EFFICACY AND TOLERABILITY OF SUB-ANESTHETIC KETAMINE IN POSTPARTUM DEPRESSION

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Population: 10 female patients, age: 18-45
Number of Sites: 1
Study Duration: 2 years

General Information

Perinatal Depression (PND) is a seriously disabling form of mood disorder that occurs during pregnancy or within 12 months of the post-partum period(1). An untreated or protracted form of PND can adversely impact on mother, child and family well-being. PND is relatively common, affecting one in 8 women in the general population (2). Current treatments, including psychotherapy and antidepressants, are only effective in about half of PND patients and may take a few weeks to work. The current project aims to bridge this gap by studying the feasibility, safety, and effect of a single administration of a sub-anesthetic dose of ketamine on mood in patients with severe PND.

BACKGROUND AND RATIONALE

Perinatal depression (PND) is a non-psychotic major or minor depressive episode that occurs during pregnancy or within 12 months of the post-partum period (1). The nature of symptoms is the same as a depressive episode characterized by depressed mood, anxiety, sleep difficulties, suicidal thoughts, tiredness and diminished interest in pleasurable activities. The prevalence of PND is estimated to be 10-15% and may be even higher up to 25 % in low-income women (2). History of depression, experiencing anxiety and stressful life events during pregnancy and poor social support are considered as strong predictors of PND (2). Women with severe PND are at increased risk of self-harm and suicide, marital difficulties, and significant parenting difficulties (3). Severe maternal depression affects children by increasing the risk of emotional and behavioral and physical health problems and cognitive difficulties and (3). Thus early screening and intervention are critical in reducing the negative impact of PND in the mother and child, family and the community.

The Edinburgh Postnatal Depression Scale (EPDS) is the most commonly used screening tool for PND (2). Analysis of a large sample of EPDS (N=663) by international postpartum depression consortium (19 international sites) found that anxiety and anhedonia were the prominent symptom dimensions with post-partum onset in PND (8). **Moderate and severe anxious subtypes are the most common subtype during a late postpartum period representing about 70 % of PND**. Psychotherapeutic and pharmacological interventions are the current standard of care for moderate and severe PND. A systematic review of SSRIs have shown to have a modest effect in PND (Remission rates (46.0% vs. 25.7%; pooled risk ratio, 1.79)(9). However, current modalities take longer (>6 weeks for SSRI and >8-12 sessions for therapy)(3) but access to specialist therapists is not widely available (3). Despite some progress, nearly 50% of depressed patients do not unfortunately, fully respond to pharmacological treatment (10). The aetiopathogenesis of PND is less known and various neurobiological and psychosocial models have been proposed. Pregnancy is associated with marked changed changes in reproductive hormones (estradiol and progesterone) and therefore, such changes cause depression in vulnerable women (11). It is proposed that rapid changes in gonadal hormone may cause changes in brain γ-aminobutyric acid (GABA) and glutamate and therefore cause a **cortical excitatory-inhibitory imbalance**, which may contribute to depression (12). Interestingly novel neurosteroid allopregnanolone a positive allosteric modulator of γ-aminobutyric acid (GABAA) receptors, has been showing promising treatment for post-partum

depression (12). Identifying novel therapeutic targets for PND is a critical priority as prolonged illness can lead to the poor functional outcome (3). Consequently, there are two primary challenges in antidepressant research: (a) developing rapidly acting, safe and effective antidepressant treatments, and (b) developing noninvasive clinically useful biomarkers of antidepressant response with a focus on early indicators of treatment response.

Clinical studies of Ketamine in depression: The serendipitous discovery of the rapid antidepressant effect of ketamine, a widely used anesthetic drug, has opened up development of novel glutamate-based antidepressant treatment strategies. Sub-anesthetic dose (0.5 mg/kg over 40 minutes) of ketamine improves depression symptoms in patients with TRD (4, 5, 13), bipolar depression (14) and post-traumatic stress disorder (15) and also in reducing suicidal ideation (SI) in depressed patients (16, 17). The improvement in depression scores w seen as early as 2 hours; with 71 % of patients deemed as responders at 24 hours (defined as 50% improvement on 21 items HDRS) and the antidepressant effects persisted in up to 35% of the patient at the end of 7 days (4). A subsequent study found that **early antidepressant response to the first infusion was highly predictive of a sustained response to subsequent infusions** (18). Ketamine improved depression symptoms in patients with anxious depression with a longer time to relapse than those with nonanxious depression (19). In summary, ketamine's beneficial effects on mood and suicidality are very promising but further research is required to understand the ketamine's rapid antidepressant effect. The exact underlying neural mechanisms involved in ketamine's rapid antidepressant effect is currently unclear (20). Emerging evidence suggests that ketamine induces early increases in the excitatory synaptic drive through glutamate activity likely through AMPA and initiates synaptic plasticity processes in cortico-limbic regions presumably mediating the antidepressant effects (21, 22).

