Study Protocol

Official Title: Repeated neurocognitive measurements in depressed patients

ClinicalTrials.gov ID (NCT number): NCT04916548

Protocol Date: 06/03/2021

Scientific Background

Depression is one of the most prevalent and costly class of mental health condition, with a collective public disease burden of staggering proportions. While efficacious treatments have been available for decades, remission rates are low, relapse rates are high, and disorder prevalence rates remain notably consistent, with only 12.7% of patients receiving minimally adequate treatment. A more integrative model of depression mechanisms—in particular, anticipated increases in flexible processing across cognition, information processing, and neural networks—requires strongly validated measurements with good psychometric properties, and strong relationships to both naturally occurring and experimentally induced (i.e., via ketamine) changes in depressive symptoms. The proposed study will enable us to develop and refine a battery of neurocognitive and performance-based measures that meet these criteria, and will reveal new knowledge about the mechanisms of depression.

The proposed project is not a simple extension of any one of the investigators' programs of research. Rather, it leverages the overlapping and unique expertise of the research team in order to advance a set of shared aims that no member of the collaborative would be able to accomplish on their own. Dr. Fournier brings expertise in longitudinal neuroimaging and in examining how individual differences in the functioning of the emotion regulation and self-related processing neural circuitry among depressed adults affects treatment response and real-world functioning. Dr. Price has expertise in longitudinal neuroimaging and the study of intravenous ketamine's rapid impact on both depressive symptoms and neurocognitive markers (including fMRI indices). Dr. Young brings expertise in examining neural responses during positive memory recall as a biomarker of major depressive disorder, with a focus on developing neurobehavioral interventions targeting these responses. Dr. Pecina has over ten year of experience conducting longitudinal interventional studies in patients with depression using multimodal neuroimaging in order to identify specific mechanisms through which specific treatments exert their effects. Dr. Jones has expertise in

examining the mechanisms through which self-referential, cognitive, motivational, and emotional systems assessed at multiple levels (e.g., structural MRI, functional MRI, peripheral psychophysiology, and ecological momentary assessment) give rise to depression, anxiety, and related disorders.

The aims of the project are innovative in several key respects. First, almost nothing is currently known about the true natural stability of potential biomarkers of depressive illness. This information is vital for the development and assessment of novel interventions, and it may help to resolve some of the heterogeneity and conflicting results in the published literature. Second, to our knowledge, no prior work has examined the degree to which the biomarkers proposed above may be altered by a single dose of ketamine. Third, very little work has examined the unfolding relationship of abnormalities in brain function and real-world functional outcomes. This information is critical for understanding not only the practical significance of abnormalities in brain function but for beginning to unpick possible mechanisms through which differences in biological functioning can affect an individual's lived experience. The expertise of each member of the collaborative, detailed above, is necessary to achieve these aims. Moreover, the results of this work will lay a core foundation for future, mutually beneficial collaborative work among members of the research team as they seek to identify and develop more effective ways to treat depression that are grounded in neuroscience.

Ketamine is a glutamatergic agent used routinely for induction and maintenance of anesthesia. In randomized controlled trials, subanesthetic (typically, 0.5mg/kg) intravenous ketamine exhibits well-replicated, rapid, potent (i.e., metaanalytic Cohen's d=1.4, a large effect) antidepressant effects, even in difficult-to-treat conditions such as treatment-resistant depression and bipolar depression. Antidepressant effects begin app. 2 h post-infusion (after acute dissociative and euphoric side effects subside) and continue far beyond the drug's elimination half-life of 2.5-3h.

The rapidity and magnitude of ketamine's effects on depressive-like behavior are attributed to its ability to rapidly and profoundly reverse neuroplasticity deficits. In this study, we will utilize ketamine as a rapid-acting experimental probe to decrease clinical symptoms and enhance neuroplasticity, and will measure the resulting effect on our neurocognitive battery and relationships to symptoms.

Study Objectives

In this project, we aim to harness our collective expertise in neuroimaging and treatment research to A) track the functioning of a collection of potential neurobiological targets for depression over time, B) examine how fluctuations in the functioning of those targets relates to real-world functioning, and C) in a subset of the sample, determine how the functioning in those targets is altered by a single dose of ketamine. We expect this work to provide the critical foundation for several collaborative future projects aimed at developing novel therapeutics. It will provide vital pieces of information regarding the stability, real-world importance, and malleability of possible neurobiologically based treatment targets.

Building on our prior work, we plan to evaluate the natural stability and fluctuations in four potential neural biomarkers for depression: 1) altered self-related processing, 2) deficits in autobiographical recall of positive events, 3) deficits in cognitive control, and 4) dysfunction in the communication among large-scale cortical networks. In addition, we will evaluate whether variability in the functioning of these systems is associated with real-world outcomes, including interpersonal functioning, employment functioning, and quality of life. Finally, as a proof of concept that these markers are alterable, we will examine how a single dose of ketamine alters the functioning of these targets.

