engage in patrolling behavior. To our knowledge, this trait has not been demonstrated in females.

Post SI, the lack of a sucrose preference in dominants is interesting when compared to the deterioration in CSS, higher FCM and diminished exploratory behavior demonstrated by subordinates. This indicates that subordinates become more stress responsive after SI, whereas dominants become anhedonic. An alternative interpretation is that subordinates consume more sucrose in response to stress, similar to 'binge-eating' behavior. These findings collectively demonstrate a distinction between stress and anxiety, and indicate an integrated, adaptive function for rank, stress status and role assignment.

The next aim examines the influence of rank on vulnerability to psychosocial stress produced by an unstable social environment. A cohort of adult female C57/Bl6J mice ($n = 36$) is currently undergoing 7 weeks of SIS, in which cage mates are randomized every 3 days to disrupt hierarchies as they become established. CE is performed during SIS to identify rank, and FCM is taken. After, mice will undergo behavioral testing for anxio-depressive phenotypes and changes in attention and cognition.

Keywords: Social Behavior, Anxiety and Depression, Females, Social Stress, Social Dominance

Disclosure: Nothing to disclose.

P310. Increased Effort Expenditure in Major Depression Following a TNF-Alpha Antagonist is Mediated by Change in Systemic Immunometabolism

Sarah Etuk, Emma Hahn, Brittany DeVries, Jessica Cooper, Nadia Irfan, Dannielle Harrison, Makiah Nuutinen, Asim Lal, Amanda Arulpragasam, Shabnam Hossein, Bobbi Woolwine, Ebrahim Haroon, Jennifer Felger, Andrew Miller, Michael Treadway*

Emory University, Atlanta, Georgia, United States

Background: Evidence suggests that increases in inflammation and alterations in systemic immunometabolism may contribute to the pathophysiology of motivational anhedonia in major depressive disorder (MDD). MDD patients have been shown to exhibit elevated levels of peripheral blood inflammatory biomarkers, particularly C-reactive protein (CRP), tumor necrosis factor (TNF)-alpha, interleukin-6 (IL-6), and IL-1 beta, which have in turn been linked to motivational deficits in both animals and humans. Specifically, stimulation of cytokines has been shown to reduce willingness to expend effort for rewards. Further, these effects have been found to be strongest in patients with both high inflammation and altered protein and genomic signaling within pathways related to glucose metabolism. These metabolic changes have been hypothesized to reflect an increased reliance on glycolysis (as opposed to oxidative phosphorylation) within activated immune cells. Taken together, these data raise the possibility of an immunometabolic-dependent pathway that contributes to the development of motivational anhedonia for depressed patients with high inflammation. To date, however, only a few studies have explored the impact of pharmaceuticals that target inflammation on motivational anhedonia in depressed patients. Here, we present novel results from a newly-completed study (NCT03006393) aimed at identifying the mechanisms by which inflammation and immunometabolism contribute to motivational anhedonia in depressed patients.

Methods: Effort-based decision-making and peripheral inflammatory markers were assessed in 60 patients with current MDD at a baseline session, after which 37 patients with CRP > 3 mg/L were randomized to receive a single infusion of either the TNF-alpha antagonist infliximab (5mg/kg) or saline solution as part of a double-blind, placebo-controlled, randomized clinical trial. Motivated behavior was using an effort-based decision-making task (EBDM) during which participants made a series of choices about how much physical effort (rapid button presses) they were willing to expend in exchange for varying amounts of monetary reward. Effort discounting was assessed by examination of choices at each effort level (20%, 50%, 80%, or 100% of a participant's maximum press rate) as well as by a well-validated computational model. For this model, a free parameter 'k' is fit to each participant's choices and represents the extent to which effort reduces the value of reward. Plasma samples were also collected at each time point, and were assayed for TNF soluble receptor II (TNFRII) and five markers of systemic glucose metabolism: adiponectin, resistin, leptin, glucose, and insulin. These six markers were combined to form a composite measure of TNFRII and glucose metabolism.

Results: At baseline, the overall proportion of effortful choices as well as the k discounting parameter were associated with measures of anhedonia and fatigue, including the apathy-motivation index, and the anhedonia subscale from the IDS-SR ($ps < .05$). Following randomization, there was a significant treatment X time interaction for TNFRII with a reduction for patients receiving infliximab relative to placebo ($p = 0.024$), but not glucose metabolism. We also observed a significant group by time interaction such that patients receiving infliximab showed a decrease in effort discounting (lower k parameter) relative to placebo ($p = 0.045$). We also observed a treatment by time by effort interaction ($p < .05$) such that this effect was most pronounced at the higher levels of effort (80% and 100%). Further, we observed that post-infusion decreases in plasma TNFRII and glucose metabolism predicted increases in effortful choices at the highest effort level (controlling for age and sex, $p = 0.009$) as well the k discounting parameter ($p = 0.033$). Finally, a bootstrapped mediation analysis found that change in plasma TNFRII and glucose metabolism significantly mediated the relationship between treatment assignment (infliximab or placebo) and change in effortful choice ($p < 0.05$).

