Study: # 7977 entitled Pregabalin Trial for the Treatment of Alcohol Use Disorder (GABI2)

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PI: **Mariani, John J**	Title: Pregabalin Treatment of Alcohol Use Disorder.	
Received: 06/14/2019	FOA: PA19-054 Clinical Trial:Required	Council: 01/2020
Competition ID: FORMS-E	FOA Title: NIH Exploratory/Developmental Research Grant Program (Parent R21 Clinical Trial Required)	
1 R21 AA028371-01	Dual:	Accession Number: 4318515
IPF: 1590919	Organization: NEW YORK STATE PSYCHIATRIC INSTITUTE	
Former Number:	Department: 110 NYPI Substance Use Disorde	
IRG/SRG: AA-3 (03)	AIDS: N	Expedited: N
Subtotal Direct Costs (excludes consortium F&A) Year 1: 150,000 Year 2: 125,000	Animals: N Humans: Y Clinical Trial: Y Current HS Code: 30 HESC: N	New Investigator: Early Stage Investigator:
Senior/Key Personnel:	*Organization:*	*Role Category:*
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John Mariani	Research Foundation for Mental Hygiene, Inc.	PD/PI

- Type (Primary/Secondary/Other)	- Name of outcome	- Timeframe (how often and when it will be assessed)	Description
primary	Proportion of heavy drinking days	Weekly	The proportion of the heavy drinking days (defined as any day where the number of standard drinks was at least 5 for men and at least 4 for women) per week as measured by the timeline follow-back (TLFB) method.
secondary	Percent Days Abstinent	Assessed weekly	The percent days abstinent per week as measured by the TLFB method
secondary	Drinks per drinking day	Assessed weekly	Standard drinks per day of drinking as measured by the TLFB method
secondary	Drinks per week	Assessed weekly	Standard drinks per week as measured by the TLFB method
secondary	Percent Participants Abstinent	Assessed weekly	Percent of participants abstinent by week in each study arm

Data Analysis

a. Primary Outcome Measures

i) The proportion of heavy drinking days (defined as any day where the number of standard drinks was at least 5 for men and at least 4 for women) per week as measured by the timeline follow-back (TLFB) method

b. Secondary Outcome Measures

i) The percent days abstinent: The percent days abstinent per week as measured by the TLFB method

ii) Drinks per drinking day: Standard drinks per day of drinking as measured by the TLFB method

iii) Drinks per week: Standard drinks per week as measured by the TLFB method

iii) Percent Participants Abstinent: Percent of participants abstinent by week in each study arm

Exploratory outcome measures:

(i) Alcohol craving—as measured by the OCDS
(ii) Sleep disturbance—as measured by the MOS-Sleep
(iii) Anxiety symptoms—as measured by the HAM-A
(iv) Alcohol withdrawal—as measured by the CIWA-Ar
(v) Quality of life—as measured by the QLES
(vi) Retention, medication compliance, rates of adverse effects

c. Sample size: A total of 50 participants will be recruited with 25 randomized to each of the two treatment groups.

d. Randomization: Participants will be randomly assigned to receive either medication or placebo. The randomization sequence will be balanced in blocks of random size (4, 6, 8) to prevent clinicians from guessing what the next patient's treatment might be. Additionally, the randomization will be stratified by gender and the severity of alcohol use (> 35 standard drinks/week). The purpose of the stratification is to distribute these potential confounding factors equally across treatment groups. To the extent that these stratification variables

are predictive of outcome, stratifying by them should enhance statistical power to test treatment effects (Fleiss et al. 1986).

e. Intent to Treat / Dropouts and missing data: The primary analyses in this study will be on the intent-to-treat (ITT) sample, i.e. on all randomized participants taking at least one dose of study medication and returning for at least one post-randomization assessment.

Dropout: Based on prior experience, we expect dropout to be about 30% in both the treatment group and placebo group. If a subject drops out despite our encouragement to stay in the study, we will record the reason for dropout and make all efforts to obtain a final assessment from this subject. Dropouts will be analyzed whether missing at random or not and appropriately incorporated in the model (see Section below).

f. Accounting for dropout in the analysis: We will account for unobserved data and dropouts by examining the primary outcome variables using longitudinal mixed effects models (MEM) (Brown & Prescott, 1999; Diggle, et al., 2002) using PROC GLIMMIX in SAS®. MEMs do not require complete measurements data to estimate the outcome variable. The inferences from analyses with missing data are valid provided that they are "missing at random" (Little & Rubin, 2002). 'Missing at random' (i.e the missing mechanism does not depend on the value of the unobserved outcome) is un-testable in most medical research and in our study as well. In summary, participants who dropout will be part of longitudinal mixed effect model and the results of such model will be unbiased as long as the missing data are missing at random. If we suspect that the missingness is not at random, one can assume either parametric or semi-parametric models for the missingness that does depend on the unobserved outcome value and do the analysis (Diggle & Kenward, 1994; Kenward, 1998; Liu, et al., 1999; Rotnitzky, et al., 1998; Scharfstein, et al., 1999). Comparison of the inferences from assuming various models for the missingness provides a measure of the validity of the efficacy estimate from the model that assumes missing 'at random'. We plan to perform a sensitivity analysis based on these two approaches to assess the effect of the assumption of missing 'at random' on the inference.

