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General Information

Key Personnel (in addition to PI): **First Name:** Wolfgang

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Are external grants or funds being used to support this research?: No external grants or funds are being used to support this research.

How did you learn about the YODA Project?: Colleague

 [2017-1676_cois.pdf](#)

Certification

Certification: All information is complete; I (PI) am responsible for the research; data will not be used to support litigious/commercial aims.

Data Use Agreement Training: As the Principal Investigator of this study, I certify that I have completed the YODA Project Data Use Agreement Training

Associated Trial(s): [NCT00518323 - A Randomized, Multicenter, Double-Blind, Weight-Based, Fixed-Dose, Parallel-Group, Placebo-Controlled Study of the Efficacy and Safety of Extended Release Paliperidone for the Treatment of Schizophrenia in Adolescent Subjects, 12 to 17 Yea](#)
[NCT00334126 - A Randomized, Double-blind, Placebo-controlled, Parallel Group Study to Evaluate the Efficacy and Safety of Paliperidone ER Compared to Quetiapine in Subjects With an Acute Exacerbation of Schizophrenia](#)
[NCT00249132 - A Canadian multicenter placebo-controlled study of fixed doses of risperidone and haloperidol in the treatment of chronic schizophrenic patients](#)
[NCT00077714 - A Randomized, Double-blind, Placebo- and Active-controlled, Parallel-group, Dose-response Study to Evaluate the Efficacy and Safety of 2 Fixed Dosages of Paliperidone Extended Release Tablets and Olanzapine, With Open-label Extension, in t](#)
[NCT00083668 - A Randomized, Double-blind, Placebo- and Active-controlled, Parallel-group, Dose-response Study to Evaluate the Efficacy and Safety of 3 Fixed Dosages of Paliperidone Extended Release \(ER\) Tablets and Olanzapine, With Open-label Extension,](#)
[NCT00078039 - Trial Evaluating Three Fixed Dosages of Paliperidone Extended-Release \(ER\) Tablets and Olanzapine in the Treatment of Patients With Schizophrenia](#)
[NCT00085748 - A Randomized, 6-Week Double-Blind, Placebo-Controlled Study With an Optional 24-Week Open-Label Extension to Evaluate the Safety and Tolerability of Flexible Doses of Paliperidone Extended Release in the Treatment of Geriatric Patients Wit](#)
[NCT00088075 - A Randomized, Double-Blind, Placebo-Controlled Clinical Study of the Efficacy and Safety of Risperidone for the Treatment of Schizophrenia in Adolescents](#)
[Risperidone versus haloperidol versus placebo in the treatment of schizophrenia](#)
[The safety and efficacy of risperidone 8 mg qd and 4 mg qd compared to placebo in the treatment of schizophrenia](#)
[NCT00524043 - A Randomized, Double-Blind, Placebo- and Active-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of a Fixed Dosage of 1.5 mg/Day of Paliperidone Extended Release \(ER\) in the Treatment of Subjects With Schizophrenia](#)

What type of data are you looking for?: Individual Participant-Level Data, which includes Full CSR and all supporting documentation

Research Proposal

Project Title

Placebo Effects in Schizophrenia

Narrative Summary:

Response to antipsychotics is often difficult to measure, which in turn has resulted in numerous failed trials in that drugs have not shown superiority over placebo. Therefore, it is critically important to investigate placebo effects in this population in order to optimize the design of future clinical trials to mitigate such challenge. To this end, we will combine placebo-controlled double-blind trial data to provide evidence to screen potential placebo responders with schizophrenia. These results will be expected to provide critical insights in the design of future clinical trials in patients with schizophrenia so as to reduce failure of placebo-controlled antipsychotic clinical trials.

Scientific Abstract:

Background: Response to antipsychotics is often difficult to quantify, which in turn resulted in a number of failed trials in that drugs have not established superiority over placebo treatment. In light of an increasing number of failed antipsychotic trials, it is important to investigate placebo effects in this population in order to optimize the design of future clinical trials.

