Cover page:

Title: Investigation of the NMDA Antagonist Ketamine as a Treatment for Tinnitus

NCT03336398

IRB approval date: March 4, 2025

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Lay Summary of Proposed Research

This section is intended to provide a basic overview of the study including a description of its purpose, study procedures, and subject population. The summary should provide a concise overview of the study for non-scientific and scientific members of the IRB. Please avoid medical or technical terminology. In general, the abstract of a grant does not provide a suitable lay summary.

Tinnitus, or ringing in the ears, is a very common problem that often accompanies hearing loss. It affects up to 1 in 10 adults, and about 30% of people who experience chronic tinnitus find it very distressing. In these patients, symptoms of depression and anxiety often accompany tinnitus and there are no approved treatments. Clinical trials are ongoing to test a glutamate NMDA receptor antagonist (called esketamine), which is injected into the inner ear. However, the preliminary results with this medication show that it only works for tinnitus that results from acute injury. It does not treat tinnitus resulting from progressive hearing loss.

Research in humans and animals suggest that the neurotransmitters glutamate and GABA are important in the development and maintenance of tinnitus. This data shows that overactivation of the NMDA receptor and a decrease in GABA signaling in the brain play a crucial role. Studies from our institution show that ketamine, which an antagonist at the NMDA receptor, increases GABA levels in the brain in subjects with depression. Thus, in this experiment, we will test the effect of ketamine on tinnitus since it blocks the NMDA glutamate receptor and increase GABA levels.

Background, Significance, and Rationale

In this section, provide a brief summary of the status quo of the relevant work field and how the proposed study will advance knowledge. Specifically, identify the gaps in knowledge that your project is intended to fill. If no gaps exist that are obviously and directly related to your project, explain how your proposed research will contribute to the overall understanding of your field. Describe potential impacts of your project within your field of study and in a broader context. Provide a critical evaluation of existing knowledge. The literature review does not have to be exhaustive.

Tinnitus has a prevalence of approximately 1 in 10 adults in the United States (Bhatt, 2016). Among those with tinnitus, 36% had nearly constant symptoms and almost 30% of those report that their tinnitus as a big or a very big problem. Currently there are few effective treatments for tinnitus, and no approved medications. Cognitive behavioral and retraining therapy provide some relief, but many patients fail to respond (Bhatt, 2016).

Animal research and human studies indicate that maladaptive plasticity plays a role in tinnitus, which involves glutamatergic signaling largely at the NMDA and AMPA receptors. Additionally, GABA signaling has been shown to be impaired in tinnitus. Rodent models show a diminished sensitivity to GABA signaling (Llano et al., 2012) and human

magnetic resonance spectroscopy (MRS) studies show decreased GABA levels in the auditory cortex (Sedley et al., 2015). Ketamine is a non-competitive NMDA receptor antagonist that has also been shown to activate AMPA receptors (Zanos et al., 2016), and modulates ongoing plasticity. Additionally, ketamine activates a subpopulation of cortical GABAergic interneurons and projection neurons and increases GABA levels in the human brain, measured with MRS (Rodriguez et al., 2015, Milak et al., 2016). Ketamine is FDA approved as an anesthetic, and recent work has demonstrated its efficacy in treating refractory depression and chronic pain. Importantly, these demonstrate that low dose ketamine, at doses lower than those required for anesthesia, are effective in lifting depressed mood and improving the sensation of chronic pain (Radvansky et al., 2015).

For many, tinnitus has an important affective component to it, with distress and co-morbid symptoms of depression and anxiety (Guitton 2012, Pattyn et al., 2016). The onset and severity of tinnitus can correlate with stressful events (Guitton 2012, Pattyn et al., 2016), and it has been posited that stress lowers the threshold of perception, and unmasks tinnitus (Guitton, 2012). Tinnitus then triggers more anxiety and depressed mood, which in turn reinforces the symptoms (Guitton, 2012, Pattyn et al., 2016). An advantage of ketamine may be its effect on depression and anxiety, in addition to tinnitus, to interrupt this cycle.

Our goal is to perform a proof-of-concept preliminary study of ketamine in tinnitus associated with sensori-neural hearing loss. MRS imaging will be used to assess ketamine-induced changes in GABA in the auditory cortex.