Preliminary Studies: To assess the safety, pharmacokinetics and antidepressant efficacy of a sub-anesthetic dose of intravenous ketamine in depression. We studied the effect of ketamine in five patients (n=5) with TRD who received a single intravenous infusion dose of ketamine (0.5 mg/kg) for 40 mins. Four out of five patients successfully responded to ketamine at 24 hrs and tolerated ketamine well; thus supporting the feasibility of the procedure. However, the therapeutic effect of ketamine has not been studied in PND.

PRIMARY HYPOTHESES AND SPECIFIC AIMS

Severe Perinatal Depression (PND) is a major depressive episode that occurs during pregnancy or onset within 12 months of the birth of a child. The prevalence of severe PND in the general population is estimated to be 5-10% (2). PND is a seriously disabling condition and can increase the risk of self-harm and health complications in mother can deleteriously affect the cognitive, emotional and social development of the child and increases the substantial economic burden on families and society (3). Selective Serotonin Reuptake Inhibitors (SSRIs) and psychotherapy are the main available treatment modalities for PND. While they are effective in some, it takes longer to work and half of the patients do not fully recover from depression. A faster onset of antidepressant action will be critical in enabling faster relief from depression and may increase the chance of full recovery. The main objective of this study is to investigate the rapid antidepressant effect of low sub-anesthetic dose of ketamine in PND.

Aims

To assess the safety, pharmacokinetics and antidepressant efficacy of a sub-anesthetic dose of intravenous ketamine in perinatal depression

A single, intravenous, sub-anesthetic dose of ketamine in patients with Treatment-Resistant Depression (TRD) induces a significant (50%) reduction in depression symptoms within 2 hours of administration with 65% of depressed patients respond by 24 hours and up to 35% maintain response until the end of 1 week (4). Our in-house pilot data, in consistent with worldwide studies, show that ketamine (N=5) can be safely administered to depressed patients and improves depression symptoms when assessed at 24 hrs post infusion. Ketamine has not been studied in the treatment of PND where there is a significant unmet need.

The dosing of ketamine (0.5 mg/kg over 40 mins) for antidepressant treatment was developed from research studies in the 1990s based on use in healthy participants (36). However, newer studies show some patients respond to lower dose and tolerated better (fewer side effects) by the patients (37). IV Ketamine reaches a peak within a few mins with an elimination half-life of 2–3 hrs (38). Ketamine's clearance may be 20% higher in women than in men (39). Ketamine is mostly metabolized in norketamine (80%) and persists more than 5 h after administration (38). It is important to evaluate ketamine's pharmacokin etic data in PND to improve safety for the

breastfeeding mother and the baby. Ketamine and its metabolites will be evaluated in PND patients receiving ketamine 0.5 mg/kg or 0.2 mg/kg at 30 mins, 2 hours and 4-5 hrs after ketamine infusion. All adverse medical and psychiatric events with onset or worsening after the administration of ketamine will be included in the analysis.

The proposed experiment will be a proof-of-concept study in which we will evaluate the safety, pharmacokinetics, and efficacy of ketamine 0.5 mg/kg and 0.2 mg/kg over 40 minutes in a double-blinded and crossover fashion separated over one week (5) (dose used in antidepressant clinical trials) in PND patients who are not currently breastfeeding. The primary outcome measure of efficacy will be the Hamilton Depression Rating Scale (HAMD-17) at 24 hours and additional secondary anxiety and mood scales. (6). Any adverse medical and psychiatric events will be recorded and summarized. Ketamine and its metabolites will be evaluated at 30 mins, 2 hours and 24 hrs.

Hypothesis 1): Ketamine will significantly decrease (>50%) in HAM-D17 scores at 24 hrs after infusion from baseline. The 0.5 mg/kg dose will be more efficacious that 0.2 mg/kg in improving depression symptoms.

Hypothesis 2) Ketamine will improve anxiety symptoms in PND (as measured using HAM-Anxiety and EPDS) at 24 hrs after infusion in patients with PND. Anxious subtypes are the most common subtype during a late postpartum period representing about 70 % of PND. (40)

Hypothesis 3) Ketamine infusion will be tolerated well by the patients with fewer side effects at 0.2 mg/kg compared to 0.5 mg/kg.