Conclusions: The results of the study indicate that administration of the anti-inflammatory agent infliximab to patients with current MDD and high inflammation increases the willingness to expend effort, a hallmark of motivational anhedonia. Moreover, this effect appears to mediated by changes in markers of TNF signaling in combination with markers of glucose metabolism. These results highlight the potential for the combination of inflammatory and immunometabolic biomarkers and anti-inflammatory treatment strategies to identify and treat motivational impairments.

Keywords: Precision Medicine for Mood Disorders, Immune Modulation, Effort Based Decision Making Task, Anhedonia, Computational Models of Decision Making

Disclosure: Blackthorn Therapeutics: Consultant (Self)

P311. Zelquistinel (GATE-251): Results of a Phase 1 Single Ascending Dose Study to Evaluate the Safety, Pharmacokinetics, and EEG Effects of a Novel Rapid Acting, Orally-Bioavailable NMDA Receptor Modulator

John Donello*, Jeffrey Burgdorf, Kirk Bertelsen, Leonardo Terjo, Roman Rosipal, Joseph Moskal, Ronald Burch, Anantha Shekhar

Gate Neuroscience, San Clemente, California, United States

Background: Major depressive disorder (MDD) is a common disabling and potentially life-threatening condition estimated to affect > 300 million people worldwide. Glutamatergic mediated plasticity and modulation of NMDA receptor activity have been employed in developing rapid-acting treatments for MDD. GATE-251 (also known as AGN-251751) is a NMDA receptor modulator

that binds to a unique site on the receptor. In animals, zelquistinel has oral bioavailability greater than 90%, and provides efficacy in several animal models of depressive-like behavior. This Phase 1 first-in-man study evaluated safety, pharmacokinetics and GATE-251 as well as EEG measures of NMDAR activation in healthy volunteers.

Methods: This double-blind, randomized, placebo-controlled study evaluated healthy male or female subjects aged 18-55 years, with supine heart rate of 50-100 bpm who used no other drugs for at least 14 days prior to this study and were negative in drug of abuse screens. Part A of the study evaluated safety, plasma pharmacokinetics and EEG following single fasting doses of 100 microg, 1 mg, 3 mg, 10 mg, 25 mg, or 50 mg GATE-251 as an oral solution, compared to a water placebo (randomization 6:2 drug: placebo). A separate group studied a 1 mg dose in female subjects. Part B evaluated safety and CSF pharmacokinetics of single doses of 1 mg or 10 mg fasted and 1 mg fed ($N = 5, 3, 3$) in subjects with indwelling lumbar catheters. Part C evaluated plasma PK in fasted male subjects compared to subjects who received a high-fat breakfast ($N = 5, 3$).

Results: Safety: In this study no serious adverse events were reported, nor were any clinically significant changes in plasma chemistry, hematology or urinalysis observed. No subjects experienced clinically significant changes in vital signs or ECG. There were no treatment emergent psychotomimetic symptoms (as measured by changes in C-SSRS, BPRS + or CADSS) from predose baseline to end of study. Treatment-related adverse events (TRAEs) were few: in Part A ($N = 14$ placebo, $N = 42$ GATE-251) there were no TRAEs in the placebo group and 1 in the 1 mg GATE-251 group: headache. In Part B ($N = 4$ placebo, $N = 12$ GATE-251), there were no TRAEs in the placebo group and 2 in the 10 mg group: 1 lumbar puncture syndrome, 1 disturbance in attention. In Part C ($N = 0$ placebo, $N = 6$ GATE-251), there were no TRAEs.

Pharmacokinetics: In Part A, GATE-251 exhibited rapid absorption and dose-related increases in exposure assessed as Cmax or AUC. T1/2 was similar across doses at 0.5 hr, and was not different in male vs female subjects. In Part B, transport into the CSF was significant, with a Tmax of 4 h. Too few sampling times prevented calculation of T1/2 in CSF. A high fat meal slowed absorption of GATE-251 compared to fasted, with reduced Cmax exposure, although AUC exposure was not affected.

