INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY (ISCTM) 15TH ANNUAL (2019) SCIENTIFIC MEETING POSTER ABSTRACT

The Neurophysiological Effects of Intravenous Alcohol as Potential Biomarkers of Ketamine's Rapid Antidepressant Effects

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The Methodological Question Being Addressed: Efficacy-stratifying biomarker guided, pharmacological magnetic resonance imaging (Pharmaco-MRI) clinical study in treatment-resistant major depressive disorder (TRD)

Introduction (Aims): A single subanesthetic dose of the glutamate modulator ketamine has rapid and robust antidepressant effects in TRD. A family history of an alcohol use disorder in a first-degree relative (Family History Positive, FHP) is one of the strongest identified predictors of an improved antidepressant response to ketamine. FHP is also associated with differential response to alcohol. Like ketamine, alcohol has effects on multiple neurotransmitter systems including N-methyl-D-aspartate (NMDA) receptor antagonism. One of the primary mechanistic hypotheses for ketamine's antidepressant action is NMDA receptor blockade-induced intrasynaptic release of glutamate from major output neurons, *e.g.* cortical pyramidal cells, and preclinical and clinical studies have demonstrated this acute glutamate "surge." Based on these findings, we hypothesize that ketamine's enhanced antidepressant efficacy in FHP TRD subjects relative to TRD subjects without a family history of an alcohol use disorder (Family History Negative, FHN) is, at least in part, attributable to rapid synaptic glutamate release. We also hypothesize that alcohol similarly augments glutamate release in this biologically-enriched subgroup.

Methods: To test these hypotheses, we designed an open-label study of 21-65 year old TRD subjects. This study was initiated at the NIH/NIMH in 2015 and is in the process of transitioning to UIHC. We plan to recruit a total of 25 FHP and 25 FHN TRD subjects, which was extrapolated from the effect sizes observed in previous intra-scanner ketamine MRS studies. The study consists of two phases. The preliminary phase is a medication taper (if needed) and psychotropic medication-free period for at least two weeks. The experimental phase comprises two pharmacokinetically-defined basal-bolus alcohol and one subanesthetic dose (0.5mg/kg x 40 minute) ketamine infusions. The first alcohol infusion establishes the pharmacokinetic profile for the second alcohol infusion occurring during 7T-MRI, including spectroscopy of a $2cm^3$ voxel placed in the ventromedial prefrontal cortex/ventral anterior cingulate cortex (vmPFC/vACC). The ketamine infusion will also occur during 7T-MRI. The reliability of vmPFC/vACC glutamate detection both within and across sessions was demonstrated previously. The primary outcome measure is the mean change in Montgomery-Åsberg Depression Rating Scale score from baseline(pre-ketamine)-to-one week post-infusion, where we observed ketamine's greatest antidepressant effect in FHP TRD subjects. Other outcome measures include neurophysiological response to alcohol, and vmPFC/vACC glutamate and resting state functional MRI response to both ketamine and alcohol.

Results: At the NIH/NIMH, 11 subjects signed consent and 8 completed all experimental procedures. 3 subjects were excluded prior to the first infusion. Preliminary MRS data (without stratification by family history) will be presented.

Conclusions: We anticipate that this study will provide key mechanistic insights on ketamine's improved antidepressant response in a biologically-enriched subgroup to systematically develop more efficacious, personalized treatments.

Disclosures: One or more authors report potential conflicts which are described in the program.