METHODS

Research Design and Methods: All human subjects' research will be conducted with full approval from the IRB at the University of Texas Health Science at Houston. We will recruit PND patients (N=10) who will be administered a single intravenous infusion of Ketamine either at 0.5 mg/kg or 0.2 mg/kg over 40 minutes in a double-blinded and crossover fashion separated by minimum 7 days, with the order being randomized and balances across subjects. Two doses will help decide the safe, tolerable and effective dose for PND subjects will undergo a standard screening interview visit to confirm eligibility evaluations including SCID-4 interview (27) and collection of demographic, clinical and medical history. To ensure medical stability, each patient will have a physical examination and urine toxicology screen to rule out the recent undisclosed use of illicit substances. It will also be requested that the patient provide a record of lab results to indicate adequate health for inclusion.

We will pre-screen potential participants over the phone to minimize the invitation to non-eligible participants. Eligible patients that want to participate in the study will be scheduled to have a screening visit to review consent and determine eligibility.

The total duration of the commitment of the study is minimum of 4 weeks. Extension of the timeline can occur depending on the time between the screening visit and the first infusion dose. The total commitment should not exceed 3 months. There will be a minimum 7 days between the 2 infusions. Patients who qualify will complete the infusions on another day at UTHealth Clinical Research Unit at Memorial Hermann-TMC, Houston. University of Texas Health Science Center at Houston Memorial Hermann-TMC 6411 Fannin St.or at our Harris County Psychiatric Center (HCPC) where they will be given the ketamine infusion by the study nurse. Patients will be advised to follow the American Association Preoperative Fasting Guidelines prior to infusion.

There will be two appointments where they will be administered a single intravenous infusion of Ketamine either at 0.5 mg/kg or 0.2 mg/kg over 40 minutes in the first infusion visit and a second infusion visit where they will receive the infusion that was not given on the first visit, where there will be a minimum of 7 days between infusions.

Before the infusion, the psychiatrist and anesthesiologist will evaluate the patient. During the infusion, patients will be asked constantly about "how they feel" and will be monitored co ntinuously by the registered nurse under the supervision of an Anesthesiologist. EKG and pulse-oximetry will be monitored throughout the procedure to

check for hemodynamic changes. After the completion of 40 min infusion, patients will rest for two-four hours under the observation of clinical nurse.. After the infusion both psychiatrist and anesthesiologist will evaluate the patient. Patients may complete clinical questionnaires after this session at HCPC or CRU for approximately 30 minutes. After the first infusion, patients will be contacted one day after over the phone and after the second infusion, patients will be contacted one day after and 7 days after the infusion. During the phone call, patients will be asked about their physical health, will be asked about adverse events and respond questionnaires that evaluate mood status.

Recruitment: The current project will ensure robust and timely recruitment through coordination with ongoing studies at the UT Center of Excellence on Mood Disorder (CEMD) (Dr. Jair Soares, Departmental Chair). Dr. Selvaraj runs a perinatal clinic focused on pregnant or postpartum women with mood disorders in the psychiatry department. Dr. Selvaraj also collaborates with Dr. Sibai, UTHealth Department of Obstetrics, Gynecology and Reproductive Sciences on a postpartum research project. Additionally, a large research participant registry has been set up by this UT center (n = 4952 over the last 5 years, of which 80% have a mood disorder history).

Recruitment will also be facilitated through the UT Research Match program. On average, 200 patients have a higher report of depression and mental health problems in the last year and of which nearly 100 patients had higher EPDS scores that meet PND criteria. The perinatal psychiatry clinic will facilitate clinical recruitment. Subject recruitment will include initial identification of cohort pool using selection criteria and subsequent review of identified patient records before final vetting and consent.

Study Population: We will enroll 10 patients with Perinatal Depression (PND) in this study. Participants will be female adults, aged 18-45 years, who meet the criteria for PND. Participants will be recruited without regard to race, religion or ethnicity. Participants will be postpartum and no longer breastfeeding or will be willing to stop breastfeeding during the study. Participants will be recruited through flyers and clinic referrals in the Houston area. Women of all ethnic backgrounds will be recruited to participate. It is anticipated that the subject demographic profile will closely mirror the larger population of individuals with PND from which they are recruited. We will do so by posting flyers at community medical clinics, outpatient mental health clinics and local business in the area

Inclusion Criteria:

1) Female subjects, ages 18-45 years

2) Experienced a major depressive episode in the postpartum period beginning within the first 4 weeks following delivery and with moderate or severe symptoms (>12 EPDS or >14 HAM-D).

3) No or partial response to adequate doses of SSRI medications to treat PND for longer than 6 weeks.

4) PND patients will be requested to maintain a stable dose of antidepressants while enrolled in the study trial.

5) Patients that can speak and read the English language are able to understand the study procedures and sign the informed consent

Exclusion Criteria:

1) No current or past psychosis or severe personality disorder.

2) No current substance abuse or dependence.

3) No serious and imminent suicidal or homicidal risk.

4) No recent or history of major and unstable medical problems that affect brain anatomy, neurochemistry, or function.

