Principal Investigator

First Name: Hiroyuki
Last Name: Uchida
Degree: M.D., Ph.D.
Primary Affiliation: Keio University School of Medicine, Department of Neuropsychiatry
E-mail: hiroyuki.uchida.hu@gmail.com
Phone number: 81.3.5363.3829
Address: 35 Shinanomachi, Shinjuku-ku

City: Tokyo
State or Province: Tokyo
Zip or Postal Code: 160-8582
Country: Japan

2017-1701

General Information

Key Personnel (in addition to PI): **First Name:** Wolfgang
Last name: Fleischhacker
Degree: M.D.
Primary Affiliation: Department of Psychiatry and Psychotherapy, Medical University Innsbruck

First Name: Kaoruhiko
Last name: Kubo
Degree: M.D.
Primary Affiliation: Department of Neuropsychiatry, Keio University School of Medicine

First Name: Fumiaki
Last name: Kumagai
Degree: M.D.
Primary Affiliation: Department of Neuropsychiatry, Keio University School of Medicine

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
depot.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): NCT00590577 - A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Dose Response Study to Evaluate the Efficacy and Safety of 3 Fixed Doses (25 mg eq., 100 mg eq., and 150 mg eq.) of Paliperidone Palmitate in Subjects With Schizophrenia
NCT00111189 - A Randomized Double-blind Placebo-controlled Parallel Group Study Evaluating Paliperidone Palmitate in the Prevention of Recurrence in Patients With Schizophrenia. Placebo Consists of 20% Intralipid (200 mg/mL) Injectable Emulsion
NCT00210548 - A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Dose-Response Study to Evaluate the Efficacy and Safety of 3 Fixed Doses (50 mg eq., 100 mg eq., and 150 mg eq.) of Paliperidone Palmitate in Subjects With Schizophrenia
NCT00101634 - A Randomized, Double-blind, Placebo-controlled, Parallel-group, Dose-response Study to Evaluate the Efficacy and Safety of 3 Fixed Doses (25 mg eq, 50 mg eq, and 100 mg eq) of Paliperidone Palmitate in Patients With Schizophrenia
NCT00074477 - A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of 50 and 100 Mg-eq of Paliperidone Palmitate in Patients With Schizophrenia
NCT00253136 - Risperidone Depot (Microspheres) vs. Placebo 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

Response to Placebo Treatment and Non-response to Active Drug Treatment in Clinical Trials of Long-Acting Injectable Antipsychotics for Schizophrenia

Narrative Summary:
Poor adherence to study medications in clinical trials obscures interpretation of placebo response. Placebo-controlled trials of long-acting injectable (LAI) antipsychotics that secure a drug delivery to patients provide an ideal dataset to investigate placebo effects. On the other hand, despite the assured drug delivery, lack of adequate improvement with LAI antipsychotics is often observed. We will characterize subjects with schizophrenia who showed response with placebo injection and those who failed to show response despite LAI treatment. These results will be expected to provide critical insights in the design of future clinical trials and utilized for individually tailored treatment.

Scientific Abstract:
Background: Poor adherence to study medications in clinical trials obscures interpretation of placebo response. Placebo-controlled trials of long-acting injectable (LAI) antipsychotics provide an ideal dataset to investigate placebo effects. On the other hand, despite the assured drug delivery, lack of adequate improvement with LAI antipsychotics is often observed.
Objective: Objectives are to examine demographic and clinical characteristics associated with placebo response or occurrence of side effects in patients with schizophrenia receiving placebo injection and to compare blood drug concentrations between responders and non-responders.
Study Design: A post-hoc analysis of placebo-controlled double-blind trial data.
Participants: Data from participants in the following studies will be used: NCT00101634, NCT00111189, NCT00210548, NCT00253136, NCT00590577, and NCT00074477.
Main Outcome Measures: Positive and Negative Syndrome Scale scores.
Statistical Analysis: First, placebo responders will be categorized into subtypes according to their symptom trajectories. Second, demographic and clinical characteristics of subjects who showed response or side effects with placebo treatment will be characterized. Third, blood concentrations of risperidone/palipridone will be compared between responders and non-responders. Finally, a threshold of blood risperidone/pariperidone concentration below which a chance of response significantly increases will be explored.

