Title Page:

Grant: Quetiapine Pharmacotherapy for Cannabis Dependence

IRB# 6623

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Data Analysis created on November 07, 2011
Amended April 11, 2018

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Trial Registration: clinicaltrials.gov Identifier: NCT01697709

Data Analysis

1) **Data analysis plan as submitted in R01 application on 11/07/2011**
2) **Amended data plan created on April 11, 2018**

OMB Number: 4040-0001
Expiration Date: 06/30/2011

APPLICATION FOR FEDERAL ASSISTANCE
SF 424 (R&R)

3. DATE RECEIVED BY STATE	State Application Identifier

1. * TYPE OF SUBMISSION
☐ Pre-application ☒ Application ☐ Changed/Corrected Application

2. DATE SUBMITTED: 11/07/2011
Applicant Identifier: PD/2011/01094

4. a. Federal Identifier: DA031010
b. Agency Routing Identifier:

5. APPLICANT INFORMATION
*** Organizational DUNS:** 167204994000O

* Legal Name: Research Foundation for Mental Hygiene, Inc.
Department: 110 NYPI Substance Abuse
Division:
* Street1: NYPI
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County / Parish: New York
* State: NY: New York
Province:
* Country: USA: UNITED STATES
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6. * EMPLOYER IDENTIFICATION *(EIN) or (TIN)*: 114114984ZA2

7. * TYPE OF APPLICANT: M: Nonprofit with 501C3 IRS Status (Other than Institution of Higher Education)
Other (Specify):
Small Business Organization Type ☐ Women Owned ☐ Socially and Economically Disadvantaged

8. * TYPE OF APPLICATION:
☐ New ☒ Resubmission
☐ Renewal ☐ Continuation ☐ Revision

If Revision, mark appropriate box(es).
☐ A. Increase Award ☐ B. Decrease Award ☐ C. Increase Duration ☐ D. Decrease Duration
☐ E. Other (specify):

* Is this application being submitted to other agencies? Yes ☐ No ☒ What other Agencies?

9. * NAME OF FEDERAL AGENCY: National Institutes of Health

10. CATALOG OF FEDERAL DOMESTIC ASSISTANCE NUMBER:
TITLE:

11. * DESCRIPTIVE TITLE OF APPLICANT'S PROJECT:
Quetiapine Pharmacotherapy for Cannabis Dependence

12. PROPOSED PROJECT:
* Start Date: 07/01/2012
* Ending Date: 06/30/2016

*** 13. CONGRESSIONAL DISTRICT OF APPLICANT**
NY-015

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3. Data Analysis

a. Outcome Measures and Covariates

i. Primary outcome measures:

1) Marijuana use: The daily dollar value of marijuana used averaged over a one-week period as recorded by the Timeline Followback method and confirmed by creatinine-normalized quantitative urine THC levels.
2) Abstinence initiation: The number of abstinent days per week as recorded by the Timeline Followback method and confirmed by creatinine-normalized quantitative urine THC levels.

ii. Secondary outcome measures: These measures are designed to capture changes in marijuana consumption patterns and other symptoms not measured by the primary outcome measures.

1) Urine toxicology: twice weekly urine toxicology samples negative for cannabinoids - dichotomous longitudinal
2) Marijuana withdrawal symptoms: measured by weekly Marijuana Withdrawal Checklist (MWC) – continuous longitudinal
3) Marijuana craving: measured by weekly Marijuana Craving Questionnaire (MCQ) – continuous longitudinal
4) Sleep disturbance: measured by the Medical Outcomes Study—Sleep Scale (MOS-SS) – continuous longitudinal

iii. Covariates:

1) Demographic characteristics (e.g., gender, rage, age)
2) Baseline presence of co-occurring mood or anxiety disorders
3) Baseline severity of marijuana use (measured by the quantity of marijuana consumed per using day at baseline)
4) Additional treatment services (measured by the Treatment Services Review)

iv. Other measures: Adverse effects, as measured by the Systematic Assessment for Treatment and Emergent Events (SAFTEE), will assessed, including potential effects on compliance and outcome.

b. Sample size and randomization:

A total of 150 patients will be recruited over a 4-year period and randomized to the double-blind treatment trial, with 75 patients randomized to each of the two treatment groups, quetiapine arm and placebo arm. The randomization sequence will be balanced in blocs of random size (4, 6, 8) to prevent clinicians from guessing what the next patient's treatment might be.