Specific Aims and Hypotheses

Concisely state the objectives of the study and the hypothesis or primary research question(s) being examined. There should be one hypothesis for every major study procedure or intervention. For pilot studies, it is important not to overstate the study's objectives. If there are no study hypotheses, describe broad study goals/aims.

Specific Aim 1: To test the effect of ketamine in subjects with tinnitus. We will use a randomized, cross-over design in 40 subjects. Each subject will receive ketamine (0.5 mg/kg IV) versus placebo. Subjects will serve as their own controls and the sessions will be performed in a controlled laboratory environment with experienced personnel. We will use the dose of ketamine that has been shown to be effective in depression and anxiety disorders (0.5 mg/kg), administered intravenously, to allow the delivery to be paced and carefully controlled. The outcome measures will include measures of tinnitus burden, depression and anxiety.

Specific Aim 2: To investigate changes in GABA in the auditory cortex before and after ketamine administration. An MRS imaging study has shown a decrease in GABA levels in the right auditory cortex in tinnitus subjects (Sedley et al., 2015). Our group has shown that ketamine (0.5 mg/kg IV) increases cortical GABA, measured with MRS, in subjects with obsessive compulsive disorder and depression (Rodriguez et al., 2015, Milak et al., 2016). Thus, our hypothesis is that ketamine will increase GABA levels in the auditory cortex, in subjects suffering with tinnitus. We will investigate the correlation between the change in GABA with symptom improvement.

Description of Subject Population

In this section, you are to describe each subject population of the study. The demographics of the population should reflect the gender and ethnic distribution of each population being studied. Enter each subject population's sample size, Gender, Racial, and Ethnic breakdown, and finally, describe each subject population.

Example:

Sample subject population:

Subject Population	Number of completers required to accomplish study aims	Projected number of subjects who will be enrolled to obtain required number of completers	Age range of subject population
Participants with tinnitus	30	60	21-60

Suicide Risk Management Plan

This section will include all information regarding the Suicide Risk Management Plan.

Any participant reporting suicidal ideation or behavior to any member of the research team will be evaluated. If the patient is an active suicide risk, 911 will be called and/or the participant will be escorted to the Emergency Department. If the participants is not an active risk, they will be provided with referrals for outpatient treatment. If the participant has outpatient treatment in place, their clinician will be notified.

Recruitment Procedures

This section will include all information regarding your study's recruitment process/procedures.

Describe settings where recruitment will occur. Subjects will be recruited through advertisements or word of mouth

How and by whom will subjects be approached and/or recruited? As above

Clinical Trials:

Please provide the NCT Registration Number for your Clinical Trial. **NCT03336398**

YOU MUST REGISTER AT ClinicalTrials.gov IMMEDIATELY UPON RECEIPT OF IRB APPROVAL AND PRIOR TO ENROLLMENT OF THE FIRST SUBJECT. YOU WILL BE PROVIDED WITH A NCT REGISTRATION NUMBER ON REGISTRATION. PLEASE REVISE THIS SECTION OF THE PROTOCOL SUMMARY FORM TO INCLUDE THE NCT NUMBER AND RE-SUBMIT AS AN AMENDMENT TO THE IRB.

Concurrent Research Studies

In this section, please identify if subjects in this study participate in or will be recruited from other studies.

Describe where subjects are recruited from. [N/A]

Describe the recruitment source for (Must provide IRB Number, PI and Title). [N/A]

Inclusion/Exclusion Criteria

This section details your study sample(s) and addresses the requirement for risk minimization.
You may choose to divide your sample by population (healthy controls vs. patient population) or by procedure (subjects who will have an MRI vs. those who will not) and then define different sets of criteria for each.

For each sample, create or insert a table to describe detailed criteria for study inclusion and exclusion and the method you will use to ascertain each criterion. The method of ascertainment may describe tests, scales and instruments. When relevant, indicate the level of training of the person who will make the assessment (e.g. clinical interview by a psychiatrist).

Inclusion/Exclusion Criteria need to be numbered and listed in outline form (see Table template below).