Brief Project Background and Statement of Project Significance:
Mechanisms underlying placebo response are multifactorial and complex; psychological, methodological, and administrative factors are expected to be involved in this phenomenon. Among them, poor adherence to study medications in clinical trials obscures interpretation of placebo response. In this respect, long-acting injectable (LAI) antipsychotics provide a reliable drug delivery to patients whose adherence with oral medication is suboptimal

(McEvoy, 2006; Patel et al., 2009). Therefore, placebo-controlled double-blind trials of LAI antipsychotics are expected to provide an ideal dataset to shed further light on placebo effects and placebo-active drug differentials. 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 in previous clinical trials for schizophrenia (Alphs et al., 2012). It should be noted that these findings are based on the results of clinical trials of oral antipsychotic drugs; the nature and degree of placebo effects may differ among drug formulations. Analysis of clinical trial data of patients with schizophrenia who showed response with placebo injection will allow us to explore demographic and clinical characteristics associated with placebo effects in this population.
On the other hand, despite the assured drug delivery, lack of adequate improvement with LAI antipsychotics is often observed (Hough et al., 2010; Kramer et al., 2010). As such, characterization of LAI nonresponsive patients, including demographic and clinical characteristics and pharmacokinetic profile, will improve our understanding of treatment resistance to a continuous dopamine blockade in schizophrenia. Especially if there is unique pharmacokinetic profile in such difficult-to-treat patients, the results will be utilized to provide individually tailored better treatment for them (e.g. further dose titration).
We therefore propose a post-hoc analysis of placebo-controlled double-blind trial data of LAI antipsychotics in order to provide evidence to characterize subjects with schizophrenia who showed clinical response with placebo injection and those who failed to show response despite LAI paliperidone/risperidone treatment. Associations between blood concentrations of risperidone/paliperidone and clinical effects will also be explored.
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, and to be utilized for individually tailored treatment for such difficult-to-treat patients.

Specific Aims of the Project:
The aims of this analysis are five-fold: (1) to compare symptom trajectories between placebo and active drug (i.e. LAI risperidone/paliperidone) responders; (2) to identify demographic and clinical characteristics associated with placebo response or occurrence of side effects in patients with schizophrenia who were receiving placebo injection; (3) to examine whether early placebo improvement at week 1 or 2 will be associated with placebo response at the endpoint, in order to guide systematic screening of potential placebo responders; (4) to compare blood concentrations of risperidone/palipridone between responders and non-responders; and (5) to explore a threshold of blood risperidone/pariperidone concentration below which a chance of response significantly increases.

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: NCT00101634, NCT00111189, NCT00210548, NCT00253136, NCT00590577, and NCT00074477.

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; blood risperidone/paliperidone concentrations.

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 their 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 or 2, to predict response at endpoint, 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 (True Positive + True Negative) / Total N, and area under the curve (AUC) of receiver operating characteristic (ROC) will be calculated. Fifth, blood concentrations of risperidone/palipridone will be compared between subjects who showed response and those who did not. This analysis will also be conducted regarding side effects with their incidence rates of >5%. Finally, a threshold of blood risperidone/pariperidone concentration below which a chance of response significantly increases will be explored, using chi-squared test.
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 31th 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:
Alphs, L., Benedetti, F., Fleischhacker, W.W., Kane, J.M., 2012. Placebo-related effects in clinical trials in schizophrenia: what is driving this phenomenon and what can be done to minimize it? Int J Neuropsychopharmacol 15(7), 1003-1014.
Hough, D., Gopal, S., Vijapurkar, U., Lim, P., Morozova, M., Eerdekens, M., 2010. Paliperidone palmitate maintenance treatment in delaying the time-to-relapse in patients with schizophrenia: a randomized, double-blind, placebo-controlled study. Schizophr Res 116(2-3), 107-117.
Kramer, M., Litman, R., Hough, D., Lane, R., Lim, P., Liu, Y., Eerdekens, M., 2010. Paliperidone palmitate, a potential long-acting treatment for patients with schizophrenia. Results of a randomized, double-blind, placebo-controlled efficacy and safety study. Int J Neuropsychopharmacol 13(5), 635-647.
Marder, S.R., Davis, J.M., Chouinard, G., 1997. The effects of risperidone on the five dimensions of schizophrenia derived by factor analysis: combined results of the North American trials. J Clin Psychiatry 58(12), 538-546.
McEvoy, J.P., 2006. Risks versus benefits of different types of long-acting injectable antipsychotics. The Journal of clinical psychiatry 67 Suppl 5, 15-18.
Patel, M.X., Taylor, M., David, A.S., 2009. Antipsychotic long-acting injections: mind the gap. Br J Psychiatry Suppl 52, S1-4.