5) Not diagnosed with cardiovascular disorders.

6) No increased risk of laryngospasm or active upper respiratory infections.

7) Not diagnosed with intellectual disability or neurodegenerative diseases.

8) Mothers that are currently breastfeeding.

9) No current pregnancy.

Clinical and diagnostic assessments:

Screening evaluation will obtain family history and demographic data. An estimated duration of a complete screening visit will be approximately 3 hours or less. Copies of any recent medical evaluations (past medical history, physical exam, etc.) will be requested from treating clinicians and health care providers. We will perform a urine drug screening (UDS) to rule out the recent undisclosed use of illicit substances. Also we will perform a urine pregnancy test. We will also complete a physical examination, height and weight and vital signs. Demographic information is obtained through a standardized form and covers: age, race, gender, education (information both on siblings and their parents), religion, and socioeconomic status.

Patients will complete mood questionnaires rating the severity of the clinical symptoms:

1) SCID–I Interview
2) Hamilton Depression Rating Scale (HAMD-17)
3) Montgomery-Asberg Depression Rating Scale (MADRS)
4) Edinburgh Postnatal Depression Scale (EPDS) scale
5) Young Mania Rating Scale (YMRS)
6) Clinical global improvement (CGI)
7) Brief Psychiatric Rating Scale (BPRS)
8) Generalized Anxiety Disorder (GAD-7)
9) Columbia Suicide Severity Rating Scale (C-SSRS)
10) Hamilton Anxiety Rating Scale (HAM-A)
11) Beck Depression Inventory (BDI)
12) Snaith-Hamilton pleasure scale (SHAPS) (29).

We will also collect exploratory data on subjective anhedonia (SHAPS) measurements to investigate ketamine's effect on specific reward and motivation functioning in this spectrum of psychiatric patients.

All aforementioned assessments may be administered in a standard manner involving researcher or self-report questionnaires on paper, or they may be administered using Qualtrics, which is a HIPAA compliant electronic data collection tool widely used in research. When the latter is used, participants will be invited to complete questionnaires on a computer or tablet.

Assessment	**Screening (at BBSB)**	**Infusion Day 1 (at HCPC or CRU)**		**Infusion Day 2 (at HCPC or CRU)**		**Follow up post infusion 1 and again post infusion 2 Day 1 (by phone)**		**Follow up post infusion 2 Day 7 (by phone)**
		Before Infusion	After Infusion	Before Infusion	After Infusion	Post infusion 1	Post infusion 2	Post infusion 2
Informed Consent	X							
Eligibility Review	X	X		X				
Demographics and Psychiatric/Medical History	X							
Physical Examination	X	X		X				
Assessment by anesthesiologist and psychiatrist.			X		X			
Urine Drug screen	X	X		X				

Urine pregnancy test	X	X		X			
Vital Signs	X	X		X			
Height and Weight measurement	X						
Blood Collection		X	X[1]	X	X[2]		
Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I)	X						
Hamilton Depression Rating Scale (HAMD-17)	X	X	X	X	X	X	X
Montgomery-Asberg Depression Rating Scale (MADRS)	X	X	X	X	X	X	X
Edinburgh Postnatal Depression Scale (EPDS) scale	X	X	X	X	X	X	X
Young Mania Rating Scale (YMRS)	X		X		X		
Clinical global improvement (CGI)	X		X		X		
Brief Psychiatric Rating Scale (BPRS)	X		X		X		
Generalized Anxiety Disorder (GAD-7)	X	X	X	X	X	X	X
Columbia Suicide Severity Rating Scale (C-SSRS)	X		X		X		
Hamilton Anxiety Rating Scale (HAM-A)	X		X		X		
Snaith-Hamilton pleasure scale (SHAPS)	X		X		X		
Beck Depression Inventory (BDI)	X	X	X	X	X	X	X
AE Report	X		X		X	X	X
Concomitant Medications	X		X		X		
Study Contact Card given			X		X		

[1] Done at 30 minutes after infusion (+/-10), 2 hours after infusion (+/- 30 minutes) and 4-5 hours after infusion.

Patients that are unable to arrive to the appointment with a caregiver will be reimbursed transportation up to $50 dollars on infusion days. They will receive a phone call that same day to ensure safe arrival home.

All of the above clinical questionnaires will be completed at the screening visit as well as on the ketamine infusion day, except the SCID-I, which will only be completed at the screening.

All data collected on paper forms will be stored in locked cabinets, while electronic data is stored on our secure password protected server (maintained by the UTHealth Medical School Information Technology Department). All electronic records will identify study participants only by a study code, and the electronic file linking codes to individual identifiers will be destroyed once data collection is complete.

