue

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Randomized controlled trial of ketamine for treatment of multiple sclerosis-related fatigue

A. Background of the study

Multiple sclerosis (MS) is an inflammatory, demyelinating and degenerative disease of the central nervous system and, after trauma, is the most common cause of disability in young adults, affecting more than 400,000 individuals in the US.(1,2) Of all the symptoms that can occur with MS, chronic fatigue is the most common and disabling, reported by at least 75% of patients at some point.(3–5) Fatigue limits patients' daily activities,(6) and challenges employment, resulting in substantial socioeconomic consequences.(7) Despite this negative impact, fatigue treatments have been inconsistently studied, in part due to poorly understood underlying pathophysiological mechanisms.(8), (9) Yet to be defined biological processes and lack of clear treatment targets have also hampered the development of drugs for fatigue. As a result, there are no medications approved by the Food and Drug Administration (FDA) for the treatment of MS fatigue. Although several agents have been tested for fatigue, methodological limitations in the design, execution and reporting of those trials have not allowed meta-analyses or systematic reviews to conclude about efficacy. Instead systematic reviews have recommended performing rigorously designed trials to confirm drug effect.(10,11)

We recently reported that riluzole, a medication with anti-glutamatergic effects, increased the fatigue severity in patients with relapsing MS who had participated in a clinical trial evaluating potential neuroprotective effects of riluzole versus placebo.(12) Three other clinic trials which examined memantine effects on cognition in patient with MS also reported worsening fatigue as a major side effect.(13–15) Memantine main mechanism of action is blocking the N-methyl D-aspartate (NMDA) glutamate receptor. These observations prompted us that glutamatergic transmission probably plays an important role in fatigue pathogenesis and modulating these pathways could have potential therapeutic effect on MS-related fatigue. A recent paper reported that ketamine, an NMDA receptor blocker with different kinetics compared to memantine, had a strong and prolonged effect in reducing fatigue in bipolar patients who participated in a clinical trial, evaluating anti-depressive effects of ketamine versus placebo. Interestingly, the effect of ketamine on fatigue was independent of its antidepressant effects. The reduction in fatigue scores started in less than one hour after the infusion and lasted for two weeks. However, this was a post-hoc analysis of a clinical trial and the possibility of a false positive finding cannot be rule out.

Intravenous (IV) ketamine infusion has been used in many clinical studies for treatment of treatment-resistant depression and refractory pain.(16,17) Depression and fatigue are highly correlated in patients with MS.(18) If ketamine improves fatigue scores in MS, it is possible that improvement in depression is the underlying cause of fatigue improvement. So, to explore if ketamine has anti-fatigue effects independent of its anti-depressive effects, we will recruit fatigued, non-depressed patients with MS in this study.

Demonstrating anti-fatigue effects of ketamine in MS would argue for an important role of glutamatergic pathways in fatigue pathogenesis and provide a new treatment target for this disabling condition.

B. Objectives

The primary objective of this study is to determine if modulating glutamatergic transmission with ketamine is safe and efficacious in improving MS-related fatigue. These objectives will be answered in a proof of concept, randomized controlled trial of ketamine versus an active placebo (midazolam) in patients with relapsing or progressive MS who have clinically significant fatigue.

1. Primary question and response variable

To determine if treatment with ketamine as opposed to midazolam improves fatigue severity in patients with MS. We hypothesize that one infusion of ketamine, as compared to midazolam, in patients with MS, will be associated with improvement of fatigue scores over one week.

The primary outcome of the study will be Daily Fatigue Severity measured at or around 9 pm on days one through day seven post-infusion. It is a single item question: 'how much fatigue (tiredness, weariness, problems thinking clearly) have you felt today?' with responses from 0 'None at all' to 10 'Extreme Fatigue'. It has shown very good correlation with the validated fatigue measure, "Chalder Fatigue Questionnaire" in patients with MS.

2. Secondary questions and response variables

Secondary outcomes of the study include NeuroQOL fatigue item bank, Fatigue Severity Scale (FSS), Beck Depression Inventory (BDI) and Epworth Sleepiness Scale (ESS) at days seven and 14 after the infusion and modified fatigue impact scale (MFIS) at day 28 post-infusion.