Objective: Objectives are three-fold: to compare symptom trajectories between placebo and active drug responders to identify demographic and clinical characteristics associated with placebo response or occurrence of side effects in patients with schizophrenia; and to examine whether early placebo improvement is associated with placebo response at the endpoint.

Study Design: A post-hoc analysis of placebo-controlled double-blind trial data.

Participants: Data from participants in the following studies will be used: NCT00077714, NCT00078039, NCT00083668, NCT00085748, NCT00088075, NCT00249132, NCT00334126, NCT00518323, NCT00524043, RIS-USA-1, and RIS-USA-72.

Main Outcome Measures: Positive and Negative Syndrome Scale scores.

Statistical Analysis: First, symptom trajectories between placebo and active drug responders will be compared.

Placebo responders will be categorized into subtypes according to their symptom trajectories. Second, optimal criteria for screening of potential placebo responders in a placebo lead-in phase will be investigated. Third, demographic and clinical characteristics of subjects who showed response or side effects with placebo treatment will be characterized.

Brief Project Background and Statement of Project Significance:

Response to psychotropics is often difficult to quantify, which in turn has contributed to a number of failed trials in that drugs have not established superiority over placebo treatment. This may be especially true for antipsychotic clinical trials as symptom improvement with placebo treatment has been increasing since 1960 (Rutherford et al., 2014). In light of an increasing number of failed trials for schizophrenia, it is critically important to investigate placebo effects in this population in order to improve our understanding of placebo effects as well as to optimize the design of future clinical trials to mitigate such challenge.

Recent clinical trials frequently adopt a lead-in phase, in which placebo is given to participants in an effort to exclude placebo responders. However, the criteria adopted for exclusion of such participants have been arbitrary (e.g. a more than 25% total score reduction in the Positive and Negative Syndrome Scale [PANSS] or Brief Psychiatric Rating Scale [BPRS]) (Downing et al., 2014; Hamilton et al., 1998) and empiric. Systematic investigation of the magnitude and timing of placebo response and occurrence of side effects in patients with schizophrenia and how it differs from reaction to an active drug treatment would offer us a unique opportunity to shed light on critical issues in clinical trials in schizophrenia.

Mechanisms underlying placebo response are multifactorial and complex; psychological, methodological, and administrative factors are expected to be involved in this phenomenon. Among them, previous studies have focused on certain demographic and clinical characteristics in association with greater placebo response in patients with schizophrenia. For example, male gender and older age are reportedly associated with greater placebo effects (Alphs et al., 2012). Analysis of patient-level data of placebo responders/non-responders from previous clinical trials will allow us to provide more detailed information on demographic and clinical characteristics associated with placebo response, such as individual symptom severity at baseline (e.g. less negative symptoms). Moreover, we could make use of early symptomatic trajectories to predict longer term outcome.

We therefore propose a post-hoc analysis of placebo-controlled double-blind trial data in order to provide evidence to guide systematic screening of potential placebo responders with schizophrenia. First, we will compare symptom trajectories between placebo and active drug responders in acute phase trials. Placebo responders will be categorized into subtypes according to their symptom trajectories. Second, optimal criteria for screening of potential placebo responders in a placebo lead-in phase will be investigated. Third, we will try to characterize demographic and clinical characteristics of subjects who showed response or side effects with placebo treatment, respectively. These results will be expected to provide critical insights in the design of future clinical trials in patients with schizophrenia so as to reduce failure of placebo-controlled antipsychotic clinical trials in patients with schizophrenia.

Specific Aims of the Project:

The aims of this analysis are three-fold: (1) to compare symptom trajectories between placebo and active drug responders in acute phase trials; (2) to identify demographic and clinical characteristics associated with placebo response or occurrence of side effects in patients with schizophrenia; and (3) to examine whether early placebo improvement at week 1 is associated with placebo response at the endpoint, in order to guide systematic screening of potential placebo responders.