Patients will arrive fasting from midnight on study visit day have blood draws and complete questionnaires at our clinical research suite at UTHealth's Biomedical and Behavioral Sciences building (BBSB) at 1941 East Road, Houston TX 77054 or at UTHealth CRU at Memorial Hermann-TMC, Houston. University of Texas Health Science Center at Houston Memorial Hermann-TMC 6411 Fannin St.or at UT Health Harris County Psychiatric Center (HCPC)

Placement of IV: For both of the infusion days, after the initial evaluation is done, patients will be placed one intravenous line in each arm. One line will be used for the ketamine infusion and the other line will be used for the collection of blood samples and to reduce discomfort for patients with frequent blood draws. If the sample is not obtained from the IV line due to clotting, the patient will be asked if they would like to have a blood draw using a BD Vacutainer.

Medical Monitoring: During the infusion, patients will receive continuous monitoring from the nurse and the attending and after the completion of 40 min infusion, patients will rest for two hours under the observation of clinical nurse and reassessed again by anesthesiologist/psychiatrist (advance life support trained) at 2 hours after infusion. Patients will be discharged from the hospital unit between 2-4 hours after the infusion with a responsible adult for the study visit. Patients will be contacted on days 1, 2 and 7 post-infusion for a follow-up assessment of mental state by telephone and will be scheduled for study visits.

Stopping Rules: Any worsening of depression symptoms - if patients score a 3 on item 3 of the HDRS or 3 on item 10 of the MADRS or total HDRS score (first 21-items) increases by 5 points or more from one visit to the next weekly visit. The C-SSRS will be administered to monitor suicidal ideation and behavior. Increased observation consists of daily phone calls with study physicians and/or increasing visit frequency based on the PI's clinical judgment.

Blood tests: Ketamine and norketamine plasma levels will be collected before and 30 minutes, 2 hours and 4 to 5 hours after the infusion**.** Samples will be stored at BBSB for analysis. Analyses will be performed by Gas Chromatograph-Mass Spectrometer (30).

Clinical measures - Clinical rating and questionnaires will be administered. Treatment response will be operationally defined as 50% improvement from baseline in the HAM-D17 scores.

POTENTIAL RISKS/DISCOMFORTS

Diagnostic procedures and questionnaires: Some of the questions asked during the screening may be considered sensitive information, including drug use history and psychiatric history. Answering these questions may be psychologically discomforting to some subjects. There are also risks associated with loss of confidentiality.

Ketamine infusion: The most commonly reported side effects during the 4 hour period after each infusion include feeling strange or unreal (58.3%), abnormal sensations (54.2%), blurred vision (30.0%), feeling drowsy or sleepy (48.5%) and headaches (30-40%). Based on previous evidence, we do not expect ketamine to impair

cognitive functions such as memory, attention or language. If patients are currently taking certain medications on a daily basis within 24 hours prior to and/or after receiving ketamine, they will not be able to take these medication(s) while receiving a ketamine infusion without clearance or approval of the physicians involved in administering ketamine. Medications include: Sedatives (e.g., clonazepam, lorazepam, alprazolam); Antibiotics (e.g., azithromycin, clarithromycin); Antifungal agents (e.g., ketoconazole); Tramadol. This is due to concerns for potentially increased sedation or trouble breathing. One third of the patients exposed to standard repeated infusions of IV ketamine reported some kind of hemodynamic change such as elevated blood pressure (BP) and/or heart rate (Murrough et al., 2013b) that usually resolves shortly after the ketamine infusion (aan het Rot et al., 2010; Murrough et al., 2013b). It has been reported that initial hypertensive episodes and transient tachycardia are predictive of hemodynamic changes with subsequently repeated ketamine infusions (aan het Rot et al., 2010). Ventricular premature contractions, hypotension, and non-significant changes in oxygen saturation have also been reported with low-dose (0.5mg/kg) ketamine infusions over 40 minutes.

Confidentiality: Loss of confidentiality is a highly unlikely but potential risk associated with this study. Some participants may find questions annoying or intrusive and neuropsychological testing might induce some fatigue and sensation of boredom. The venipuncture (insertion of small IV due to the need for IV infusion of ketamine) might produce some mild pain, bruising, bleeding, infection, and in some cases, even induce fainting. Side effects associated with ketamine injection are rare and, if any, of transient duration. The most commonly reported side effects during the 4-hour period after each infusion include feeling strange about body sensations58.3%), or abnormal sensations (54.2%), blurred vision (50.0%), feeling drowsy or sleepy (45.8%) (Murrough et al., 2013b) and headaches (30-40%) (aan het Rot et al., 2010). Based on the previous evidence, we do not expect ketamine to impair cognitive functions such as memory, attention, and language (aan het Rot et al., 2010).