c. 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 patients. Marijuana consumption and marijuana abstinence, are assessed repeatedly over time and we will try to collect them at all study assessment points. We will account for unobserved data 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. 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'. One can also compute a local sensitivity index which measures the change in the estimated treatment effect in a neighborhood of the 'missing at random' model for missingness (Rotnitzky, et al., 2001). 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.

d. Significance testing and preliminary analyses:

All tests for main effects will be performed at two-tailed significance α=5%, all tests for interaction effects will be performed at significance level α=15%. 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 (ethnicity, gender, age) 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 covariates (specified in Section 3.a.iii) may be associated with

treatment outcome. For this reason, we will adjust for these covariates in all models used to test the study hypotheses. These covariates will be included in all models as main effects regardless of their statistical significance or whether they differ between treatment groups. Interactions of covariates with treatment will be explored as secondary analyses addressing moderator effects. In the secondary analyses, 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.

e. Hypotheses testing

i. Primary hypotheses:

Hypothesis 1: *Quetiapine will significantly reduce marijuana consumption as compared to placebo.*
The following model will be used:

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

where Y_{ijt} is the daily dollar value of marijuana used averaged over a one-week period by the i^{th} subject in the treatment group j at week t (t =1, 2, ..., 12); U_i is the vector of covariates; I_i is the indicator variable for treatment with quetiapine; s_j 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 β_{12}= 0). If so, the effect of time will be estimated for each group separately and the groups will be compared (using contrast) in the last time point t=12. If the interaction term is not significant (i.e., the difference between the treatment arms does not change over time), we will refit the model without the interaction term and test the significance of the main effect of treatment (i.e. rejecting the null hypothesis that β_1 = 0).

Hypothesis 2: *Quetiapine will significantly promote abstinence from marijuana use as compared to placebo.*

To test the primary hypothesis 2, we will use the same model as in (1) where Y_{ijt} is the number of abstinent days for the i^{th} subject in the treatment group j at week t (t =1, 2, ..., 12). We will first test the interaction effect of group and time as described for Hypothesis 1.

ii. Secondary hypotheses:

Hypothesis 3: *Over time, the proportion of weekly urine toxicologies negative for cannabinoids will be significantly greater in the quetiapine group as compared to the placebo group.*

This hypothesis will be tested using the following model:

$$(2) \qquad \text{logit}(\, Y_{ijt}=1) = \beta_0 + \beta_1 I_i + \beta_2 t + \beta_3 t^* I_i + \beta_4 U_{ij} + s_i + \varepsilon_{ijt}$$

where Y_{it} is a dichotomous measure indicating whether the i^{th} subject in the treatment group j has a positive urine for cannabinoids at week t (t =1,2, ..., 12) with Y_{it} = 1 for positive urine and Y_{it} = 0 for negative urine; U_i is the vector of all appropriate covariates; I_i is the indicator variable for treatment with quetiapine; s_j 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 β_{12}= 0). If so, the odds ratio for the negative urine in quetiapine arm relative to placebo arm will be estimated for each group separately and the groups will be compared (using contrast) in the last time point t=12. If the interaction term is not significant (i.e., the difference between the treatment arms does not change over time), we will refit the model without the interaction term and test the significance of the main effect of treatment (i.e. rejecting the null hypothesis that β_1 = 0).

Hypothesis 4: *Over time, subjects in the quetiapine group will experience significant reduction in the pattern of marijuana withdrawal symptoms (measured as mean Marijuana Withdrawal Checklist score per week) compared to the subjects in the placebo group.*

Hypothesis 5: *Over time, subjects in the quetiapine group will exhibit significantly reduced marijuana cravings (as measured by Marijuana Craving Questionnaire) compared to subjects in the placebo group.*

Hypothesis 6: *Over time, subjects in the quetiapine group will experience significantly less sleep disturbance (as measured by the Medical Outcomes Study Sleep scale) compared to subjects in the placebo group.*

To test the secondary hypotheses 4, 5 and 6, we will use the same model as in (1) where Y_{ijt} is the appropriate outcome variable (as specified for each hypothesis) for the i^{th} subject in the treatment group j at week t (t =1, 2, ..., 12). We will first test the interaction effect of group and time as described for Hypothesis 1.