What is the purpose of the analysis being proposed? Please select all that apply. Participant-level data meta-analysis

Participant-level data meta-analysis uses only data from YODA Project

Research Methods**Data Source and Inclusion/Exclusion Criteria to be used to define the patient sample for your study:**

Datasets of the following studies will be used: NCT00077714, NCT00078039, NCT00083668, NCT00085748, NCT00088075, NCT00249132, NCT00334126, NCT00518323, NCT00524043, RIS-USA-1, and RIS-USA-72.

Main Outcome Measure and how it will be categorized/defined for your study:

Positive and Negative Syndrome Scale (PANSS) scores. Response will be defined as a percentage score reduction of 25% or more at endpoint in the PANSS.

Main Predictor/Independent Variable and how it will be categorized/defined for your study:

Age groups (e.g. <60 or >=60); sex; baseline PANSS positive, negative, and general psychopathology subscale scores, and PANSS Marder 5-Factor scores (Marder et al., 1997); score reductions in PANSS total scores from baseline to week 1.

Other Variables of Interest that will be used in your analysis and how they will be categorized/defined for your study:

Years of education, ethnicity, duration of illness, and cognitive performance scores (when available).

Statistical Analysis Plan:

First, scores of the PANSS at baseline and week 1 and thereafter will be extracted. Differences in the degree of change in the PANSS scores (i.e. PANSS positive, negative, and general psychopathology subscale scores, and PANSS Marder 5-Factor scores) (Marder et al., 1997) over time in placebo and active drug groups will be investigated using a mixed-effects model for repeated measure (MMRM), that contained treatment group (placebo or active drug) and week, and group-by-week interaction as factors. This analysis will be repeated solely for placebo and active drug responders to examine if their response patterns are similar or different as a group. In addition, those placebo and active drug responders will be categorized into subgroups according to their symptom trajectories by using latent class analysis. Second, rates of response (i.e. a percentage score reduction of 25% or more at endpoint in the PANSS) will be calculated for those on placebo and active drugs, and compared using chi-squared tests. Third, multiple logistic regression analysis will be performed to evaluate association between placebo response at endpoint or PANSS score or percentage reduction from baseline to endpoint, and demographic and clinical characteristics that include baseline PANSS scores, gender, age, races, years of educations, and PANSS score change from baseline to week 1 in those receiving placebo. This analysis will also be performed for side effects with the incidence rates of >5%. Fourth, if PANSS score change from baseline to week 1 is found to be associated with subsequent placebo response, the following analysis will be performed. The prediction performance of binary classification in early placebo improvement at week 1, to predict response at week 6, will be examined. To this end, sensitivity, specificity, positive predictive values (PPV), and negative predictive values (NPV) of the consecutive cut-off points in increments of 5% between a 5% to 50% reduction in PANSS scores from baseline to week 1 or 2 will be calculated. To seek the optimal cut-off point, both the accuracy, defined as $(\text{True Positive} + \text{True Negative}) / \text{Total N}$, and area under the curve (AUC) of receiver operating characteristic (ROC) will be calculated.

Available case analysis will be performed. Statistical analyses will be performed using SAS (SAS Institute Inc., Cary, North Carolina). A p-value of <0.05 is considered to indicate statistical significance (two-tailed).

Project Timeline:

The anticipated project start date is the 1st of July, and analysis completion date will be the 31st of August. A manuscript will be drafted by the 31st of October, and it will be submitted for publication by the 31st of December. Results will be reported back to the YODA Project by the 30th of April.

Dissemination Plan:

The manuscript will be submitted to academic journals whose target audiences include psychiatrists, pharmacologists, and general practitioners such as American Journal of Psychiatry, British Journal of Psychiatry, and Journal of Clinical Psychiatry.

Bibliography:

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