Participants with tinnitus

CRITERION	METHOD OF ASCERTAINMENT
Inclusion:	
1. Subjects aged 21-60	Self-report
2. Tinnitus associated with at least mild sensori-neural hearing loss of at least 6 months duration	Medical History
3. Score on the Tinnitus Handicap Inventory (THI) of at least moderate symptoms	Tinnitus Handicap Inventory (THI)
Exclusion:	
1. DSM-V psychiatric disorders other than mild-moderate depression and anxiety, including substance use disorder	Psychiatric Interview.

2. History of recreational ketamine use, recreational PCP use, or an adverse reaction to ketamine	Medical/Psychiatric Evaluation
3. Currently taking psychotropic medication (e.g. antipsychotics, tricyclic antidepressants, monoamine oxidase inhibitors, or benzodiazepines).	Medical/Psychiatric Evaluation
4. Presence or positive history of significant medical or neurological illness, including high blood pressure, cardiac illness, abnormality on EKG, head injury	Medical/Psychiatric Evaluation, Physical Exam, EKG
5. Pregnancy, abortion, or lack of effective birth control during 15 days before the scan	Medical Assessment, pregnancy test
6. Metal implants, pacemaker, other metal (e.g. shrapnel or surgical prostheses) or paramagnetic objects contained within the body which may present a risk to the subject or interfere with the MR scan. Medicinal patch that cannot be removed for the scan.	Medical/Psychiatric Evaluation, Physical Exam (NYSPI)

Consent Procedures

Explain, in this section, the procedures for obtaining consent from study participants.

If the eligibility screening for this study is conducted under a different IRB protocol, enter the NYSPI IRB# Screening is conducted under this protocol only.

Waiver of Consent / Authorization

The following sections are to be completed for the appropriate waiver/alteration of consent.

Waiver of Consent for use of Protected Health Information (PHI)

What records do you wish to review?

What information are you seeking access to? [ ]

Describe your plan to protect identifiers from improper use and disclosure. [ ]

Describe your plan to destroy the identifiers as soon as possible, consistent with the conduct of the research, or provide a health or research justification for retaining the identifiers or explain how retention is required by law. [ ]

Explain why the research could not be practicably carried out without the information (for which you are requesting access). [ ]

Explain why the research cannot be practicably carried out without the waiver. [ ]

Explain how/if subjects will be provided with additional pertinent information after participation. [ ]

Justification for Waiver or Alteration of Consent

Waiver of consent is requested for the following. [ ]

Explain why your research cannot be practicably carried out without the waiver or alteration. [ ]

Describe whether and how subjects will be provided with additional pertinent information after participation. [ ]

Waiver of Documentation of Consent

Would the consent form signature be the only link between the subject's identity and the research data? [ ]

Is breach of confidentiality the main study risk? [ ]

Is consent for this research procedure ordinarily not required outside of the research context? Explain. [ ]

Describe the study component(s) for which waiver of documentation is requested. [ ]

Waiver of Parental Consent

Explain why parental/guardian consent is not a reasonable requirement to protect the minor participants in this study. [ ]

If parental consent is waived, describe a mechanism that will be substituted to provide appropriate protections for the subjects. [ ]

Independent Assessment of Capacity

This section is designated for those studies that have been identified where subjects May Lack capacity to consent.

Describe the Methods/procedures for capacity assessment. [N/A]

If your study involves subjects who DO LACK capacity to consent, please justify. [ ]

Procedures for surrogate consent. [ ]

Study Procedures

Provide a clear, concise narrative of study procedures with special attention to the subjects' involvement. Detail the overall study timeline and location of study procedures, list all interventions, assessments and interviews, estimate the duration of each procedure, provide dosing schedules, identify study personnel involved in each procedure, and provide credentials for relevant personnel. If treatment is provided, specify the minimum credentials for providing that treatment. For complicated study designs, we strongly encourage attaching tables, flow-charts, and study algorithms.

Screening: Screening will occur in two steps. The first will be a virtual visit and the second will be in person. Subjects will be provided with the screening CF prior to the virtual visit, either an electronic (via encrypted email) or paper (via standard mail) version. Screening consent and can be signed by a trained research assistant/study coordinator (Alex Grassetti) or a study physician. Participants may provide verbal (not written) consent for the screening process in order to minimize in-person contact and travel. If verbal consent is to be obtained, study personnel will ensure that the participant has an electronic (via encrypted email) or paper (via traditional mail) copy of the consent form and has had sufficient time to read it through and form questions. Study personnel will discuss the document, the study, and any other questions the participant might have. The consent process will include discussion of the technology HIPAA-compliant platforms to be used.

The screening visit will include: 1) a collection of blood samples (about 15 cc) for routine medical tests and a pregnancy test (females of childbearing potential); 2) a urine sample for urine analysis and toxicological screen; 3) an EKG; 4) a diagnostic interview 5) a physical exam.

Screening will also include the following scales: The Tinnitus Functional Index (TFI): The TFI is a widely used and reliable self-administered test to determine the degree of functional impairment in tinnitus patients (Meikle *et al*, 2012). 2) The Tinnitus Handicap Inventory (THI), a widely used and reliable self-administered test to determine the degree of distress in tinnitus patients (Newman et al., 1996). The THI consists of 25 questions that cover three domains: functional, emotional, and catastrophic; 3) Visual Analogue Scale (VAS), a straight line of 10 mm with no numbers other than 0 (no tinnitus) to 100 (maximal experience of tinnitus). The subject marks their level of tinnitus (loudness and annoyance) on the line, and the outcome is measured in millimeters; 4) The Beck Depression Inventory (BDI), a 21 question multiple choice inventory used to asses depressed mood, including irritability, physical symptoms of depressed mood, and

distress; 5) Profile of Mood States (POMS), is a questionnaire used to assess mood states, and includes scales that investigate depression/dejection, tension/anxiety, fatigue/inertia, confusion/bewilderment. 6) The Beck Anxiety Inventory (BAI), a 21-item self-report measure of anxiety. The scales will be obtained at screening, at the beginning and end of the ketamine/placebo sessions, and daily for 10 days after the sessions. As much as the screening procedures as possible will be acquired remotely via a HIPAA compliant method**.** The questionnaires will be completed via Qualtrics (remotely) prior to the in-person visit.

MRI scans and ketamine infusion:

The research team will review the imaging facility safety guidelines with the participant and answer any questions they may have. While at the imaging facility participants will be required to wear a mask not containing metal (KN-95) and gloves. The participant will be met in the lobby of the imaging facility by a single member of the research team, also wearing an MRI compatible mask and gloves, at this time their temperature will be checked to ensure they do not have a fever. Participants with normal temperatures will be escorted down to the scanner. The participant and the research team will wear metal-free masks throughout the interaction, from first physical contact between researcher and staff in the lobby to seeing the subject off in the lobby after the scan. If the researcher deems it appropriate, the participant may shift their mask to their chin while in the scanner.

Prior to ketamine or placebo administration, the subjects will be positioned in the MRI scanner. The MRS scans will be obtained with 0.5 mg/kg IV of ketamine hydrochloride in saline or saline alone, administered over 40 minutes. The MRS data frames will be acquired (as follows: one pre-ketamine, and 5 following the 40-minute ketamine infusion. Each scan session is up to 2 hours in time. A study physician (Drs. Martinez or Wai) will be present during the ketamine and placebo infusions. The two scan sessions will occur on different days, separated by at least 14 days.

Vital signs will be constantly monitored prior to, during, and after the ketamine infusion until the end of the MRS scan. Blood pressure and heart rate will be monitored and recorded at baseline and at 5-minute intervals and throughout the ketamine infusion. After that, vital signs will be acquired every 10 minutes until at least 90 minutes have passed since the beginning of infusion. The ketamine will be stopped for systolic BP increases to > 180 mm Hg and remains > 180 mm Hg for more than **5** minutes, or diastolic BP increases to > 110 mm Hg and remains > 110 mm Hg for more than 5 minutes. Subjects will be asked to stay until: 1) at least 1 hour after the end of the MRS scan has passed, 2) there are two measurements at least 15 minutes apart that are within 10 mmHg of the baseline systolic and diastolic blood pressure; 3) the acute subjective effects of ketamine have subsided. They will be assessed by a study physician prior to being discharged home. Transportation home will be provided for using a car service.

Briefly, a high-speed localizer imaging series will be obtained, followed by a volumetric T1-weighted spoiled gradient recalled echo scan. Brain spectra containing GABA and Glutamate/Glutamine (Glx) resonances will be acquired of the auditory cortex using the volume-selective PRESS J-editing difference method. Data will be acquired from a voxel oriented parallel to and placed superiorly abutting the Sylvian fissure and centered on Heschl's sulcus, encompassing most of Heschl's gyrus, including the primary auditory cortex, the planum temporale, the superior temporal sulcus,

planum polare, and small portions of the insula and middle temporal gyrus adjacent to these auditory regions. The GABA and Glx peak areas will be quantified as ratios relative to the area of the unsuppressed voxel tissue water.

Statistical Plan and Data Analysis:

Specific Aim 1: To test the effect of ketamine in subjects with chronic tinnitus induced by hearing loss. The primary clinical outcome measures will be the severity of tinnitus, which will be fitted with a mixed linear effects model, with each outcome modeled as a function of infusion type (active ketamine vs placebo), infusion order (ketamine first vs placebo first), baseline scores, and post-infusion time (day after infusion, vs week after infusion). The test of the hypothesis will be the main effect of infusion type, and for descriptive purposes the difference in post-infusion scores (and 95% confidence limits) between active ketamine and placebo will be calculated from the model.

Specific Aim 2: To investigate changes in GABA in the auditory cortex in tinnitus subjects, before and after ketamine administration.

The GABA/W values will be fitted using a mixed linear effects model, with infusion type (ketamine vs placebo), infusion order (ketamine first vs placebo first), and MRS data frame, as fixed effects, and subject and scan (nested within subject) as random effects. When the overall F test reaches significance ($p < 0.05$, 2-tailed) a post hoc analyses will be conducted to identify the potential effects of ketamine at each of the 6 MRS acquisitions. Analysis across the six 13-min acquisitions will give a more detailed picture of which time points are driving the trend. The effect of ketamine of Glx/W will be included as an exploratory analysis.

Criteria for Early Discontinuation

Define criteria that will be used to exit or drop subjects from the study and operationalize. Indicate the time points when such criteria will be applied, and describe the rating instruments, parameters, and thresholds that will lead to a decision to terminate a subject's participation and the role of the person who will make these determinations. Studies which include a medication taper and discontinuation may be asked to include an independent medical monitor (an MD not on the study team) who will aid the study team in determining whether study discontinuation is needed. In addition, explain procedures for managing subjects who are withdrawn from the protocol.

For treatment studies: To minimize risks to subjects, operationalized drop-out criteria should be defined so that subjects who worsen, or in some cases, fail to improve, are removed from the study and offered standard care. The threshold for drop-out should consider the level of risk associated with non-improvement for the specific disorder, the availability of alternatives, and the typical required duration of treatment. For example, emergence of suicidal intent, or psychosis, should prompt immediate clinical evaluation and withdrawal from the study.

Subjects will be withdrawn from the study if

1. They request it for any reason.

2. Systolic BP increases to > 180 mm Hg and remains > 180 mm Hg for more than 5 minutes, or diastolic BP increases to > 110 mm Hg and remains > 110 mm Hg for more than 5 minutes.

3. Negative subject response to ketamine, such as dysphoria, anxiety, paranoia, or any adverse event.

4. Subjects experience a worsening of depressive symptoms or an BDI > 31 and/or the participant is found to be at risk of suicide by the study clinician.

5. The PI judges that it is medically unwise to continue in the study, for example if the subjects are unable to comply with the study procedures and rules.

Blood and other Biological Samples

Describe how the sample will be used and indicate, when relevant, the amount of the sample. The IRB wants to know that the sample is sufficient for the purposes of the study, but that sampling is limited to what is minimally necessary.

If you've indicated that you intend to store a sample for future use, indicate where the sample will be stored, how long the sample will be stored, and to what purposes the sample will eventually be put. Check the IRB website at https://irb.nyspi.org/investigators/guidance/genetic-research for specific guidance and additional information about future use of DNA samples.

Blood samples totaling 15 mL will be obtained at screening.

Research Related Delay to Treatment

Research involving participants who are in need of treatment invariably involves delay to care, and this delay is associated with risk. Scheduling of procedures must be carefully organized to minimize delay. Other delay must involve only that minimally necessary to accomplish the aims of the research while respecting subject well- being and safety. Describe the delay, by virtue of research participation in this study, before a participant can receive treatment of known efficacy or standard care routinely offered in the community.

There is no delay to care in this study.