3. Exploratory questions and response variables

Our colleagues at Kennedy-Krieger Institute have developed a paradigm to capture individual differences in subjective evaluation of physical effort. This paradigm can potentially replace or complement patient-reported fatigue in future clinical trials. Please see the appendix 1 at the end of this protocol for the details.

4. Adverse effects

The occurrence of AEs will be sought by non-directive questioning of the participant up to one hour after the infusion is finished and at one week after the infusion.

C. Design of the study

This is a randomized, double blind, active placebo-controlled trial of ketamine (versus midazolam) for treatment of multiple sclerosis-related fatigue.

1. Study population

Patients with multiple sclerosis and at least moderate fatigue (defined as modified fatigue impact scale (MFIS) score >33)

(a) Inclusion criteria

- Age between 18 years 65 years.

- Females of childbearing age must have a negative urine pregnancy test at baseline and use an effective method of contraception during the study.

- Diagnosis of MS (according to the 2010 McDonald criteria).

- Ambulatory (at least 20 feet using bilateral assistance).

- Fatigue reportedly present and screening MFIS score >33.

- Internet and email access and able to use a computer or tablet

(b) Exclusion criteria

- Beck Depression Inventory (BDI) score of more than 30.

- Neurodegenerative disorders other than relapsing or progressive MS.

- Breastfeeding or pregnant.

- History of coronary artery disease or congestive heart failure.

- Uncontrolled hypertension at screening (history of high blood pressure and screening systolic blood pressure >160 or diastolic blood pressure>100).

- History of severe liver disease, including cirrhosis.

- Terminal medical conditions.

- Currently treated for active malignancy.

- Alcohol or substance abuse in the past year (except marijuana or other cannabinoids).

- A history of intolerance or allergic or anaphylactic reaction to ketamine or midazolam

- Clinically unstable medical or psychiatric disorders that require acute treatment as determined by the PI.

- History of severe or untreated coronary artery disease or history of congestive heart failure.

- History of prior ischemic or hemorrhagic stroke and cerebral vascular aneurysms.

- History of recurrent seizures or epilepsy.

- Taking any disallowed therapy(ies) as noted in Appendix 2.

2. Sample size assumptions and estimates

With a two-sided alpha of 0.05, 12 participants in the ketamine group and 6 participants in the midazolam group, the study will have 80% power to detect 3 points difference on the Daily Fatigue Severity score.

3. Enrollment of participants

Participants will be recruited from Johns Hopkins multiple sclerosis clinic.

(a) Informed consent

The study investigators, or a person designated by the investigators will explain the IRB approved study consent to study participants and obtain signed informed consent from each subject. The study participants will be given ample time to review the consent, and are encouraged to ask questions during the consent process. The study participants are also encouraged to ask questions about the study throughout their study participation period. The investigator or designee must also explain to the subjects that they are completely free to refuse to enter the study or to withdraw from it at any time, for any reason. The study participants will be notified about any new study information during the study participation period, and will be re-consented when applicable. A copy of the signed informed consent form will be given to the subjects for their records.

(b) **Assessment of eligibility**

After signing the informed consent form, patients will undergo screening assessments, which include: recording demographic variables, medical and medication history, vital signs, physical examination, assessment of Expanded Disability Status Scale (EDSS), administration of the Daily Fatigue Severity question, modified fatigue impact scale (MFIS), NeuroQOL Fatigue item bank, fatigue severity scale (FSS), Epworth Sleepiness Scale and BDI, and for females of child-bearing potential, a urine pregnancy test. If any physical examination or EDSS has been done clinically in the previous 30 days, there is no need to repeat them and those values can be used for screening purposes.

Study participants will be enrolled into the study after the study physician confirms participants' eligibility to move forward with the study. We will notify the study participants about their eligibility before planning the baseline fatigue assessment.

