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General Information

Key Personnel (in addition to PI):  
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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?: Internet Search

Conflict of Interest

https://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_2019dt_0.pdf  
https://yoda.yale.edu/system/files/yoda_coi_robmcc.pdf  
https://yoda.yale.edu/system/files/in_coi_nelft_21092021.pdf  
https://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_2019_sj_0.pdf

Certification

https://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_2019dt_0.pdf  
https://yoda.yale.edu/system/files/yoda_coi_robmcc.pdf  
https://yoda.yale.edu/system/files/in_coi_nelft_21092021.pdf  
https://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_2019_sj_0.pdf
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

2. NCT00650793 - R076477-SCH-703 - A Randomized, DB, PC and AC, Parallel Group, Dose-Response Study to Evaluate the Efficacy and Safety of 3 Fixed Dosages of Extended Release OROS Paliperidone (6, 9, 12 mg/Day) and Olanzapine (10 mg/Day), With Open-Label Extension, in the Treatment of Subjects With Schizophrenia - Open Label Phase
3. NCT00111189 - R092670PSY3001 - 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
4. NCT00752427 - R076477-SCH-702 - 24 week extension of 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 With Schizophrenia
5. NCT0078039 - R076477-SCH-303 - Trial Evaluating Three Fixed Dosages of Paliperidone Extended-Release (ER) Tablets and Olanzapine in the Treatment of Patients With Schizophrenia
6. NCT00085748 - R076477-SCH-302 - 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 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

The effects of antipsychotic discontinuation and reinstatement

Narrative Summary:

Discontinuation and associated relapse are often proposed to have long term negative effects. This, however, is based upon naturalistic data and it is not possible to determine whether discontinuation has a causally important long-term effect. In the current study we intend to examine data from trials in which after a period in which subjects are randomised to placebo or active antipsychotic treatment they are subsequently all treated with antipsychotics in an open label fashion. We will examine whether the period of antipsychotic discontinuation has any impact on longer term outcomes during the open label period, we will also examine the effect that rate of discontinuation has on outcomes.

Scientific Abstract:

Background: Discontinuation of antipsychotics in individuals with schizophrenia is associated with a relapse of psychotic symptoms. Discontinuation and associated relapse are often proposed to have long term deleterious effects over and above the acute relapse. This, however, is primarily based upon naturalistic data and it is therefore not possible to determine whether discontinuation has a causal long-term effect.

Objective: To determine the longer term clinical impact of a period of antipsychotic discontinuation. This will be
based on outcomes after participants have had antipsychotic treatment reinstated.

Design: Examine data from trials in which after a period of randomisation to placebo or active antipsychotic treatment, participants are subsequently treated with antipsychotics in an open label fashion. We will examine whether the initial period of antipsychotic discontinuation has an impact on longer term outcomes during the open label period.

Participants: Individuals with schizophrenia who have been randomised to placebo or antipsychotic treatment in a randomised controlled trial and subsequently followed up during open label antipsychotic treatment.

Outcome Measures: Symptom severity measured using the PANSS. Cognitive symptoms measured by the BACS. Motor side effects measured by the AIMS. Akathisia measured by the Barnes Akathisia Scale. Metabolic side effects indexed by weight and measures of blood sugar and lipids.

Statistical Analysis: The above outcome measures will act as dependent variables, while randomisation group will act as the primary predictor variable. A mixed effect model will be constructed with randomisation group as a fixed effect, and participant and time point as random effects. Analyses will consider if and when outcome variables for the two randomisation groups overlap.

**Brief Project Background and Statement of Project Significance:**

Discontinuation of antipsychotics in individuals with schizophrenia is associated with a relapse of psychotic symptoms. Discontinuation and associated relapse are often proposed to have long term deleterious effects over and above the acute relapse. This, however, is based upon naturalistic data and it is therefore not possible to determine whether discontinuation has a causal long-term effect. There are very few randomised controlled trials that have examined this issue and the evidence from these has been conflicting with one suggesting that antipsychotic discontinuation may have some long-term benefits (1). In the current study we intend to examine data from trials in which following a period in which individuals are randomised to placebo or active antipsychotic treatment, they are subsequently treated with antipsychotics in an open label fashion. We will examine whether the period of antipsychotic discontinuation has any impact on longer term outcomes during the open label period.

**Specific Aims of the Project:**

To determine the clinical impact of a period of antipsychotic discontinuation following antipsychotic reinstatement

**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 populations
- Confirm or validate previously conducted research on treatment effectiveness

**Research Methods**

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

Data sources will be randomised controlled trials of antipsychotics in the treatment of schizophrenia. All studies in which subjects enter an open label period of follow up following a period of randomisation to placebo vs active treatment will be included.

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

Outcome measures will include the following:
- Positive and Negative Syndrome Scale: Total score and subscales (positive, negative, general)
- Barnes Akathisia Rating Scale
- Brief Assessment of Cognition in Schizophrenia
- Abnormal Involuntary Movement Scale
- Simpson Angus Scale
- Schizophrenia Quality of Life Scale
- Clinical Global Impression
Personal and Social Performance Scale
Laboratory markers of metabolic side effects
Weight

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

The main predictor variable is the group to which the participant is randomised during the double blind period of the trial.

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

Demographic variables including age and gender, and drug half life will be examined to see if any associations differ across these variables.

Statistical Analysis Plan:

The above outcome measures will act as dependent variables, while randomisation group will act as the primary predictor variable. A linear mixed model will be constructed with randomisation group as a fixed effect, and participant and time point as random effects. Analyses will consider if and when outcome variables for the two randomisation groups overlap.

Software Used:
R

Project Timeline:

3 months – data cleaning
2 months - data analysis
4 months- manuscript preparation

Dissemination Plan:

Findings will be disseminated via publication in clinical journals (e.g. JAMA Psychiatry, Lancet Psychiatry) and presentation at scientific conferences (e.g. Schizophrenia International Research Society)

Bibliography: