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Pharmacogenetic Treatment With Anti-Glutaminergic Agents for Comorbid PTSD & AUD

Original Sample Size and Data Analysis + Modified Sample Size and Data Analysis

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Item 1. ORIGINAL rationale and sample size calculations

We will screen 498 individuals to reach a randomized sample of 332.

We performed a simulation study assuming 52% of those taking pregabalin in the NI/I or I/I genotype group would have no heavy drinking days and that 20% of those taking pregabalin in the NI/NI genotype group and in those taking placebo in either genotype group would have successful outcomes as defined above. We further assumed equal cell sizes in each cell of the treatment-group-by-genotype 2 X 2 layout. The analysis model for the simulation was: Successful Outcome (Y/N) = Genotype Group + Treatment + Treatment-by-Genotype, where dependent and independent variables are dichotomous. Logistic regression was used to test the interaction term. We analyzed 5000 simulated datasets under the above specifications. We set the alpha-level equal to .05 for the single primary hypothesis and used a two-sided test. The null hypothesis that the interaction = 0 was rejected in 80% of datasets when a sample size of 332 (83 subjects/cell) was used. One third of the subject population is predicted to have the NI/I or I/I genotype, however ½ of the study sample needs to have this genotype by the study design, hence individuals with the NI/I or I/I genotype must be over-sampled. Therefore, to achieve the target of N = 332 individuals randomized to treatment with 83 subjects per cell, the study will likely need to be screen 498 individuals or more (1/2 of 332 times 3). Software package SAS version 9.3, was used to perform the simulations.

Item 2. ORIGINAL plan for data analysis

Preliminary Descriptive Analyses: After data cleaning, descriptive statistics and frequency tables will be used to summarize primary and secondary outcome measures, demographics, and baseline characteristics. Patient characteristics and baseline clinical variables will be summarized by group with summary statistics. Highly skewed variables may be transformed prior to formal testing. Descriptive summaries will be performed for the safety measures (e.g. vital signs, adverse events).

Specific Aim: To test the hypothesis that patients with AUD and PTSD treated with pregabalin and having the non-insertion/insertion or insertion/insertion (NI/I or I/I) variant of the SLC6A1 gene for GABA transporter (GAT-1) will be more likely to not drink heavily and to have a clinically meaningful reduction in either Cluster B or Cluster E PTSD symptoms than pregabalin-treated patients with the NI/NI genetic variant and placebo-treated patients.

Primary Outcome Variable Construction: The primary outcome will be a composite of "no heavy drinking days" and a clinically meaningful reduction in either Cluster B or Cluster E PTSD symptoms.

(1) A heavy drinking day is defined as 5+ standard drinks per day for men and 4+standard drinks per day for women. No heavy drinking days is defined as 0-1 day with 5+ standard drinks per day for men and 0-1 day with 4+standard drinks per day for women over the post-TQD 6-week period. We will allow 1 day of heavy drinking in the 1st and 2nd 3-week periods (i.e. 2 "slip-ups") to improve power.

(2) Cluster B and Cluster E PTSD symptoms will be measured with the CAPS-V. Because a new version of the CAPS-5 for DSM V has recently been released, at the beginning of the analysis phase we will do a literature review and consult experts to identify a clinically meaningful reduction for the 5-item cluster B and the 6-item cluster E CAPS-5 (for DSM V) scale scores. Currently we are aware that a 10-point reduction for the total CAPS-4 (DSM IV) has been used previously as a clinically meaningful reduction (e.g. King et al)168. For the cluster B and E subscales, the scale score reduction for the post-TQD period will be the post-treatment score (after week 12) minus the baseline (week 1) score. We will use the week 1 baseline score as baseline for determining if CAPS subscale scores are meaningfully reduced during the last month of the post-TQD period. We will use the 1-month version of CAPS-5. A clinically meaningful reduction in both 8-week periods is consistent with a reduction in the pre-TQD period and maintenance of the reduction in the post-TQD period. Otherwise, if there is not a meaningful reduction in the pre-TQD period, but there is a meaningful reduction at post-treatment (post week 16), this is consistent with an individual not achieving a meaningful reduction until the post-TQD period. We will obtain the PCL weekly to explore PTSD symptom patterns over time in greater detail.

Finally, we will be able to construct the composite outcome for the primary aim: If an individual meets the criteria for no heavy

drinking days during the post-TQD period and if they have a clinically meaningful reduction in the CAPS score at post-treatment (week 12) relative to baseline (week 1) for either the cluster B or E CAPS subscales, then the outcome value will equal one, otherwise, if they do not have a clinically meaningful reduced score for Cluster B and Cluster E at post-treatment or they do not meet the criteria for no heavy drinking days during the post-TQD period, then the outcome value will equal zero.