(c) Intervention allocation (e.g., randomization method)

One of the study team members who has no role in the assessment of participants will generate a randomization table and send it to the pharmacist who will be dispensing the medication. Participants will be randomized in block sizes of 3 and 6 to ketamine versus midazolam in a 2:1 ratio.

(d) Baseline examination

Participants will be randomized within 30 days of screening visit. For the patients who we can verify the eligibility during the screening visit and can receive the infusion during the same visit, the screening measures will be considered the baseline measures.

Baseline assessment will include vital signs, Daily Fatigue Severity, MFIS, NeuroQOL fatigue item bank, FSS, BDI, Epworth sleepiness scale and subjective effort evaluation.

4. Intervention(s)

(a) Description and schedule

Within four hours of the baseline assessment, patients will receive ketamine of midazolam infusion.

Participants who are assigned to ketamine group will receive an IV infusion of ketamine 0.5 mg/kg over 40 minutes. Participants who are assigned to midazolam group will receive an IV infusion of midazolam 0.05 mg/kg over 40 minutes. The infusions will be done through a peripheral IV access on the participants' upper extremity. The infusion will be done by an ACLS-certified research nurse under the supervision of an ACLS-certified neurologist (the PI).

The infusions will be performed at Johns Hopkins Clinical Research Unit (CRU). CRU is staffed by BLS-certified nurses and is equipped with a full crash cart, standard emergency drug box, oxygen and a defibrillator. The Hospital Emergency Medical Response team in the event of a medical emergency. Please see the Appendix 3 for the details of the infusion procedures.

Participants will be monitored for one hour after finishing the infusion. Immediately after the infusion and at the end of one hour, participants will be questioned about adverse drug reactions. The subjective effort evaluation will be repeated at this time.

5. Follow-up visit description and schedule

After the Baseline (infusion) visit, all the subsequent assessments will be done remotely. Patients will receive an email with instructions on how to answer a group of questionnaires.

On days one through seven post-infusion, the patient will be assessed by Daily Fatigue Severity question. On day seven post-infusion, participants will answer the following questionnaires on the web: NeuroQOL, FSS, ESS and BDI. A study team member will also contact the participants using email or phone on day 7 to inquire about the adverse events that could have happened since the infusion.

Table 1 – The schedule for study procedures and assessments

Tests and assessments	Screening visit	Infusion visit	Days 1 through 7 Post-infusion	Week 1 post-infusion	Week 2 post-infusion	Week 4 post-infusion
Informed Consent	X					
Inclusion/exclusion criteria	X					
Medical history	X					
Vital signs	X	X				
Physical examination	X					
Urine pregnancy test	X					

Ketamine/midazolam infusion		X				
EDSS	X					
Subjective effort evaluation		X (before and after the infusion)				
Daily Fatigue Severity	X	X	X			
MFIS	X					X
NeuroQoL Fatigue	X			X	X	X
FSS	X			X	X	X
Beck Depression Inventory	X			X	X	X
Epworth Sleepiness Scale	X			X	X	X
Side effects assessment		X		X		

6. Ascertainment of response variables

(a) Data collection and quality control

We will use REDCap (Research Electronic Data Capture) [https://projectredcap.org/], a secure web application to build and manage online surveys and databases, collect data, create the trial database and access the data for analysis.

During the screening visit, data will be collected using case report forms (on paper), however, all the questionnaires during the screening and baseline visits will be answered directly on a computer or tablet by the participant. The information that is captured on paper case report forms will be entered into REDCap by the study coordinator. The study PI will double check the data entered by the study coordinator for completeness and accuracy.

After the baseline/infusion visit, all the outcomes will be collected through a web interface. Study coordinator will review the process to make sure the questionnaires are answered in a timely manner.

7. Assessment of Adverse Events

Ketamine and midazolam are FDA-approved anesthetic which have been in clinical use for many years and have well-known adverse effect profiles. Ketamine has also been used off-label for the treatment of pain and depression and our proposed study is based on the dosage and route of administration used in several clinical trials for treatment of depression.

Our infusions will be performed in a clinical research setting (Johns Hopkins Clinical Research Unit), under the supervision of an ACLS certified neurologist and by a ACLS certified nurse with experience in performing these infusions.