Clinical Treatment Alternatives

Describe what other treatment or assessment options are available to subjects who do not participate in research.

Alternative treatments are cognitive behavioral and retraining therapy. Subjects will be made aware that these alternatives exist.

Risks/Discomforts/Inconveniences

"Risk" is a broad term used to convey the potential for harm, burden, and inconvenience related to research participation. Use this section to provide a comprehensive description of foreseeable physical, psychological, social, interpersonal, and economic risks introduced by the research. Include the source of the information. Consider both the probability and magnitude of harm and its impact. Describe the foreseeable harms associated with the research (untoward effects of a medication) and those related to delay to individualized treatment. Include data from the literature, and local data, if available, on risk rates and subject experiences with research procedures. Describe procedures in place to minimize risk. In general, please create a numbered list of risks/categories of risk, and in general put the list in the order of significance or level of risk, the most significant risks should be listed first.

Risks include:

1) Ketamine infusion.

Ketamine is an FDA-approved dissociative anesthetic. Ketamine exposure at the subanesthetic dose to be used in this study can be associated with a moderate dissociative state, which is well tolerated in the majority of cases. There is extensive clinical experience with ketamine used at anesthetic doses and no long-term detrimental effects of ketamine exposure have been reported. It is possible that ketamine administration will increase the risk of psychosis, even in normal subjects. Ketamine is a street drug of abuse, and thus poses the risk that exposure during this study may predispose subjects to subsequent abuse of this drug. For this reason, a history of any past or present problems with substance use will be obtained on screening; history of substance or alcohol dependence or diagnosis of abuse in the prior year will be exclusionary.

An increase in vital signs can also occur with the infusion of ketamine. Subjects will be closely monitored for changes in blood pressure or heart rate, and the infusion will be stopped if needed. As described above, the ketamine will be stopped for systolic BP increases to > 180 mm Hg and remains > 180 mm Hg for more than 5 minutes, or diastolic BP increases to > 110 mm Hg and remains > 110 mm Hg for more than 5 minutes. After the scan, the monitoring of subjects will continue and blood pressure will be obtained until there are two measurements at least 15 minutes apart that are within 10 mmHg of the baseline diastolic blood pressure. After the subject is transferred back to the examination room, the blood pressure and heart rate will be obtained manually by the research assistant or nurse.

Ketamine administration has the potential to produce agitation or hyperarousal. If needed, this will be treated with intravenous diazepam and the study terminated. The risks of exposing healthy subjects to a drug of abuse potential will be minimized by explaining this risk to prospective subjects, and by excluding from the study any subjects with documented or suspected prior substance or alcohol history of dependence or abuse as outlined in the inclusion/exclusion criteria.

2) MRI scanning: It may be uncomfortable to lie motionless in the scanner (MRI) and it may cause some subjects to feel anxious. While there have been no reports of any long-term effects caused by magnets of the same or even higher strength, the long-term effects of being placed in a magnet of this strength (3 Tesla) are unknown. The MRI scanner uses

a large magnet to take pictures of the brain and is not associated with any known medical risks, except for persons who have a heart pacemaker, or have metal in their body (e.g. shrapnel or surgical prostheses) which may be affected by the magnet. Subjects will be asked to notify us if this is the case. There is also the risk of burns from medicinal patches during the MRI; therefore, subjects will be asked to remove any patches prior to the scanning session. Also, although there are no known risks associated with pregnancy, we will not scan someone who is pregnant. Therefore, for women of childbearing years, pregnancy testing will be conducted the day of the MRI. Some people have reported sensations during the MRI scan such as "tingling" or "twitching" (or, very rarely a painful sensation), which are caused by changes in the magnetic field that can stimulate nerves in your body. Occasionally, some people experience nervousness or claustrophobic feelings due to the scanner's small space. Despite these sensations, in our experience, no one has had sensations from the scanning that did not stop as soon as the scanning stopped.

3) Intra-venous catheters. There is a small risk of infection and bleeding associated with intravenous catheters. The risk of this will be minimized by using proper techniques.