The Human derived biological sample (HDBS) bank administered by the University of Texas Health Science Center Houston (UTHSC-H) will remain with UTHSC-H unless the UTHSC-H agrees to release and/or transfer the samples. Please be aware that if the PI leaves the University, the samples within the HDBS bank will remain the property of UTHSC. The University's ownership includes the right to transfer ownership to other parties, including commercial sponsors.

Adequacy Of Protection Against Risks

Recruitment and Informed Consent: Participants will be self-referred in response to various study advertisements via flyers. Individuals who call for information will be given a brief description of the study. Those interested will then be asked to answer questions about their disease status. A trained research assistant will conduct this telephone-screening interview. Eligible subjects will be scheduled for an in-person screening visit at the BSBB.

Once eligible for the study screening visit, they will be invited for study Day #1, which will begin with the presentation of the informed consent form. The consent form will detail the requirements of study participation (e.g., # of visits, type of data collected, time commitment, etc.) Subjects will be told that the purpose of the study is to evaluate neurophysiological measures to study the effect of ketamine on PND. Subjects will be informed that they will have to attend a total of 2 visits (screening/baseline and 1 study visit) and 2 follow up phone calls. Other information on the consent form will include a full description of study requirements, reimbursement, risks, benefits, alternatives, and the role of the local IRB. All questions will be answered before written consent is requested. Informed consent will be obtained only by the PI or a trained senior member of the staff (e.g. study coordinator).

The research protocol, consent form, and all assessment/advertising materials will be reviewed and approved by the Committee for the Protection of Human Subjects (CPHS) at UTH.

Protections against risk

1. *Risks related to diagnostic procedures/questionnaires:* As noted above, the primary risks related to these procedures are participant discomfort and loss of confidentiality. Regarding participant discomfort, we will make clear that we ask for this sensitive information as part of the consent process. Further, while subjects may be uncomfortable reporting these issues, the risks of serious sequelae are extremely low. Regarding confidentiality, we have rigorous procedures in place to ensure confidentiality of data,

including locked cabinets for confidential files, participant coding, secure computer systems, and rigorous training of personnel. Computer systems are secure and strictly monitored by University IT staff. Laboratory staffers are trained in confidentiality of participant information. No information is allowed to leave the lab or to be accessed by a computer outside of the university's secure computer system, and all data are further protected by permissions and passwords given only to necessary research personnel. No information will be published in a form in which the participant can be identified. We will also obtain a Certificate of Confidentiality for this study to provide additional protection for sensitive information.

2 *Risks related to study medication:* The following procedures will be taken to safeguard against adverse medication events: (1) careful initial intake evaluation to determine eligibility based on inclusion/exclusion criteria; (2) thorough physical evaluation prior to infusion, consisting of physical examination, standard laboratory tests, electrocardiogram, urine toxicology screen, pregnancy test and vital signs; (3) Monitoring of concomitant illicit drug use at each visit with self-report, urine and/or breath testing; (4) Review of medication response, adverse events, and medication compliance with the study nurse; (5) Regular evaluation of all medical information. In the event that contraindicated medical conditions and/or other serious adverse symptoms arise after initiation of the medication, medication will be discontinued and the subject will be examined.

3 *Risks related to alternative treatments:* As noted above, we believe that our therapeutic interventions provide treatment that is considerably superior to most, if not all, treatment opportunities in the community. Nevertheless, we will refer patients to other facilities upon request or when required by other circumstances. We will also conduct regular literature searches on alternative treatments, and in the event that an alternative treatment emerges with clearly superior efficacy, we would suspend the current study and provide all participants with referrals for this alternative treatment.

4 *Study withdrawal*: The research study and participation is completely voluntary. Participants can withdraw from the study at any time without giving a reason and without any consequence. A decision not to take part or to stop being a part of the research project will not change the services available to them from the UTHSC-H, Department of Psychiatry or HCPC or CRU. The investigators could stop participation if an unfavorable or unexpected reaction is noticed.

5 *Unanticipated Hospitalizations:* If a patient needs to be hospitalized for worsening of symptoms or for their own personal safety, they will be removed from their study participation and their study treatment will end at that time.

6 *Risks of blood draw:* There are minimal risks involved in having the blood draw for the study. The blood sample will be drawn from a peripheral vein by a trained staff person. The risks involved are related to local bruising but these will be minimized by the use of trained personnel.

Potential benefits of the proposed research to the participants and others

All assessment and services provided in these studies will be free. The treatments may help in PND and prevent relapse. Subjects will be told if the unusual information is discovered during the study that will make a difference in treatment for this or other problems. By taking part in this research, subjects will help others with similar problems because this study is likely to identify how the treatment works and could also lead to the development of biomarkers for monitoring treatment response.