Primary Analysis: The primary hypothesis will be tested with a logistic regression model with a main effect for genotype (2 groups) and treatment group (2 groups) and the interaction term between treatment and genotype. Significance of the interaction term ($p<.05$, two-sided) will determine whether pregabalin is more effective in one genotype versus the other. The null contrast of this test of interaction in terms of success proportions on a log-odds scale will be: (PREGAB–PLACEBO)NI/I-or-I/I – (PREGAB–PLACEBO)NI/NI = 0. If this test is significant ($p\leq .05$), we will conduct post-hoc tests of pregabalin vs. placebo for each genotype group to identify for which genotype group pregabalin is effective. Odds ratios with 95% confidence intervals will be reported to evaluate effect size.

Secondary Aims:

(1) We will test whether one of the two pregabalin*genotype groups will be more predictive of the ability to not drink heavily in the pre-TQD period (1st 6 weeks). The analysis for this aim is parallel to the primary aim.

(2) We will perform the same test as secondary aim one except change the outcome to clinically meaningful reduction of PTSD Cluster B or E symptoms. For this aim, the change in Cluster B or E symptoms to determine if it meets the clinically meaningful reduction threshold will be the 6-week cluster B or E subscale score minus the baseline subscale score.

(3) We will determine whether the treatment effects of pregabalin vs. placebo on the composite outcome (No Heavy Drinking and Cluster B or E ↓) are significantly different post- vs pre-QTD periods by genotype group. Analysis: The omnibus difference in differences contrast of proportions tested in this aim, on a log-odds scale, will be: [(PREGAB -PLACEBO)post-TQD – (PREGAB-PLACEBO)pre-TQD]NI/I-or-I/I – [(PREGAB-PLACEBO)post-TQD – (PREGAB-PLACEBO)pre-TQD]NI/NI = 0, where the difference between pregabalin versus placebo in the pre-TQD 8-week period is contrasted with that in the post-TQD period within each genotype and in turn these contrasts are contrasted between the 2 genotype groups. The explanatory terms in this logistic regression model will be main effects for treatment group, genotype group, and time-period (pre- vs. post-TQD) and 2-way and 3-way interaction terms. If the test of the above null contrast is significant, post-hoc tests will be conducted within each genotype group.

(4) Upon completion of the trial, we will perform a genome-wide expression analysis, integrated with clinical and other data, to determine more precisely the neurobiological correlates associated with therapeutic efficacy and adverse events, and their associations in the molecular pathways governing glutamate and GABA signaling systems.
Exploratory Aims: We will collect other weekly PTSD symptom and alcohol use measures (e.g. PCL and TLFB) with which to explore patterns of response pre- and post-TQD, and we have experience using sophisticated models to analyze repeated measures. Co-PI Johnson has co-authored statistical methods research articles on some of these methods169,170. We will also examine effects of pregabalin on functional outcomes (e.g. Q-LESQ, WHO DAS-II, SF-36) which we are assessing at all major time points. We will generally use mixed-effects models to analyze these repeated measures. We will also extend all primary and secondary analyses to the follow-up assessment and report relapse rates during the 3-month period between post-treatment and the follow-up assessment with 95% confidence intervals. These will be estimated for each of the treatment by genotype cells.

Handling of Missing Data: Participants who are lost to follow-up and thus have not demonstrated successful outcome will be assumed to have not had a successful outcome.

Item 3. MODIFIED plan for data analysis

Data collection took place at the University of Maryland School of Medicine in Baltimore, MD. Data collection began in July 2017 and ran until June 2019 when the research center where the study was running shut down. The study resumed at a new research center in July 2019 and ran until research was shut down due to the COVID 19 pandemic in March 2020. Data collection resumed in October 2020 and, with the exception of a one-month COVID-related shutdown in January 2021, ran until the data collection window closed in December 2021.

Because of these interruptions in data collection, we modified data analysis plans and performed a power analysis based on the new analytic approach. We calculated sample size for a Cohen's d effect size equal to 0.31 (at week 12) based on prior studies of pregabalin. We assumed cumulative attrition equal to 25% and correlation among repeated measures equal to 0.55. With power=0.80 and alpha-level=.05/2=.025 (2 main effect hypotheses), the required sample size was N=198 randomized. The online RMASS (Repeated Measures and Sample Size) calculator based partly on Hedecker (1999) was used to perform the calculation.