iii. Exploratory Analyses

We will explore whether there are differences between the two groups with respect to treatment retention (in terms of the percentage of participants in each group completing the trial) and the number of adverse effects (as measured by the adverse and serious adverse event form), and examine the effect of treatment on global functioning (as assessed by the CGI-O and CGI-S). Substance use other than marijuana will also be monitored on a weekly basis and we will explore whether there are effects of treatment on these outcomes. We will examine other moderators and mediators to explore causal mechanisms, which can inform further basic and clinical work, as well as the design of future trials. Prior studies have examined the effect of baseline level of craving (Kampman, et al., 2002) and depressed mood on outcome, and we also plan to explore these as moderators of outcome. We plan to test the mood, irritability, withdrawal, craving, and sleep measures as moderators or mediators of treatment effect and to explore which of these may be involved in the mechanism of action of any beneficial effect of quetiapine on marijuana use.

f. Power Analysis

The sample size was chosen to ensure sufficient power (at least 80%) of a two-sided test with level of significance α=0.05 for detecting difference between the two experimental treatments with respect to both, the daily dollar value of marijuana used averaged over a one-week period and the number of days per week of marijuana abstinence, that would be in the medium-sized range of effect size and clinically meaningful.

For the primary hypothesis 1, we assume that 1) the within-subject correlation is about 0.25 (conservative estimate, larger and more plausible correlations result in more powerful study), 2) the standard deviation of the daily dollar value of marijuana used averaged over a one-week period (as observed by pilot study) at baseline is $35 and at week 12 is at least $8 (a conservative estimate based on the standard deviations from the pilot study $34.28 and $7.68, respectively; see Section C.1), 3) the mean difference between groups at week 12 is at least $14 (based on the improvement from the pilot study: We assume that the quetiapine group will exhibit reduction of at least $25, while placebo group will exhibit reduction of at most $11; see Section C.1) and 4) attrition rate of 20%. Under these assumptions, 75 subjects in each group (60 subjects after attrition) guarantee with at least 80% power detecting a corresponding effect size of 0.41 = 14/34.28 significant.

For the primary hypothesis 2, we assumed that 1) the within-subject correlation is at least 0.25 (conservative estimate, larger and more plausible correlations result in more powerful study), 2) the variance of the number of days per week of marijuana abstinence is about 1.5 times of the mean, and 3) the mean number of days per week of marijuana use in the placebo group during the treatment phase will be 2.0 times that of the active treatment group, which approximately corresponds to a effect size of around .35 for the outcome at logarithm scale. Under these assumption, 75 subject per group result in study with at least 80% power to detect an effect size of at least .35 significant.

g. Timeline

The entire proposed project will be completed within 48 months of the initiation date (see table 3). Three months will be required for staff training and other preparation. Active recruitment will continue for 42 months allowing for time for all enrolled participants to complete the study before the 48 month period ends. During active recruitment, 3-4 participants per month will be enrolled. This recruitment flow is feasible based on our past success in recruitment of cannabis-dependent individuals (see Preliminary Studies).

Table 3—Study Timeline

Study Year				
1	2	3	4	
Staff Training	Active Recruitment (42 months)			Complete study measures

4. Future Directions: Our research group has taken the lead in exploring pharmacologic treatments for cannabis dependence. If this phase II proposal demonstrates that quetiapine is effective, it would be the first medication effective for cannabis-dependent individuals and provide a strong basis to pursue a larger, definitive Phase III efficacy trial. Failure to find an effect would prompt attention to exploratory analyses for hypotheses about whether there are responsive subgroups, or focus attention on alternative candidate medications.

Prepared by Jean Choi
4/11/18

Revised QUEST Primary Analyses Plan-updated 4/11/2018

Preliminary analyses on both primary outcome measures showed there to be a non-normal distribution. Therefore, data analyses was amended to account for this.

The primary outcome of marijuana use as measured by the daily dollar value of marijuana used averaged over a one-week period as recorded by the Timeline Followback method was analyzed using a longitudinal mixed effect model. A random intercept was used to account for the between-subject variances and the negative binomial distribution was used to model the non-normal distribution of marijuana use.

The primary outcome of marijuana use as measured by the number of abstinent days as recorded by the Timeline Followback method was analyzed using a multinomial logistic regression model. At each observed week in the study, marijuana use days were categorized into three groups: High Use (or 0-2 abstinent days), Medium Use (or 3-5 abstinent days) and Low Use (or 6-7 abstinent days).