(a) Type and frequency

Participants will be monitored for the development of adverse events from the beginning of infusion to one hour-post infusion. They also will be questioned for the emergence of adverse events up to one-week post-infusion. The occurrence of AEs will be sought by non-directive questioning of the participants.

An Adverse event (AE) is the appearance or worsening of any undesirable sign, symptom or medical condition occurring after the start of the study medications, even if the event is not considered to be related to study drug.

All patient-reported AEs must be recorded with the following information:

- The severity grade (mild, moderate, severe)

- Its relationship to the study medications (suspected/not suspected)

- Its duration (start and end dates)

- If it constitutes a serious adverse event (SAE)

An SAE is defined as an event which:

- is fatal or life-threatening

- results in persistent or significant disability

- constitutes a birth defect/congenital abnormality

- requires inpatient hospitalization for at least 24 hours or prolongation of existing hospitalization for at least 24 hours. Pre-planned, elective hospital admissions are not considered SAEs.

- is medically significant

All AEs should be treated appropriately. Treatment may include one or more of the following: no action taken; study drug dosage adjustment; study drug permanently discontinued; concomitant medication given; non-drug therapy given; patient hospitalized.

(b) Instruments

Adverse events will be graded according to Common Terminology Criteria for Adverse Events (CTCAE), version 4 and is provided to the investigator in a separate handout entitled “Common Terminology Criteria for Adverse Events v4.0”. Adverse events not listed by the CTCAE will be graded using the following criteria:

Grade 1: Discomfort noticed but no disruption of normal daily activity

Grade 2: Discomfort sufficient to reduce or affect normal daily activity

Grade 3: Inability to work or perform normal daily activity

Grade 4: Represents an immediate threat to life.

8. Data analysis (Statistical Analysis Plan)

Because of the short duration of the study, there will be no interim analysis.

Patient demographics and other baseline characteristics, will be summarized using frequency distributions (for categorical variables) and descriptive statistics of mean, standard deviation, minimum, median and maximum (for continuous variables).

Background information includes MS subtype, prior medication, past/current medical conditions, duration of the disease, baseline fatigue level and baseline EDSS.

For the analysis of the primary and secondary outcomes, we will use a linear mixed model with restricted maximum likelihood estimate and an unstructured covariance structure. Both the allocation group and time will be within-subject covariate and the interaction between them will be included in the model. The models will be adjusted for the baseline value of the outcome variable. In sensitivity analysis, we will further adjust the fatigue models for the change in the Beck Depression Inventory score. The purpose of these adjustments is to try to separate the anti-depressive effects of ketamine from its anti-fatigue effects. The analysis will be done according to intention-to-treat principal.

Post-hoc simple effects tests will be used to evaluate the difference between the two groups at each time point. Significance will be evaluated at $p<0.05$, two-tailed.

For the analysis of the exploratory outcome, we will use student T-test to compare the change in the subjective effort valuation (after-the -infusion value minus before-the-infusion value) between the ketamine and midazolam groups.

D. Organization

1. Participating investigators

-Bardia Nourbakhsh, MD, MAS, Principal Investigator: Dr. Nourbakhsh is an assistant professor in the department of Neurology at JHU. He will oversee the overall conduct of the entire research project. He will be present during in the infusion room during the study medication infusions. He has been involved in designing clinical trials of symptomatic treatment in MS for the past few years and has completed formal education in epidemiology, biostatistics and trial design as part of the Masters’ in Clinical Research. He is currently the PI of a multi-center study of fatigue medications in MS.

- Adam Kaplin, MD, PhD, Co-investigator: Dr. Kaplin is an assistant professor in the departments of Neurology and Psychiatry at JHU. He has extensive experience in the design and execution of clinical trials and use of ketamine in psychiatric diseases. Along with Dr. Nourbakhsh, he will oversee the conduct of the trial and participate in data analysis and preparation of reports and manuscripts.

- Vikram Chib, PhD: Dr. Chib is an assistant professor of Biomedical Engineering. He has expertise in modeling of behavioral and neural data related to decision-making and learning.

