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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?: Colleague

Conflict of Interest

https://yoda.yale.edu/system/files/conflict_of.pdf
https://yoda.yale.edu/system/files/sv_6m4tghhxg7w7uxe-r_2dtrlqt1yv9qtsr.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. 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

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

Research Proposal

Project Title

Long term risk for relapse in patients suffering from schizophrenia randomized to oral placebo - A historical prospective study

Narrative Summary:

This study will assess relapse rates in schizophrenia patients who are enrolled in maintenance trials which compare antipsychotic drugs to placebo. It is hypothesized that patients with moderate to severe negative symptoms and low scores on PANSS items measuring agitation/cooperativeness have reduced risk to exacerbate when randomized to placebo compared to the rest of the patients randomized to placebo.

Scientific Abstract:

Background
Most schizophrenia patients are prescribed antipsychotics to maintain remission of positive symptoms, hence, to reduce the risk of relapse. Depending on the specific study, relapse rates of patients randomized to placebo varies between 30% and 70% over 9-12 months. To assess whether patient's risk for relapse differ by clinical characteristics, we intend to extract data from two long-term oral maintenance trials and assess relapse rate and clinical characteristics of patients randomized to placebo. Our hypothesis is that schizophrenia patients with moderate to severe negative symptoms and low scores on items related to agitation/cooperation, will exhibit lower risk for relapse compared to the rest of the patients assigned to placebo.
Objective
Assessing risk of relapse among schizophrenia patients receiving placebo, and determine clinical characteristics predicting relapse versus non-relapse .
Study Design
Historical prospective study.
Participants
Schizophrenia patients who participated in maintenance trials comparing oral antipsychotic drug to placebo.
Main Outcome Measure
Relapse as defined by the original studies.
Statistical Analysis
After defining the independent variables using descriptive statistics, patients receiving placebo will be divided into 2 groups according to their meeting the criteria of: DSM-5 schizophrenia, stable positive and negative symptoms as defined by the study, sum of negative symptoms prior to randomization: score of > 20 on the PANSS negative symptoms subscale (i.e., N-1 , N-2 , N-3 , N-4 , N-5 , N-6 , N-7) and ,scores < 4 on PANSS items related to cooperativeness/agitation (i.e., P4 , P6 , P7 , G8 and G14).
the cumulative distribution function of time to relapse will be estimated using the Kaplan-Meier method and a 2-sided log-rank test will assess differences between characteristics. Hazards ratio and confidence interval will then be estimated using a Cox proportional hazards model. This analysis will be identically performed on both placebo and antipsychotic drugs group.

Brief Project Background and Statement of Project Significance:

A substantial percentage of schizophrenia patients appear to suffer from chronic negative symptoms (Millan et al., 2014). Most patients are prescribed antipsychotics also after a remission of positive symptoms in order to reduce the risk of relapse.
Two clinical studies testing the efficacy of a novel drug that has no antidopaminergic properties in patients with moderate/high negative symptoms, stable positive symptoms and low scores on items related to

cooperativeness/agitation reported a rate of psychotic exacerbation over 9-12 months <15% (Data on file). This is a very low rate of relapse compared to the relapse rate generally reported on antipsychotics or on placebo (Leucht et al 2012). It is possible that the experimental drug reduces risk for relapse. On the other hand, it is possible that the specific clinical characteristics of the patients who were selected for these studies are those whose risk for relapse are very low. This possible explanation will be addressed and assessed in the proposed study.
Using the YODA platform, we intend to extract data from two long term oral maintenance trials and assess schizophrenia patients who were randomized to placebo and to active antipsychotic drug. Within the antipsychotic treated patients and the placebo treated patients the comparison will be conducted between these patients who at baseline meet criterial for high negative symptoms scores + low agitation/uncooperativeness and the rest of the patients. Baseline will be considered the last PANSS assessment before patients were assigned to either continue of antipsychotics or be withdrawn from antipsychotics and continue on placebo.

Specific Aims of the Project:

The aim of the project is to investigate if particular characteristics of schizophrenia patients lower the risk for psychotic exacerbation on placebo or on antipsychotic drugs.

What is the purpose of the analysis being proposed? Please select all that apply.
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:

We will include all schizophrenia patients who participated in maintenance trials comparing oral antipsychotic drug to placebo who successfully ended the stabilization phase and were randomized to continue on antipsychotic drug or on placebo. We will then select the patients who at the last assessment before randomization met the following criteria:
• Stable positive and negative symptoms as defined by the study
• Sum of negative symptoms prior to randomization: score of > 20 on the PANSS i.e., N-1 , N-2 , N-3 , N-4 , N-5 , N-6 , N-7)
• Scores < 4 on PANSS items related to cooperativeness/agitation (i.e., P4, P6 , P7 , G8 s, and G14).

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

Relapse rate as defined by the original studies.

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

Patients will be split into two groups. Those randomized to antipsychotic drug treatment and those randomized to placebo. Within each group, patients will then be split further into two characteristics groups. those who meet the above criterial and those who do not.

Statistical Analysis Plan:

To define our independent variables as mentioned above, we will first detect both study and control groups using descriptive statistics. Using descriptive statistics, we will then identify those patients who meet the above criterial and those who do not. To test our main hypothesis, we will then conduct, using the Kaplan-Meier method, an estimation of the cumulative distribution function of time to relapse, comparing high risk to low risk patients. Characteristics will then be compared using a 2-sided log-rank test. To estimate the hazards ratio and its corresponding 95% confidence interval, a Cox proportional hazards model with characteristics as its covariate. Lastly, we intend as a secondary aim to conduct identical analysis on the group randomized to antipsychotic drugs.
Software Used:
RStudio
Project Timeline:

• Anticipated study start date: the analysis will commence as soon as the data becomes available,
• Analysis completion date: one month after availability of data.

• date manuscript drafted and first submitted for publication and date results reported back to the YODA Project: We anticipate submitting a manuscript to publication three month after availability of the data

Dissemination Plan:

Target audiences include Researchers of schizophrenia and practicing psychiatrists. Manuscript will be potentially suitable for submission to the American Journal of Psychiatry

Bibliography:

Bobes, J., Arango, C., Garcia-Garcia, M., & Rejas, J. (2009). Prevalence of negative symptoms in outpatients with schizophrenia spectrum disorders treated with antipsychotics in routine clinical practice: findings from the CLAMORS study. The Journal of clinical psychiatry, 70(3), 0-0.
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Supplementary Material:

https://yoda.yale.edu/sites/default/files/ajp_davidson_17._7.25.17.pdf