Importance of the knowledge to be gained

Research participation will help the patients in curing PND and possibly preventing relapse. The selected medication has shown preliminary evidence of benefit in helping patients with PND. PND is highly prevalent and leads to devastating consequences on a personal and societal level. Further, this study will pilot new approaches to evaluating treatments that may lead to more personalized and effective treatments for PND. The above-stated risks are relatively mild in degree and procedures have been designed to minimize their probability. We believe this protocol has an extremely favorable risk/benefit ratio. The psychiatry department has an excellent track record in conducting similar controlled trials with the utmost attention to safety.

Reimbursement
Patients will be provided $20 for their participation in the screening visit if they qualify to complete the rest of the study. Patients will also be compensated $100 if they complete the ketamine infusion study visit.

Transportation during infusion days
Patients will be asked to be accompanied by a caregiver that will be able to transport them after the ketamine infusion and to ensure that the patients arrive home safely. If patients are unable to provide a caregiver that can transport them, we will pay for transportation up to $50 for infusion days and will call the patient to ensure safe arrival.

Follow up plan
Patients considered as participants of the study will be referred to Dr. Selvaraj as a treating psychiatrist if they are not his patients. Patients who are referred by existing providers will return under the care of their care. If they have successful treatment with ketamine, they will be referred to a list of providers in the area of Houston that provide ketamine infusions as treatment for depressive symptoms, if the patient would want to consider continuing with the treatment as needed.

Data and Safety Monitoring Plan

The principal investigator will be responsible for the Data and Safety monitoring of the study.

Data monitoring plan
Data will be collected and stored as described above in Sources of Material and analyzed with primary outcomes as described in the Statistical Plan. Trained research assistants will enter data into an existing, relational database. Allowable input values will be restricted to standardized Access entry forms so as to maintain data integrity. All observations will be double-entered to verify the accuracy, with any problems detected discussed with the PI. If necessary, the re-training of research assistants will be conducted. Due to the comparatively small and initial nature of the current trial, interim data analysis is not planned.

Safety monitoring plan
During the screening, study applicants will undergo a complete psychological and physical exam to determine their eligibility and safety of their participation in this study, per inclusion/exclusion criteria detailed above. During the treatment phase of the study, participants will be asked about adverse events at each clinic visit and vital signs will be continuously monitored during the infusion and two hours after the infusion.

All adverse events (AEs) occurring during the course of the study will be collected, documented, and reported to the Principal Investigator. The occurrence of AEs will be assessed at baseline and each visit during the treatment phase of the study. The PI, in consultation with the co-investigators, will review any AE's as soon as they are reported. The study investigators will follow all AEs to the point of a satisfactory resolution. A study participant may have their medication discontinued of may be withdrawn from the study if the Study Physician determines it is the best decision in order to protect the safety of a participant. All AEs will be assessed to determine if they meet criteria for an SAE.

Serious adverse events (SAEs), as defined by the FDA, will be evaluated at each visit. Any SAE, whether or not related to study medication, will be reported to the IRB within 24 hours. The initial SAE report will be followed by submission of a completed SAE report within 2 days. In the event that a patient either withdraws from the study or the investigator decides to discontinue a patient due to SAE, the patient will have appropriate follow-up medical monitoring. Monitoring will continue until the problem requiring hospitalization has resolved or stabilized with no further change expected, is clearly unrelated to study medication, or results in death. The outcome of SAEs will be periodically reported to IRB.

Inclusion of Women

The subjects will include only females, ages 18-45 years old, from various race/ethnic backgrounds, as reflected in the local community in the greater Houston area.

Inclusion of Minorities
Our study will include minority groups in proportions that will be representative of the ethnic/racial composition of the local community in Houston, Texas. Our projected numbers for minority enrollment are detailed in the enrollment table attached.

Inclusion of Children
Children will not be included in the study. The inclusion of children at this early stage would increase substantially the number of subjects needed for the overall project and would not be conducive to the perinatal nature of the study. At this time, we will focus on an adult population (ages 18-45 years old).

Prisoners and pregnant women
We are aware of the special protections afforded to prisoners per federal regulations. We will not actively recruit people who are incarcerated to participate in this study. We do, however, acknowledge the possibility of research participants in our target population being incarcerated during the study. If an active participant is incarcerated for an extended period of time, disenrollment from the study will be necessary. No research interaction or intervention will take place until an incarcerated participant is released from jail. Finally, neither the pregnant woman nor neonates will be enrolled in this study. Women will only be recruited postpartum and after having weaned their child.

DATA ANALYSIS PLAN - **General Data Analysis:** The data analytic strategy will use generalized linear modeling. Statistical analyses will use SAS v.9.3. Preliminary data analyses will inspect baseline, treatment from baseline differences as well as correlations between baseline variables and specified outcomes. Baseline characteristics will be compared within groups using Student's t-tests for continuous data and chi-square tests for categorical data.

