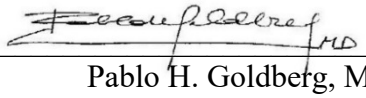
STATISTICAL ANALYSIS PLAN (SAP)

Study title	Ketamine Treatment for Pediatric-Refractory Obsessive-Compulsive Disorder (OCD)
Principal investigator	Pablo H. Goldberg, M.D. Associate Clinical Professor of Psychiatry New York State Psychiatric Institute/Columbia University New York, NY
Protocol ID	37023
ClinicalTrials.gov ID	NCT02422290
Version	1 (3/13/2013)

SIGNATURE

Principal Investigator 

Pablo H. Goldberg, MD

CONTENTS

1 INTRODUCTION

We will evaluate the feasibility/tolerability, and preliminary efficacy of ketamine, a medication that modulates glutamate in the brain, as a rapid treatment for OCD symptoms in adolescents with OCD. Our rationale for using ketamine is threefold. First, glutamatergic abnormalities in corticostriatal circuits may underlie OCD symptoms based on human imaging, genetic, and animal studies; striatal glutamatergic levels have been associated with OCD severity. Thus, medications that modulate glutamatergic neurotransmission (e.g., riluzole memantine, minocycline) may be effective. Second, riluzole and memantine have shown promise for OCD in case reports or open trials, but neither is FDA-approved for use in children; riluzole also has significant liabilities in terms of adverse events and cost. In contrast, ketamine is FDA-approved for anesthesia in children, adolescents and adults, and is routinely used at higher doses than proposed in this study. It is also used as adjunctive pain management for children and adolescents suffering from end stage medical illness. Third, we found in a small randomized controlled trial that unmedicated OCD adult patients had a near cessation of obsessional thoughts during an intravenous ketamine infusion; these effects were maintained in half of patients for up to one week (Rodriguez et al. 2013). These exciting findings lead to two questions: 1) is this type of study acceptable and feasible in youth; 2) are ketamine's effects similar in adolescents and young adults?

2 AIMS

We propose a pilot study to determine the acceptability, feasibility and potential efficacy of a single ketamine infusion in adolescents and young adults with OCD. Promising data will lead to a grant application to the National Institutes of Mental Health for a full scale randomized controlled trial.

Aim 1. To assess the feasibility/tolerability of using ketamine in adolescents with OCD

Aim 2. To assess the effects of ketamine on OCD severity

3 PROCEDURES

We will recruit 5 adolescents and young adults (post-pubertal, ages 14-20) with OCD using similar criteria as in our prior ketamine study (Rodriguez et al. 2013) with the modification that participants have attempted at least one trial of a standard treatment (i.e., SRI and/or CBT). They will be free of medication and have at least moderate OCD severity (rating on Children's Yale-Brown Obsessive-Compulsive Scale [CY-BOCS] of at least 16) and near constant obsessions. After baseline assessment and evaluation, patients will receive a single infusion of intravenous ketamine 0.5 mg/kg. Obsessional severity will be evaluated at baseline, during the ketamine infusion and during post-infusion observation using the OCD-Visual Analogue Scale; OCD and depressive severity will be evaluated using the CY-BOCS (child version) and Children's Depression Rating Scale Revised at weekly intervals for 2 weeks after infusion.

4 ANALYSIS SET

This pilot study is a non-controlled clinical trial consisting of one group of participants. Participants will be adolescents and young adults with OCD who have failed at least one trial of standard treatment. All participants will receive an intravenous ketamine infusion.

5 OUTCOMES

6.1. Primary Outcomes

i. Total number of screened participants
ii. Total number completing

6.2. Secondary Outcomes

i. CY-BOCS score at baseline, 1 week post-infusion, and 2 weeks post infusion
ii. Children's Depression Rating Scale Revised at baseline, 1 week post-infusion, and 2 weeks post

6.3 Adverse Outcomes

i. Adverse events will be assessed throughout the study period
ii. Suicidality will be obtained with the Columbia-Suicide Severity Rating Scale (C-SSRS).

6 STATISTICAL ANALYSIS

Data will be analyzed using IBM SPSS. We will report descriptive statistics for all outcomes including mean and standard deviation.