- Bridget Morris, RN, BSN, Research Nurse: Ms. Morris is a research nurse in the department of Neurology at JHU. She will explain the study and related processes to the subjects, and consent them for the study. She will be the primary subject contact for this study. She will also prepare recruitment materials and distribute according to IRB approval. She will work with the MS clinic to identify potential candidates for the study. She will pre-screen subjects and schedule study visits. She will enroll subjects, collect data, and perform data entry and cleaning. She will work closely with participants regarding completing necessary testing that is part of the primary and secondary outcomes. She will serve as the subject's point-of-contact with the study team. She will triage concerns and AEs, involving the PI as necessary. She will collect AE's. She is an ACLS-certified nurse and has experience in critical care nursing. She will be in charge of administering the ketamine or midazolam at the Clinical Research Unit.

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Appendix 1: Subjective effort evaluation paradigm:

The experiments outlined in this proposal are centered around an effort-based choice paradigm, designed by our colleague (Dr. Vikram Chib) at Kennedy-Krieger Institute, that mathematically characterizes subjective effort valuation for effort.

Physical Effort Task.

Subjects maximum voluntary contraction (MVC) will be obtained by taking the maximum force achieved over the course of three consecutive isometric grip force repetitions, each lasting 14 seconds, with a hand clench dynamometer (TSD121B-MRI; Biopac Systems Inc.; Goleta, CA USA). It is important to mention that individuals could have different subjective preferences for different types of effort (e.g., walking, arm strength exercise, etc.). In this study we chose to focus on an isometric grip task because it easily operationalizes levels of effort as a percentage of participants' maximum grip capacity. Furthermore grip recruits motor units that are readily imaged with our TMS paradigm. Future studies could examine if the mechanisms of effort valuation identified in this proposal generalize to other types of effort, however this is beyond the scope of this proposal.

(a) Association phase. Participants will be trained to associate effort levels (which will be defined relative to MVC) with the force they exert on the hand dynamometer. The effort levels will range from 0 to 100, corresponding to no exertion and a force equal to 80% of participants' MVC, respectively. A single training block will consist of five trials of training for each target level, where the targets will vary from 10 to 80 in increments of 10, and training blocks will be presented in a randomized order. Participants will be instructed to reach a target zone (defined as ±5 effort units of the target effort level) as fast as possible and maintain force within the target for as long as possible over the course of 14 seconds. This will ensure that participants exert effort for roughly the same duration regardless of the amount of effort to exert. At the end of the effort task, if individuals are within the target zone for more than 2/3 of the total time observed during squeezing (9.33 seconds), the trial will be counted as a success, and participants will be cued as such. To minimize participants' fatigue, a fixation cross (2-5 seconds) will separate the trials within a training block and 60 seconds of rest will be provided between training blocks.

(b) Recall phase. We will next gauge if participants develop a stable association between the effort levels and the effort produced. Each recall trial will involve the display of a black horizontal bar that participants will be instructed to completely fill by squeezing the transducer. For the recall phase, the full bar will not correspond to level 100 as in the association phase, but instead

will be representative of the effort level being tested on a particular trial. This will give participants a sense of what level they were squeezing for the trail, and these cues will not be confounded by visual cues that might signal effort levels. Participants will be instructed to reach the target zone as fast as possible and to maintain their produced force as long as possible. Following this exertion period, participants will be presented with a number line (from 0 to 100) and asked to select the level they believe they had just squeezed. Our preliminary investigations have shown that participants are able to accurately associate physical effort levels to amounts of effort applied, and recall these associations following effort exertion.

(b) Choice phase. To characterize and quantify their subjective effort costs, participants will be presented with a series of risky binary gambles for effort. A trial will consist of choosing between two options shown on the screen under a 4 second time constraint: (1) exerting a low amount of force with absolute certainty (the "sure" option), and (2) taking a risk which could result in either high exertion or zero exertion, with equal probability of both outcomes (the "flip" option). The effort levels in question will be conveyed using the same 0 to 100 scale used in the association phase. The effort-choice amounts have been tailored to predominately sample the effort options over which there would be indifference between the "flip" and "sure" options — if the sure option is roughly more than half the flip, we can assume that participants will choose the flip option [14]. We use this procedure to uniformly sample the prospective effort space and generate a set of 170 gambles within the 0 to 100 range.

