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General Information

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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?: Data Holder (Company)

Conflict of Interest

http://yoda.yale.edu/system/files/2018nian_05yue_01ri_jin_yuan_xian_sheng_.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):

1. NCT00249223 - Risperidone Depot (Microspheres) vs. Risperidone Tablets - a Non-inferiority, Efficacy Trial in 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

Dopamine supersensitivity psychosis in randomized controlled studies of long-acting injectable vs. oral agents of the same atypical antipsychotic

Narrative Summary:

Although some non-randomized clinical trials have shown second-generation antipsychotic long-acting injectables (SGA-LAI) to be more efficacious than the same oral agent, this superiority has not been proven in randomized controlled trials (RCTs) involving patients with schizophrenia. This lack of superiority may be related to dopamine supersensitivity psychosis (DSP), although it could also be associated with improved drug adherence in the oral agent. To explore the inconsistency among study designs, we estimate the ratio of patients with DSP among all participants in the six head-to-head RCTs and compare the ratios of patients who dropped out and those who completed the studies.

Scientific Abstract:

Background: It is noted that in RCTs, the LAI group and oral group show similar levels of drug-adherence gains, and thus canceling the advantage of LAIs over oral agents. However, factors other than the adherence level may contribute to these outcomes. Objective: The present research is aimed at RCTs with a head-to-head design comparing an SGA-LAI with the same oral agent, and explores the effects of including patients with DSP on the outcomes of RCTs. If a significant portion of DSP patients dropped out, this would suggest that the completers of the RCTs included more patients with stable clinical condition and less risk of relapse. Study Design: There are six RCTs with such a design: 2 risperidone studies (Chue et al., 2005; Bai et al., 2007); 2 aripiprazole studies (Fleischhacker et al., 2014; Ishigooka et al., 2015); 2 olanzapine studies (Kane et al., 2010; Detke et al., 2014). The relevant data will be cross-sectionally analyzed between drop-out subjects and study-completing subjects for each RCT. Participants: All schizophrenia subjects entering the screening procedure of each RCT.
Main Outcome Measure: The present research will judge whether each subject had any clinical characteristics of DSP at the screening procedure. The determination of DSP is based on antipsychotic dosage, number of hospital admissions and tardive dyskinesia (TD). Statistical Analysis: The ratios of patients with DSP among all subjects who dropped out following the screening and among all completers of the study were determined. The difference between them is examined by a chi-square-test.

Brief Project Background and Statement of Project Significance:

Both first-generation antipsychotics (FGA) LAIs and SGA-LAIs are introduced to avoid relapse for patients with poor adherence to medication through secure drug delivery and to improve psychotic symptoms and extrapyramidal symptoms (EPS) through stabilized pharmacokinetics. Several meta-analyses have strongly supported this effect of LAIs (Leuchit et al., 2011; Kishimoto et al., 2013; Zhao et al., 2016).
Ostuzzi et al. (2016) recently conducted a meta-analysis that measured the continuous ratio, derived from a total of 18 trials that compared between FGA/SGA-LAI and the same oral agent. Most antipsychotics such as risperidone, olanzapine, zuclopenthixol, fluphenazine and haloperidol failed to show superiority at a continuous ratio of each LAI to the corresponding oral agent. Aripiprazole was the only agent to marginally show the superiority of AOM. The authors concluded that LAIs were not necessarily advantageous compared to oral agents.
The most convincing reason for the lack of difference between the two forms is that under the structural trial settings, the adherence levels increased particularly in the patients assigned to the oral agent, thus diluting the superiority of LAIs that is observed in real-world applications. However, it is difficult to resolve this issue, since the RCTs contained several other problems, i.e., study subjects with comorbid disease or variations in the severity of psychopathology, and variations in the study design such as follow-up duration or dose setting. In this context, non-RCTs close to clinical practice may reflect true outcome that LAIs are advantageous to oral agents.
Patients with long-term exposure to antipsychotics, in particular under high-dose treatment, acquire hypersensitivity of dopamine D2 receptors (DRD2) in their brains, which have been demonstrated in animal models. Such patients often clinically present with episodes of relapse and/or TD, all of which were referred to as neuroleptic-induced supersensitivity psychosis in the 1970s. For such patients under treatment at a dose over the standard dose, i.e., possibly developing DSP, treatment with LAI could be useful; this approach provides a continuous blockade of DRD2 and stabilization of the blood concentrations of the agent. These outcomes could in turn reduce the amount of oral agents and the EPS and further could lessen the DRD2 hypersensitivity, all of which might contribute to the amelioration of DSP. However, such patients have a tendency toward psychotic relapse and vulnerability to stress, and therefore they may not be ideal targets in clinical trials.
Based on these findings, LAIs could be effective for patients with DSP. If an RCT is aimed mainly at patients with DSP, it would prove the superiority of LAI to oral agents. In other words, it is possible that, in the RCTs showing no difference in efficacy between the two forms, no patients with DSP participated in the study, or that they were not

included in the final analysis due to having dropped out during the study phase, since patients with DSP are vulnerable to dose-adjustment or to the switching of the agent as often occurs in the initial stage of RCTs.