8.1. Descriptive Statistics

For acceptability and feasibility, we will assess the number screened and the number completed by reporting total numbers and percentages.

8.2. Statistical Tests

For potential efficacy, continuous outcomes will be modeled as a function of time using mixed-effects regression, and the proportion of responders (CY-BOCS decrease $\geq 35\%$) and remitters (CY-BOCS ≤ 12) one and two weeks after the ketamine infusion will be computed. Differences in outcomes from baseline to 1 week post-infusion and 2 weeks post-infusion will be the independent variables. Study subjects will be considered as random effects and the proportion of responders and remitters as well as the difference of obsessional severity from baseline to post-infusion will be included as fixed effects. Sex and age will be considered as covariates. 95% confidence intervals, and p-values will be presented for each outcome variable and time point

7 MISSING VALUES

Mixed models provide adequate power without ad hoc imputations (Chakraborty & Gu, 2009). Thus, missing value will not be imputed.

8 REFERENCES

Rodriguez, C.I., Kegeles, L.S., Levinson, A., Feng, T., Marcus, S.M., Vermes, D., …, & Simpson H.B. (2013). Randomized controlled crossover trial of ketamine in obsessive-compulsive disorder: proof-of-concept. *Neuropsychopharmacology, 38*(12), 2475-2483.

Chakraborty, H. & Gu, H. (2009). *A Mixed Model Approach for Intent-to-Treat Analysis in Longitudinal Clinical Trials with Missing Values.* RTI Press Publication No. MR-0009-0903. Research Triangle Park, NC: RTI Press

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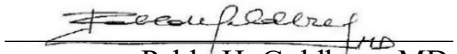
Principal Investigator 

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Aim 2. To assess the effects of ketamine on OCD severity

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BOCS) and Yale-Brown Obsessive Compulsive Challenge Scale (Y-BOCCS) at weekly intervals for 2 weeks and 3-months following after the infusion; illness severity will be rated using the Clinical Global Impressions Severity Scale (CGI-S) at weekly intervals for 2 weeks and 3-months following after the infusion.

5 ANALYSIS SET

This pilot study is a non-controlled clinical trial consisting of one group of participants. Participants will be adolescents and young adults with OCD who have failed at least one trial of standard treatment. All participants will receive an intravenous ketamine infusion.

6 OUTCOMES

6.1. Primary Outcomes

Primary outcomes will be the changes in the CY-BOCS total score and CGI-S rating from baseline to 14 days post infusion.

6.2. Secondary Outcomes

Secondary outcomes will be the changes in the OCD-VAS and Y-BOCCS total score from baseline to 14 days post infusion.

6.3 Adverse Outcomes

Adverse events will be assessed throughout the study period; suicidality will be obtained with the Columbia-Suicide Severity Rating Scale (C-SSRS).

7 STATISTICAL ANALYSIS

Data will be analyzed using IBM SPSS. We will report descriptive statistics and results from paired sample-tests to describe changes in primary and secondary outcomes from baseline to 14 days post infusion. The following subsections describe the statistical procedures.

8.1. Descriptive Statistics

All primary and secondary outcomes are continuous variables and descriptive statistics will be reported by mean and standard deviation.

8.2. Statistical Tests

In the initial SAP, we proposed a mixed-effects regression to analyze the potential efficacy of the ketamine infusion. After study completion and careful consideration of the data collected, we decided to change the SAP to compare the mean differences of the primary and secondary outcomes between the baseline assessment and 14 days post infusion using paired sample t-tests.

The normal distribution of the differences between the paired values will be tested using the Shapiro-Wilk test and outliers will be reviewed using box plot diagrams. Estimated t-values, 95% confidence intervals, and p-values will be presented for each outcome variable.

8 MISSING VALUES

Missing values will be excluded from the statistical tests pairwise.

9 REFERENCES

Rodriguez, C.I., Kegeles, L.S., Levinson, A., Feng, T., Marcus, S.M., Vermes, D., …, & Simpson H.B. (2013). Randomized controlled crossover trial of ketamine in obsessive-compulsive disorder: proof-of-concept. *Neuropsychopharmacology, 38*(12), 2475-2483.