Participants will make their choice by pressing one of two buttons on a button pad with either their first ("flip") or second ("sure") digits. The outcomes of the choices will not be provided during the trials and will therefore be unknown to participants after making a choice. All gambles will be presented consecutively, in a randomized order, and participants will be informed that ten of their choices will be selected at random and played out at the end of the experiment. This is a common procedure in behavioral economics, that ensures participants treat each option separately and that trial-to-trial choices do not influence subsequent choices. Moreover, we will focus our imaging analyses to effort valuation at the time of choice, so our imaging will not be subject to movement artifacts associated effortful exertion.

Modeling of behavioral choice data: A critical component of this proposal is our ability to extract reliable measures of participants' subjective effort value using the behavioral choice data. We will generate structural models of effort-choice in which the subjectivity of participants' choices will be characterized based on the assumption that effort cost functions can be mathematically represented by the expression: $C(e) = e^{\rho}$. C is the subjective utility/cost of an effort level e, and ρ is a curvature parameter which characterizes how individuals subjectively represent the effort level in question (i.e, risk averse or risk seeking to avoid effort). Given the options presented during the choice phase, if one assumes that participants integrate probability with utility linearly (as is common in economic choice), the expected cost of choosing the "flip" option rather than the "sure" option can be written as $C(F,S) = S^{\rho} - 0.5\,F^{\rho}$. In this expression, F is the effort level which stands as a possible outcome against no exertion under the flip option, and S is the effort level of the sure choice. The probability that a participant chooses to make a gamble is given by the Softmax function $P(F,S) = \frac{1}{1+exp(-\tau(C(F,S)))}$. The subjective effort cost curvature parameter ρ is

contained within $CE(F,S)$, and τ is a temperature parameter representing stochasticity of a participants' choice (τ = 0 means choices are random). We will use a maximum likelihood estimation (MLE) procedure to estimate both the curvature and temperature parameters for each participant, using the 170 trials of gambles F,S and associated responses.

Appendix 2: Prohibited Therapies

The table below is intended for general guidance, please contact the study team to discuss any questions or concerns regarding any specific concomitant therapies for a subject.

The pharmacotherapies listed below are permitted (Y) or excluded (N) due to potential impact on efficacy evaluation and/or subject safety or because they are indicated for exclusionary conditions.

Except where specifically noted in the protocol, the prohibited therapies listed in this table are prohibited from screening until at least 12 hours after the infusion of the study medication.

Drug Class	Episodic Use	Continuous Use	Comments
ADHD medications (eg, atomoxetine, guanfacine)	N	Y	See also "Psychostimulants" row
Amantadine	N	N	Subjects should be at least 7 days off of amantadine before receiving the study medication
Anorexiants (eg, phenteramine)	N	N	
Anticonvulsants	N	N	Subjects with seizures are excluded. Anticonvulsants used for other indications may be allowed (eg, valproate for migraine, lamotrigine for mood disorder). PI may approve the medication on a case-by-case basis
Antidepressants (*except* monoamine oxidase inhibitors)	N	Y	Episodic use (PRN) of trazodone is permitted but should not be used within 8 hours prior to the study drug administration.
Antidepressants: Monoamine oxidase inhibitors	N	N	Prohibited within the past 2 weeks prior to study drug administration