Methods to Protect Confidentiality

Describe the data management plan and the methods you will employ to protect subject privacy and the confidentiality of research data. The section should detail how information will be collected, recorded, coded, stored, transmitted, and as applicable, shared with other investigators so as to minimize risks related to breach of confidentiality. Confirm that identifiers are removed, to the extent possible, from research data, and explain if there are links between subject identity and research data, or if the data are anonymous. Also, indicate where the data are stored, who is responsible for data safekeeping, and who has access to subject identity and codes, if any, which cross-link research data and subject identity. Confirm that identifiable data are not collected, stored, or transmitted by mail, fax, on removable drives, laptops, or via the internet without proper protections, e.g. encryption.

Confidentiality will be strictly maintained. Medical charts, standard questionnaires, records, rating scales, and any other recorded information will be kept in a locked file in an office or in the record room of the New York State Psychiatric Institute. Records may be reviewed by state or federal regulatory agencies and their personnel. Research records, like other medical and clinical records, will be kept confidential to the extent permitted by law. There are legal advocacy organizations that have the authority under state law to access otherwise confidential subject records, though they cannot disclose this information without the subject's consent. Confidentiality is further supported by the use of unique ID numbers in coding some records. Data entered into a computer and/or submitted electronically will contain numerical IDs and, in some cases, initials, and will be password-protected. No identifiers (name, address, phone number, etc.) will be used that could allow direct linking of database information to individual participants. Where temporary linking of information with identifiers is necessary, such identifiers will be temporarily attached to the questionnaire, and will immediately be removed after information has been encoded. No identifying information will be used in publications. Only the research team and institutional personnel will have access to such materials.

References

Please limit references, preferably no more than twenty.

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Quality Assurance Monitoring Plan

Protocol #_____7432_____

Title:___ Investigation of the NMDA Antagonist Ketamine as a Treatment for Tinnitus

This is the Quality Assurance (QA) Monitoring Plan for the above-referenced protocol.

__Diana Martinez and Alex Grassetti___ will be the QA Monitors for the internal monitoring for this study. The Monitor will be instructed to carry out the specific monitoring activities outlined below. Section A will describe the monitoring schedule and reporting and Section B will describe the data that will be reviewed on an ongoing basis.

A. GENERAL MONITORING SCHEDULE AND REPORTING

1. PRE-STUDY MEETING (ACAR meeting)

Following development of a protocol-specific QA monitoring plan for this study and prior to initiation of such study, the Monitor/Research Coordinator, Principal Investigator(s) and research personnel will meet to review the study goals and study protocol requirements, including the following:

a. Good Clinical Practice (GCP) requirements;

b. Proper delegation of authority;

c. Informed consent procedures and documentation;

d. Reporting requirements to the IRB;

e. Procedures for enrolling subjects, including inclusion/exclusion criteria;

f. Study treatment procedures;

g. Management and reporting of adverse events (AEs), serious adverse events (SAEs), unanticipated problems (UPs), deviations and violations;

h. Timely completion of Case Report Forms (CRFs) and appropriate source documentation;

i. Regulatory documentation;

j. Reporting requirements to the Sponsor, including timely submission of information for annual reports;

k. Investigational product dispensing, administration and documentation.

2. SCHEDULED MONITORING VISITS

QA monitoring will be scheduled to take place:

a. Every 6 months during study data collection.

b. After the last subject has completed his/her participation in the study.

With approval from the IRB, the schedule may be reviewed and adjusted, depending on the following factors:

a. Rate of enrollment;

b. Prior history of protocol deviations or non-compliance with GCP;

c. Volume of data and documentation corrections required;

d. Outcomes of prior monitoring visits.

3. DOCUMENTATION OF FINDINGS

At the end of each QA review, the Monitor/Research Coordinator will meet with the site PI and research personnel to review and correct any findings from the visit and discuss how to prevent similar occurrences. Within approximately 1 week of each monitoring visit, a written monitoring report with the findings and required corrective actions will be issued to the PI and IRB Research Compliance Monitor. The PI will be required to correct any deficiencies that do not pose immediate harm to research subjects within a month of receipt of the report. At the next monitoring visit, the Monitor/Research Coordinator will confirm that the deficiencies have been addressed.

The report will include, but will not be limited to, the following:

a. A list of records reviewed (i.e., subject charts and medical records);

b. The number of CRFs reviewed by research subject identification number and visit date;

c. Whether there was any failure to report AEs, SAEs or UPs;

d. General adherence to the protocol;

B. MONITORING SPECIFICS

Unless otherwise specified below, ____30___ percent of subject files will be reviewed to obtain the required QA information.