Specific Aims of the Project:

The present research project investigates six RCTs with a head-to-head design involving SGA-LAI vs. the same oral agent, and will explore the ratio of patients developing DSP among participants who drop out, i.e., during both the pre-randomized phase following screening (the run-in period) and the subsequent randomized study phase. If a significant portion of the drop-out subjects are DSP patients, implying that more patients with DSP, who would be expected to be effectively treated with LAIs, did not complete the trials, participants group included in the final analysis could affect the trails' results.

What is the purpose of the analysis being proposed? Please select all that apply.
New research question to examine treatment effectiveness on secondary endpoints and/or within subgroup populationsNew research question to examine treatment safetyParticipant-level data meta-analysisParticipant-level data meta-analysis pooling data from YODA Project with other additional data sourcesResearch on clinical trial methodsResearch on clinical prediction or risk prediction

Research Methods

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

There are 6 RCTs that meet the requirements of our research proposal as follows: two RCTs involving RLAI vs. oral risperidone ((1) Bai et al. and (2) Chue et al.); two RCTs with AOM vs. oral aripiprazole ((3) Fleishhacker et al. and (4) Ishigooka et al.); two RCTs with olanzapine LAI vs. oral olanzapine ((5) Kane et al. and (6) Detke et al.). There has been no RCT comparing PP and oral palipridone. Since the two studies with aripiprazole ((3) and (4)) were conducted and funded by Otsuka Pharmaceutical, we will request the relevant data from them. The studies with olanzapine ((5) and (6)) were conducted and funded by Eli Lilly, and we will apply the present plan to Clinical Study Data Request.com to provide the relevant data from Eli Lilly. The data management of the first risperidone study by Dr. Bai et al. (1) were responsible for the authors themselves. Thus, the study for which we will request data that were presented to the YODA are only one RCT of risperidone by Chue et al. (2).
All of the subjects participating in the two studies (i.e., receiving the screening procedure) are included in our research project.

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

The main outcome measure is the ratio of patients with possible DSP among all patients who dropped out from the screening to the end of the study phase. This ratio is calculated with the LAI group and oral group combined, since we are primarily concerned about drop-out subjects vs. complete subjects, rather than LAI subjects vs. oral subjects, as in the original study [#1]. In addition, we plan to compare the ratio of the number of DSP patients to all completers between the LAI group and the oral group [#2].

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

The present research uses the following surrogate markers of possible DSP as main predictors: chlorpromazine-equivalent dosage of antipsychotics at the screening procedure ? 800mg/day, or number of hospital admissions ? 5, or presence of TD. If a given subject meets at least one of these three criteria, he/she is judged to be of the DSP type. These criteria are based on previous studies by our team (Suzuki et al., 2015; Yamanaka et al., 2016).

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

Psychopathological measures (Positive and Negative Syndrome Scale or Brief Psychiatric Rating Scale), EPS measures (Extrapyramidal Symptoms Rating Scale, Abnormal Involuntary Movement Scale, Barnes Akathisia Scale, Simpson-Angus Scale), timing of drop-out for patients who dropped out.

Statistical Analysis Plan:

We will use SAS as a data sharing platform if the YODA approves our project plan and provides pooled patient-

level data of the relevant trial to us.
We will show a plan for a statistical procedure using an example of an RCT (Chue et al., 2005). In this study, a total of 779 patients underwent the screening process and 157 of these patients (=o) dropped out during the run-in period prior to the randomization. In the randomization procedure, 319 patients were assigned to the RLAI group, and 321 patients were assigned to the oral group. A total of 256 patients (=a) in the LAI group and 271 patients (=b) in the oral group completed the randomized study phase of 12 weeks, while 63 patients in the LAI group (=c) and 50 patients in the oral group (=d) dropped out at any time during this phase for any reason. For each subject belonging to any of the five subgroups (o, a, b, c and d), his/her information regarding DSP (drug dosage, the number of hospital admissions and TD score at the screening) were collected, and it was judged whether the subject was or was not in a DSP state. In this way, we hypothesized that more patients with DSP were included among the drop-out subjects than among those who completed the study: i.e., (o'+c'+d')/(o+c+d)>(a'+b')/(a+b) (the variables with the prime mark represent those with DSP), which can be determined by a chi-square test (this comparison corresponds to #1). As an additional analysis, we will examine whether more DSP subjects in the LAI group than in the oral group could have completed the study: i.e., a'/a > b'/b (this comparison corresponds to #2).

Project Timeline:

?Starting date: April, 2018
?Analysis completion date: December, 2018
?Drafting manuscript date: March, 2019
?First submission date: May, 2019
?Date of reporting back to the YODA: March, 2020

Dissemination Plan:

We plan to submit to an international academic journal which is relevant to the field of clinical psychopharmacology or schizophrenia, such as the Journal of Clinical Psychiatry, Schizophrenia Bulletin, or Schizophrenia Research.

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