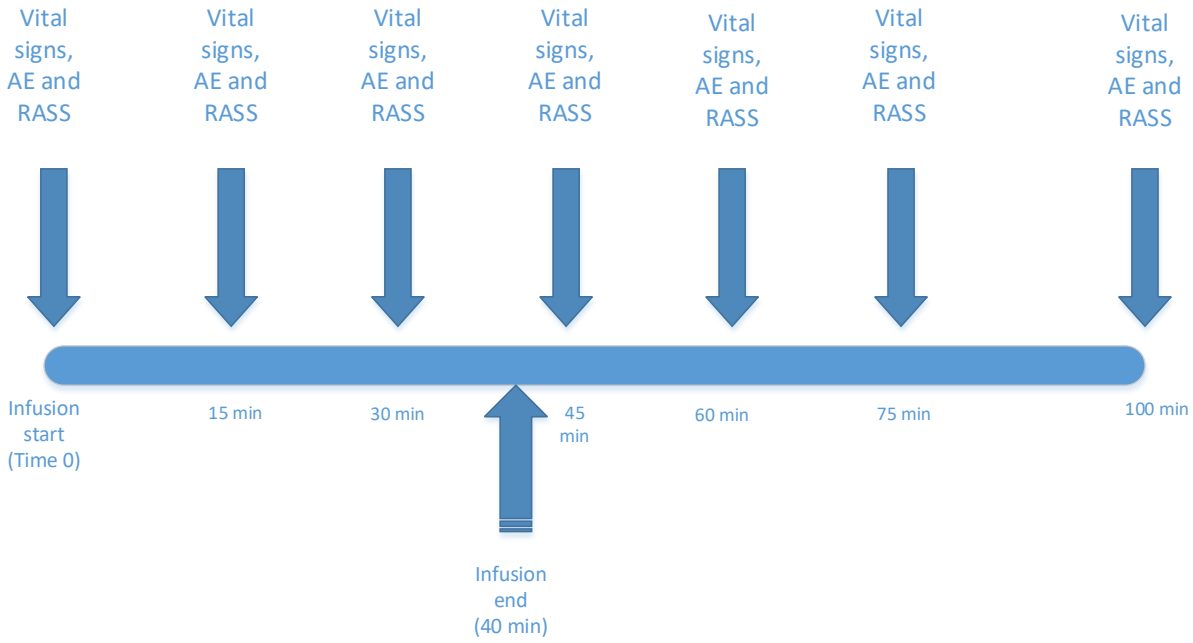
Antipsychotics	Y (for sleep only)	Y	
Benzodiazepines (at dosages equal to or less than the equivalent of 6 mg/day lorazepam)	Y	Y	Prohibited within 8 hours prior to the study drug administration. Additionally, no benzodiazepines should be used within 8 hours after study administration.
Chloral hydrate	N	N	
Clonidine	Y	Y	Prohibited within 8 hours prior to the study drug administration.
Corticosteriods	Y	N	Inhaled, intranasal, topical, and ophthalmic steroids are not prohibited. Intermittent IM/IV corticosteroids are permitted (chronic use prohibited). Episodic or continuous oral use can be permitted on a case-by-case (according to the PI)
Cough/Cold/Allergy preparations (except those containing dextromethorphan)	Y	Y	Pseudoephedrine- containing products should not be used within 12 hours prior to study medication administration.
Dextromethorphan	N	N	
DHEA	Y	Y	
Diphenhydramine	Y	N	PRN use is permitted, but should not be used within 8 hours prior to the study drug administration.
Hypnotics (Non-benzodiazepine only)	Y	Y	Do not use within 8 hours prior to the study drug administration.
Ketanserin	N	N	
Lithium	N	Y	
Methyldopa	N	N	
Metyrosine	N	N	
Opioids	Y	Y	Prescription opioid medication(s) can be continued, per clinician's
Non-vitamin K antagonist oral anticoagulation agents (eg, dabigatran, rivaroxaban, apixaban)	N	N	

Psychostimulants (eg, amphetamines, methylphenidate, and modafinil, armodafinil)	N	Y	The use of amphetamines (including prescribed amphetamines) can be continued but must not be taken within 12 hours prior to the intravenous treatment session or for 2 hours after the study drug administration.
Reserpine	N	N	
Scopolamine	N	N	
St. John's Wort	N	N	
Thyroid hormone supplement	N	Y	Subjects needing supplements must be on a stable thyroid supplement dose for at least 4 weeks prior to the study drug administration.
Warfarin	N	N	