1. INFORMED CONSENT PROCESS

a. Review the Informed Consent Process Checklist for 100% of the subjects;

b. Verify that the correct version of IRB-approved consent form was used;

c. Verify that each consent form was signed and dated;

d. Verify, by comparing the date of the consent form to the subject's medical record or other source, that the consent was signed prior to any research procedure having been performed.

2. ELIGIBILITY CRITERIA

a. Review the Eligibility Checklists for 100% of the subjects;

b. Compare the protocol inclusion/exclusion criteria against each subject's medical record or other source documentation, to determine whether the subject was eligible for inclusion in the study;

c. Confirm that the Eligibility Checklist was signed and dated by the PI prior to any research procedures having been performed.

3. ENROLLMENT AND SCREENING OF SUBJECTS

   a. Compare the number of subjects enrolled to the limit approved by the IRB;

   b. Check subject screening and enrollment logs.

4. STUDY PROCEDURES

   a. Verify that subject visits have taken place as required by the protocol;

   b. Verify that all tests have been completed as required by the protocol;

   c. Verify if any visit was out of allowable time parameters (out of window) by looking at subject visit schedules;

   d. Verify any deviations by comparing the protocol with source documentation and/or subject CRFs.

5. IRB REQUIREMENTS

   a. Confirm that all protocol procedures were approved by the IRB;

   b. Review all IRB modifications, exception requests and renewals and confirm that they have been added to the regulatory binder;

   c. Confirm that protocol deviations were approved by the PI and IRB (if necessary) unless there was a need to eliminate an immediate hazard to a subject.

6. REPORTING

   a. Verify that all protocol violations, unanticipated problems and serious adverse events were reported to the IRB on a timely basis;

   b. Verify that all safety concerns, including serious unexpected suspected adverse reactions (SUSARs) that are required by FDA regulations to be reported to the FDA have been reported on a timely basis (note no IND required).

7. CASE REPORT FORMS AND SUBJECT RECORDS

a. Verify that the PIs or his/her authorized designee has appropriately completed, signed and dated CRFs;

b. Verify that source documentation was used to complete CRFs;

c. Review data and source documents in terms of their organization, condition, completeness and legibility;

d. Verify that the data required by the protocol are reported accurately on the CRFs and are consistent with the source data/documents;

e. Verify that any dose or therapy modifications are properly documented;

f. Verify that AEs, SAEs, concomitant medications and underlying illnesses are reported accurately on the CRFs, in accordance with the protocol;

g. Verify that CRFs reflect all visits that subjects fail to make and all tests or examinations that are not performed;

h. Verify that subject withdrawals and subjects lost to follow-up are reported and explained on CRFs;

i. Ensure that appropriate corrections, additions or deletions are made, dated, explained (if necessary), and initialed by the PI or his/her/their authorized designee;

8. TRAINING OF INVESTIGATORS AND RESEARCH PERSONNEL

Verify that all required institutional and protocol specific training has been completed prior to study initiation, including training with respect to obtaining informed consent. Verify that new study team members have been properly trained and added to the Delegation of Authority Log and Training Log.

9. DELEGATION OF AUTHORITY

a. Establish the identity of all research personnel involved in the study;

b. Verify that all such personnel are listed on the Delegation of Authority Log;

c. Review study protocol to establish which responsibilities have been delegated;

d. Verify that the Delegation of Authority Log accurately reflects the delegated responsibilities, that all personnel listed have signed the log and that the training completed for specific responsibilities is also noted in the Training Log.

10. INVESTIGATIONAL PRODUCT MANAGEMENT *

a. Not applicable, this FDA has deemed that no IND is needed

11. REGULATORY BINDER

Confirm that the following essential documents are included in the Regulatory Binder in accordance with the Regulatory Binder Checklist:

a. All IRB versions of the protocol and informed consent
b. SAE reports
c. Study specific Manual of Procedures
d. Sample Case Report Forms (CRFs)
e. Protocol deviations
f. FCOI disclosures for all key personnel
g. Site monitoring log and reports
h. Delegation of authority log
i. Enrollment log
j. Sponsor correspondence
k. IRB correspondence