This study randomized n=54 Black/AA participants. The final analysis sample size for this study was N = 44 with n1=26 randomized to receive Pregabalin and n2=18 randomized to receive placebo. We re-calculated power for specific aims 1 and 2 based on the modified primary analysis model, achieved sample sizes, observed attrition rates (cumulative attrition at time point 12 equaled 40%), and average correlation among repeated measures (equal to 0.53 for HDD). We used the RMASS (Repeated Measures and Sample Size) online calculator (http://www.rmass.org) which incorporates methods developed in several articles for longitudinal designs. Under the above specifications, the detectable Cohen's d type effect size for HDD equaled 0.67 with two-sided alpha set=0.05 and power=0.80. Under the same specifications for specific aim 2 for cluster B and E subscales of the PCL-5, except for slight changes to the correlation, detectable effect sizes equaled 0.68 and 0.63.

Analysis Population: All randomized AUD/PTSD African-American participants who received at least one dose of medication. NOTE: This means that we will NOT test Specific Aim 3 – there were not enough European Americans recruited into the sample to conduct a comparison by race.

A. Describe the sample

Variables/measures we will use to describe the sample are:
- Demographics: age, sex/gender, education, SES (income and employment), collected at screening
- Life events checklist, collected at screening
- PCL, collected at screening
- CAPS, collected at screening
- TLFB30 drinks per week (DPW), drinks per drinking day (DPDD), heavy drinking days (HDD); collected at screening
- OCDS, collected at baseline
- CIWA, collected at baseline
- AUD severity defined as a symptom count from the SCID
- Smoking status defined as smoking >= 10 cigarettes in past 90 days from the "Other Drug Use" form
- Vital signs: BMI calculated from height and weight, collected at screen

B. Specific Aim 1 (SA1): To test the hypothesis that African American AUD/PTSD participants treated with pregabalin will demonstrate a greater reduction in heavy drinking days than African American placebo treated participants.

Primary outcome: HDD during the past 7 days assessed weekly during treatment with the TLFB. NOTE: We will adjust for drinking last 30 days at screening.

Secondary outcomes:
- DPW and DPDD during the past 7 days assessed weekly during treatment with the TLFB.
- Number of days abstinent (NDA) during the past 7 days assessed weekly during treatment with the TLFB. NOTE: We will adjust for drinking last 30 days at screening.
- %dCDT measured via blood samples collected at screening, midpoint (Visit 6), and end-of-study (Visit 12).
- GGTP measured via blood samples collected at screening, midpoint (Visit 6), and end-of-study (Visit 12).

SA1 Analysis: For HDD and secondary TLFB outcomes, a repeated measures mixed effects model will be used to compare change over the twelve weekly assessments between the two treatment conditions. The model will be a generalized linear or linear model depending on the distribution of the outcome. A quadratic term for time will be specified to capture non-linear change. To reduce residual error and maximize power, we will adjust for a pre-baseline assessment of the outcome. Overall, the regression model will be:

Outcome = pre-baseline Outcome + txgroup + week + week2 + weekXtxgroup + week2Xtxgroup

The analysis model for %dCDT of and GGTP will assess the time-averaged (over visits 6 and 12) difference between treatment groups adjusting for baseline. The model will account for within-individual correlations with a random effect for participant.

C. Specific Aim 2 (SA2): To test the hypothesis that African American AUD/PTSD participants treated with pregabalin will demonstrate a greater reduction in PTSD cluster B or E symptoms (or both) than African American placebo-treated participants.

Primary outcomes:
- PCL cluster B symptom severity scores, assessed weekly during treatment.
- PCL cluster E symptom severity scores, assessed weekly during treatment.
- NOTE: We will adjust for PCL score collected at screening.

Secondary outcomes:
- PCL total symptom score, assessed weekly during treatment. NOTE: We will adjust for PCL score collected at screening.
- CAPS cluster B and E symptom severity scores, assessed at weeks 4, 8, and 12 during treatment. NOTE: We will adjust for CAPS score collected at screening.

SA2 Analysis: The analysis of the primary outcomes will use the same regression model described for drinking outcomes in SA1. Analysis of the CAPS scores will be a repeated measures mixed effects model to test the difference in the mean across weeks 4, 8, and 12 adjusting for the pre-baseline score.

D. Specific Aim 4 (SA4): To test the hypothesis that the treatment responses to pregabalin in African American AUD/PTSD participants specified in SA1 and SA2 are moderated by genetic variations within SLC6A1 gene.

Analysis: This analysis will examine whether there is a difference of treatment effect between two SLC6A1 gene variant groups, i.e., the non-insertion/insertion or insertion/insertion variant group (NI/I or I/I) versus the non-insertion/non-insertion (NI/NI) variant. A binary indicator will be constructed to indicate the NI/I or I/I versus NI/NI variant. The analysis will be conducted by adding the main effect and interaction terms of this binary indicator to the above regression model to test whether there is a difference in treatment effect by SLC6A1 gene group on the primary outcomes specified in SA1 and SA2.