Appendix 3: Infusion procedure:

A. Assessment
   1. The nurse shall assess the following prior to initiation of infusion:
      a. Baseline level of sedation using Richmond Agitation Sedation Scale (RASS)
      b. Baseline vital signs, including respiratory rate, blood pressure, heart rate and pulse oximetry
   2. After initiation of the infusion, the nurse will assess and document the vital signs every 15 minutes until 75 minutes after the start of the infusion and one more time, 100 minutes after the start of the infusion (or one hour after finishing the infusion).
   3. RASS every 15 minutes until 75 minutes after the start of the infusion and one more time, 100 minutes after the start of the infusion (or one hour after finishing the infusion).
   4. Adverse effects every 15 minutes until 75 minutes after the start of the infusion and one more time, 100 minutes after the start of the infusion (or one hour after finishing the infusion).

Schedule of the assessment of vital signs, adverse effects, and RASS.



B. Intervention
   1. IV ketamine or midazolam will be administered via an infusion pump.
   2. The infusion is completed in 40 minutes. For ketamine, the total dose will be 0.5 mg/kg (administered at the rate of 0.75 mg/kg/hour). For midazolam, the total dose will be 0.05 mg/kg (administered at the rate of 0.075 mg/kg/hour)
   3. For nausea, the neurologist can decide to give IV ondansetron (4 to 8 mg) during the infusion.
   4. For the unlikely event of apnea or very low respiratory rate that can rarely happen due to midazolam, the neurologist can decide to give 0.2 to 1 mg of flumazenil.
   5. Recovery process:
      a. Participant can be discharged when the following criteria are met:
         i. Sedation score of 0 per RASS scale
         ii. Ability to swallow oral fluids/secretions
         iii. No evidence of severe hypertension or hypotension exists, or blood pressure at participant's baseline
         iv. Pulse is regular and within the range defined for that participant's age group or at participant's baseline
         v. Respiratory rate and character are within the defined rang for that participant age group or at participant's baseline
         vi. Oxygen saturation on room air is >95% or at participant's baseline
      b. Aside from asking participants open-ended question about having any new or worsening symptoms right after the infusion, they will be asked if they experienced the following symptoms: Feeling Strange or Unreal, Abnormal Sensations, Blurred Vision, Feeling Drowsy or Sleepy, Dizziness or Faintness, Dry Mouth, Numbness or Tingling, Appetite Increased, Trouble Concentrating, Slurred Speech,

Difficulties Finding Words, Hearing or Seeing Things, Headache, Ringing in Ears, Increased Salivation

6. Presence of a responsible adult (family/friend) to accompany participant at time of discharge
    a. Participant and responsible adult have received information regarding side effects/duration of sedation and have had all questions answered.
7. Written discharge instructions are provided to the participant to include recommendations for:
    a. Light activity for 24 hours
    b. No driving, dangerous activities for up to 24 hours.
    c. Diet progression as tolerated
    d. No business transactions or legally binding agreements for 24 hours.

Medical Reasons for Discontinuation:

1- In the event that the participant's systolic or diastolic blood pressure (BP) increases by greater than 25% above baseline value [baseline is defined by first BP reading before the start of the infusion, is greater than 190/110, or in the event of tachycardia >130 beats per minute. The nurse will hold the infusion and assess the blood pressure and heart rate every 5 minutes. If the blood pressure decreased to less than 165/100 or in the event of tachycardia heart rate decreased to less than 110, the infusion can be resumed. In this situation, the blood pressure and heart rate will be assessed by nurse every 10 minutes through the end of the infusion. If at any time, the blood pressure is greater than 190/110 or hear rate >130 beats per minute, the infusion will be permanently stopped.

2- In the event that the participant 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 neurologist will treat the participant according to standard protocols (ACLS).

3- In the event that the SpO2 is <94% over a 5-minute interval, the neurologist has the option of using nasal cannula to administer O2, adjusting the nasal cannula position or flow rate. If SpO2 does not increase to 94% or greater with intervention, the infusion is discontinued, and further therapy is administered by the neurologist.