Principal Investigator

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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_2019_rm.pdf
https://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_2019dt.pdf
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/jn_coi_nelft_21092021.pdf

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https://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_2019_sj_0.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

1. NCT00086320 - R076477-SCH-301 - A Randomized, Double-blind, Placebo-controlled, Parallel-group Study With an Open-label Extension Evaluating Paliperidone Extended Release Tablets in the Prevention of Recurrence in Subjects With Schizophrenia
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. NCT00216476 - RISSCH3001 - CONSTATRE: Risperdal® Consta® Trial of Relapse Prevention and Effectiveness
5. 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
6. NCT00078039 - R076477-SCH-303 - Trial Evaluating Three Fixed Dosages of Paliperidone Extended-Release (ER) Tablets and Olanzapine in the Treatment of Patients With Schizophrenia
7. 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
8. NCT01529515 - R092670PSY3012 - A Randomized, Multicenter, Double-Blind, Relapse Prevention Study of Paliperidone Palmitate 3 Month Formulation for the Treatment of Subjects With Schizophrenia
9. NCT01193153 - R092670SCA3004 - A Randomized, Double-Blind, Placebo-Controlled, Parellel-Group Study of Paliperidone Palmitate Evaluating Time to Relapse in Subjects With Schizoaffective Disorder
10. NCT01662310 - R076477-SCH-3041 - Paliperidone Extended Release Tablets for the Prevention of Relapse in Subjects With Schizophrenia: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study
11. NCT00645307 - R076477-SCH-701 - A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study With an Open-Label Extension Evaluating Extended Release OROS® Paliperidone in the Prevention of Recurrence in Subjects With Schizophrenia - Open Label Phase

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 and subsequently all treated with antipsychotics in an open label fashion. We will examine whether relapse varies according to rate of antipsychotic discontinuation the

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effect that periods of discontinuation have on long term outcome

Scientific Abstract:

Background: Discontinuation of antipsychotics in individuals with schizophrenia is associated with a relapse of psychotic symptoms. It is not clear whether the increased risk of relapse following antipsychotic discontinuation is predominantly associated with an absolute fall in receptor occupancy, or alternatively if the rate of reduction in receptor occupancy plays a significant role. In addition 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 if rate of antipsychotic discontinuation affects risk of relapse and 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 stablisation patients are randomised to placebo or active antipsychotic treatment. 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 following a period of stable treatment in a randomised controlled trial

Outcome Measures: Relapse according to original study criteria. 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:
We will determine if rate of discontinuation is associated with risk of relapse using cox proportional hazard models. For analyses regarding long term effects of discontinuation 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. Determining whether rate of withdrawal affects risk of relapse has important implications for how medication discontinuation should be approached clinically.

In addition 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 how rates of antipsychotic discontinuation affect relapse risk and 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 have a period of stable treatment followed following a period of randomisation to placebo vs active treatment will be included.

Primary and Secondary Outcome Measure(s) and how they will be categorized/defined for your study:

Outcome measures will include the following:
Relapse
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:

For examining long term effects of discontinuation 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:

For analyses focusing on initial relapse hazard ratios will be calculated using cox proportional hazards models to assess the influence of formulation (oral, 1-monthly, and 3-monthly injection). The change in hazard ratio over time will be estimated, and the effect of time varying covariates calculated including absolute receptor occupancy, rate of occupancy reduction, and multiple binary occupancy thresholds.

For analyses of long term effects 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 Reserach Society)

Bibliography:

1. Wunderink L, Nieboer RM, Wiersma D, Sytema S, Nienhuis FJ (2013): Recovery in Remitted First-Episode Psychosis at 7 Years of Follow-up of an Early Dose Reduction/Discontinuation or Maintenance Treatment Strategy: Long-term Follow-up of a 2-Year Randomized Clinical Trial. JAMA Psychiatry. 1–8.

Supplementary Material:

https://yoda.yale.edu/sites/default/files/amendment.docx

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