> **Sample size justification:** our power calculation is guided by a previous study - intravenous ketamine in TRD patients (28) with effect size (Cohen's d = 1.46) or Brexanolone in PND (effect size 1.2) (12, 32). For an effect size 1.2, a total of 10 PND patients will be required for within-subject design with probability 95 % that the study will detect a treatment difference at a one-sided 0.05 significance level.
>
> **Hypothesis:** Based on previous studies (33, 34) and our pilot Ketamine TRD patient data, we predict that ketamine infusion compared to baseline will significantly decrease HAM-D scores in PND patient at 24 hrs. The severe anxious subtype will have prominent improvement.
>
> **Analysis:** We will use linear regression to assess associations between improvements in depressive symptoms (change in the HAM-D from baseline using LOCF). A paired t-test was performed to evaluate the key efficacy measure - change from baseline in HAMD total score. We will also perform a secondary analysis comparing change from baseline to endpoint using last observation carried forward (LOCF) using a paired sample t-test. Secondary outcomes are safety and tolerability measures, including treatment-emergent AEs and changes from EPDS, GAD-7, PHQ-9, and C-SSRS. We will also investigate specific markers for treatment response.

Alternate plans: The proposal applies the widely used ketamine sub-anesthetic dose (0.5 mg/kg) as a treatment for PND. If the effect is less clear or patient experiences any adverse effects, alternate strategies will be explored (two doses of ketamine instead of single or low dose 0.3 mg/kg if adverse effects etc. respectively). Patient safety and tolerability will be the most important guiding principle. This will require an amendment in the protocol and an updated consent.

JUSTIFICATION - Research in PND is of critical importance due to its substantial burden on mother, family and child's emotional, cognitive and behavioral development. Rapid and effective treatment of severe PND is a significant unmet need. The primary goal of the project is to evaluate the safety and efficacy of sub-anesthetic antidepressant dose ketamine treatment in severe PND patients. This proposal will be the first systematic investigation of ketamine's antidepressant effect in PND. The study design is simple and robust that can provide

early treatment response signal without significant additional discomfort for patients. The results from this pilot proposal could potentially yield critical information regarding markers of treatment response in PND - a potentially high impact research area. the

Having a placebo group in this research project would not we warranted at this place since the aim is to determine if a lower ketamine dose would be as effective and with lower side effects for PND patients.

Data Handling and Record Keeping

This study will acquire, use and create individually identifiable health information (known as Protected Health Information or PHI). Confidentiality will be protected at all times by having research records identified by code number only. All research information will be stored in locked files at all times. Only authorized research staff will have access to the information gathered in this study. Only subjects capable of providing consent will be included in the study.

As per the Health Insurance Portability and Accountability Act (HIPAA), all individuals who are eligible and agree to participate in this research study will be required to sign a HIPAA research authorization prior to participation. If an individual refuses to sign the HIPAA research authorization, they will not be able to participate in this study. The HIPAA form is part of the official consent form.

Data will be stored separately from the participants' identifiers. Both will be stored on encrypted drives on computers in locked offices. Confidentiality will be protected by having research records identified by code number only. All research information will be stored in locked files at all times. Only authorized research staff will have access to the information gathered in this study. All paper data will be stored on the 3rd floor of the UT Department of Psychiatry, at the BBSB (room number 3260) in a double-locked cabinet. The electronic data will be stored on the L drive, in a subfolder labeled "BPRC", located under the subfolder "UT Center of Excellence on Mood Disorders". An Accounting of Disclosure (AOD) will be created and maintained for any disclosure of individually identifiable information (III) outside the UTHSC-H. The manual spreadsheet will include the date of the disclosure, nature or description of the III disclosed the purpose of each disclosure and the name and address of a person or agency to which the disclosure was made.. Strict monitoring of hemodynamic and respiratory changes as well as psychiatric screening will be performed during each infusion of ketamine.

Ethics

IRB approval will be sought from CPHS for the University of Texas Health Science Center at Houston. Written informed consent will be obtained directly from the subject. Privacy and confidentiality will be maintained with a special number to be used to identify the subject in the study and only the investigator and his research staff will know their name.

Quality control and assurance

No plans to have ongoing third-party monitoring. However, we will conduct routine (bimonthly) reviews of consistency, reliability, and accuracy of data collected for any paper records. Similar checks for any data in electronic form will also be conducted but in an automated fashion (e.g checking for accurate time/date stamps, file sizes etc.).

Publication Plan

We plan to present preliminary versions of the findings at conferences during the first and second year. Definitive publication of findings will occur in the 6-12 months following the end of the two-year award period.

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