EEG: GATE-251 increased resting alpha EEG power, indicative of effective central modulation and enhanced NMDAR activation. While Gate-251 induced alpha power showed an inverted U-shaped dose response relationship at higher doses, doses that optimally enhanced alpha EEG demonstrated CSF drug concentration that corresponded to concentrations that enhance NMDAR activity in vitro.

Conclusions: GATE-251 was well-tolerated oral NMDA modulator with few treatment-related AEs. There was no evidence of psychotomimetic effects over the dose range evaluated. GATE-251 was rapidly absorbed into the plasma and exposure was dose-related. No gender-associated differences were observed. In plasma, AUC exposure was not affected by a high fat meal whereas in CSF AUC exposure appeared to be enhanced. The CSF levels achieved within this dose range were robust and corresponded the concentrations necessary to modulate NMDA receptors in vitro. Translational pharmacodynamics of qEEG/ERPs and the plasma/CSF pharmacokinetics demonstrate that the assessed doses meet and/or exceed drug concentrations that are predicted to be maximally efficacious in humans.

Keywords: Fast-acting Antidepressant, NMDA Glutamate Receptors, Translational Approaches to Drug Development, Synaptic Plasticity

Disclosure: Gate Neurosciences, Anagin, Vasculonics, MindX: Founder (Self)

Karuna Therapeutics: Advisory Board(Self)

Johnson and Johnson: Grant (Self)

P312. Target Trial Emulation: Evaluating a Treatment for Metabolic Depression

Katie Watson Lin, Caleb Spiro, Kayla Carta, Alison Myoraku, Natalie Rasgon*

Stanford University School of Medicine, Palo Alto, California, United States

Background: Previous evidence suggests that pioglitazone, an insulin sensitizing medication, in patients with major depressive disorder (MDD) and insulin resistance (IR) can be useful in ameliorating non-remitted MDD. To investigate this claim, we conducted two emulated target trials (ETTs) of the effect of adjuvant pioglitazone on antidepressant response among people with type 2 diabetes (DM2). Pioglitazone was compared to two other classes of non-insulin sensitizing DM2 medications, sulfonylureas and dipeptidyl peptidase 4 (DPP4) inhibitors. It was hypothesized that the combination of antidepressant medication and pioglitazone would elicit a superior antidepressant treatment response compared to adjuvant DPP4 inhibitors or sulfonylureas over a one-year follow-up period.

Methods: The two ETTs were designed using health insurance claims from the Optum Clinformatics® Data Mart version 3.0 (Optum) (Optum Insight, Eden Prairie, MN). Poorer antidepressant response was measured by an increase of new prescriptions for antidepressants one year after the study start date. A treatment was defined as new if it had never been prescribed, or if it had not been prescribed for at least one year plus the number of days' supply of the most recent prescription.

Results: The participants in ETT1 who took pioglitazone ($n = 1308$) were more likely to be younger, male, and use statin medications when compared to users of DPP4 inhibitors ($n = 1634$). In ETT2 pioglitazone users ($n = 1,639$) were more likely to take statins, use insulin, and take a greater average of antidepressant medications in the prior year compared to those who used sulfonylureas ($n = 4,879$). After matching, the standardized mean difference for all covariates in both ETTs was <0.15, with exception of age for ETT1 (SMD = 0.17). In ETT1, instrumental variable analysis found that pioglitazone users added a new antidepressant or antipsychotic treatment 1.3 times compared to 1.7 times among DPP4 users over a 1 year follow up period. In ETT2, similar analysis found that pioglitazone users added a new antidepressant or antipsychotic treatment 0.8 times compared to 1.4 times among DPP4 users over a 1 year follow up period.

Conclusions: These findings lend evidence to the hypothesis that adjuvant pioglitazone lead to a stronger antidepressant treatment response than sulfonylureas or DPP4 inhibitors among individuals with MDD and DM2 - as measured by fewer treatment shifts and/or additions of a new antidepressant or antipsychotic. Coupled with previous evidence on the role of pioglitazone in MDD patients with IR, this evidence suggests that pioglitazone may prove useful in ameliorating treatment MDD response among people with comorbid DM2.

Keywords: Major Depressive Disorder, Emulated Target Trial, Insulin Resistance

Disclosure: Nothing to disclose.

P313. Go/NoGo EEG Data Associations Depression Severity in Depressed and Suicidal Patients

Julianne Mirmina, Diane Kim, Jessica Carbajal, Andrew Deptula, Ricardo Caceda*

Stony Brook University, Stony Brook, New York, United States

Background: Impaired inhibition has been observed in depressed and suicidal patients. The Go/NoGo task assesses cognitive and