g. Significance testing and preliminary analysis: All tests will be performed at two-tailed significance α=5%. Exceptions will be noted. Before performing specific analyses (described below), we will examine all variables for outliers. The distributions of all continuous variables will be checked for normality, and transformations will be employed, if necessary, before applying specific parametric techniques. The distribution of demographic variables and other covariate measures of at baseline in the treatment arms will be examined and described in terms of means, standard deviations, proportions and 95% confidence intervals. The covariate may be associated with treatment outcome and we will adjust for it in all models used to test the study hypotheses. Interactions of covariates with treatment will be explored as exploratory analyses addressing moderator effects. We will adjust also for baseline value of the outcome variable where appropriate. This adjustment will be based on the inclusion of main effects for the baseline. We will also explore effect moderation, i.e., baseline by treatment interactions.

h. Primary hypothesis:

Pregabalin will reduce the proportion of Heavy Drinking Days (HDD) as compared to Placebo at the end of the trial.

The following model will be used for testing:

(1) $Y_{ijt} = \beta_0 + \beta_1 I_i + \beta_2 t + \beta_3 t^* I_i + \beta_4 U_{ij} + s_i + \varepsilon_{ijt},$

Y_{ijt} is the proportion of HDD of the i^{th} subject in the treatment group j at week t (t =1, 2, …, 8); U_i is the vector of covariates; I_i is the indicator variable for treatment with pregabalin; s_i is a random intercept for subject i and ε_{ijt} is a random error term. Significant interaction t^*I_i indicates that the effect of each treatment group is different over time (that corresponds to rejecting null hypothesis that $\beta_3=0$). The effect of pregabalin at the last week ($t=8$) will be assessed by evaluating the significance of the contrast comparing the effect of pregabalin at week 8 to effect of placebo at week 8. The GEE approach will be used to appropriately model the within subject correlation using autoregressive AR(1) structure and random effects of subjects.

g. Secondary hypotheses:

The hypothesis is that pregabalin will increase the percent days abstinent (PDA) at the end of the study and over the course of the trial as measured by the timeline follow-back method. The pattern of alcohol use (amount of drinks per drinking day and drinks per week) as measured by the time line follow-back method will show greater reductions in use for the pregabalin group as compared to the placebo group, and that the percent of participants abstinent (PPA) per week in each study arm will be greater for the pregabalin group as compared to the placebo group. All secondary hypotheses will be analyzed using similar analytic methods as described above for the primary hypothesis and the preliminary effect sizes will be expressed using 95% confidence intervals.

i. Exploratory Analyses

This study gives the opportunity to explore important research questions. The quality of evidence from these analyses will be considered inferior to the evidence that results from the analysis of primary and secondary objectives. The exploratory analyses will examine possible moderators and mediators, including alcohol withdrawal, anxiety, craving, and sleep measures. The results from the exploratory analyses will be used for hypothesis generation for future studies. To test potential moderators of the treatment effect on the primary and secondary outcomes, we will test the significance of the three-way interaction effect between treatment group, time, and the proposed moderators. To test potential mediators, we will use the CAUSALMED procedure in SAS, which provides confidence interval estimates and statistical tests. We will test for and estimate the natural indirect effect. Our resulting inferences will have a causal mediation interpretation if our baseline coefficients are sufficient to control for confounding of the effect of the candidate mediator on the outcome. Additionally, we will explore whether there are differences between pregabalin and placebo groups with respect to the number of adverse effects, side effects, medication compliance, and retention in relation to the primary outcome.

j. Power Analysis

The primary purpose of this proposed R21 pilot study is to examine feasibility, acceptability, and tolerability of the proposed treatment (Leon et al. 2011, Kistin et al. 2015) intervention as well as to estimate plausible effect sizes. It is widely accepted that pilot studies cannot be powered (Kraemer et al. 2006)(NCCIH, 2017). Even though the argument for estimating effect sizes is not compelling in the light of Kraemer et al. (2006), we will estimate the effect sizes for 2 practical reasons: 1) we will rehearse analyzing the data and carefully investigate whether all assumptions are met for the analyses which will prepare us for and make us aware of all the statistical issues we can encounter in larger study, 2) we will compute 95% confidence interval as estimates of preliminary effect sizes. With 25 subjects in each arm we will be able to compute two-sample confidence intervals for difference in proportions between pregabalin and placebo with width at most of ± 27%. The 95% confidence interval provides considerably more information than testing a specific null hypothesis: it gives us a range of parameter estimates for the difference of population proportion between pregabalin and placebo. This range of plausible effect sizes can be used to estimate potential effect sizes in larger clinical trials by considering the worst possible effect size scenario from the 95% confidence intervals as plausible results of larger trial. While our argument remains that estimating effect sizes is the appropriate approach for analyzing the pilot trial outcomes, we provide the following power analysis because some reviewers expect to see power calculation as part of the application. With 25 subjects per group, and assuming that the observed proportion meeting the primary outcome (Heavy Drinking Days) in the placebo group is 54% (observed in our prior trial with this population), we have at least 80% power, at two-sided level of significance 5%, to detect a difference of 35% (HDD of 19% in the pregabalin group vs. 54% in the placebo group at the end of study).