Aim 1) track the functioning of a collection of potential neurobiological targets for depression over time.

Aim 2) examine how fluctuations in the functioning of those targets relates to real-world functioning.

Aim 3) in a subset of the sample, determine how the functioning in those targets is altered by a single dose of ketamine.

Study Design & Methods

A target sample of 40 depressed participants will complete baseline clinical, quality of life, cognitive, and functional magnetic resonance imaging (fMRI) assessments, followed by repeated assessments of each of these measures to examine their natural course over the consecutive month. In addition, in an open-label, single-arm design, a subset of participants (n=15) will receive a single dose of ketamine and a final fMRI assessment shortly after the 1-month follow-up.

Eligibility Criteria:

Inclusion Criteria:

All participants will:
1) be between the ages of 18 and 60 years,
2) score ≥ 14 on the Hamilton Depression Rating Scale (Ham-D)
3) possess a level of understanding sufficient to agree to all tests and examinations required by the protocol and must sign an informed consent document

Exclusion Criteria:

All participants:

1) Presence of lifetime bipolar, psychotic, or autism spectrum; current problematic substance use (e.g., ongoing moderate-to-severe substance use disorder);

2) Failure to meet standard MRI inclusion criteria: those who have cardiac pacemakers, neural pacemakers, cochlear implants, metal braces, or other non-MRI-compatible metal objects in their body. History of significant injury or surgery to the brain or spinal cord that would impair interpretation of results.

3) Acute suicidality or other psychiatric crises requiring treatment escalation. We will use the Columbia Suicide Severity Rating Scale (CSSRS) as both an initial exclusion criteria (CSSRS "Baseline/Screening" Version for past 1month period) and as grounds for rescue/removal (CSSRS "Since Last Visit" form). The CSSRS will be administered using a paper form by an experienced and thoroughly trained clinical assessor on the study team. Subjects with CSSRS suicide ideation scores scored "yes" on items 4 (active suicidal ideation with some intent to act) and/or 5 (active suicidal ideation with specific plan and intent) will be excluded from the study, and if enrolled, will be exited from the study and referred immediately to the nearest emergency mental health facility for additional thorough assessment and appropriate treatment referral.

4) Changes made to treatment regimen within 4 weeks of baseline assessment.

5) Reading level <6th grade as per patient self-report.

6) Patients who have received ECT in the past 2 months prior to Screening.

Ketamine phase subsample additional exclusion criteria:

1) Patients currently taking any psychotropic medication.

2) Lifetime recreational ketamine or PCP use

3) Current pregnancy or breastfeeding

4) For ketamine phase entry, patients must be reasonable medical candidates for ketamine infusion, as determined by a physician co-investigator. Serious, unstable medical illnesses including respiratory [obstructive sleep apnea, or history of difficulty with airway management during previous anesthetics],

cardiovascular [including ischemic heart disease and uncontrolled hypertension], and neurologic [including history of severe head injury] will be exclusions.

5) Clinically significant abnormal findings of laboratory parameters [including urine toxicology screen for drugs of abuse], physical examination, or ECG.

6) Uncontrolled or poorly controlled hypertension, as determined by a physician co-investigator's review of vitals collected during screening and any other relevant medical history/records.

7) Patients with one or more seizures without a clear and resolved etiology.

8) Patients starting hormonal treatment (e.g., estrogen) in the 3 months prior to Screening.

9) Past intolerance or hypersensitivity to ketamine.

10) Patients taking medications with known activity at the NMDA or AMPA glutamate receptor [riluzole, amantadine, lamotrigine, memantine, topiramate, dextromethorphan, Dcycloserinem, Sonata, Ambien, Lunesta, Acamprosate], or the mu-opioid receptor [opiate medications--morphine, oxycodone, heroin, fentanyl)].

11) Patients taking any of the following medications: St John’s Wort, theophylline, tramadol, metrizamide.

Statistical Considerations and Statistical Analysis Plan

This is a pilot study, designed to develop novel study infrastructure and novel measurement and analytic methods, leading to a small number of patients particularly for the open-label treatment arm. Analytic methods for all neurocognitive measures will be refined, optimized, and finalized based on the test-retest phase, such that they maximize psychometric properties of the metrics such as test-retest reliability and validity. Descriptive statistics (means, standard deviations) will be reported without statistical analysis, given the small number of patients receiving the study intervention, which yields low statistical power. Exploratory inferential statistical analyses and effect size comparisons (with 95% CIs) will include appropriate within-group comparisons of pre- and post-

treatment scores on all primary and secondary endpoints, and on other pre-specified outcomes as warranted.