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General Information

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SCOPUS ID:

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/20190111_yoda_project_coi_form_for_data_requestors_2018_oh.pdf  
https://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_2018_2.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. NCT00334126 - R076477SCH3015 - A Randomized, Double-blind, Placebo-controlled, Parallel Group Study to Evaluate the Efficacy and Safety of Paliperidone ER Compared to Quetiapine in Subjects With an Acute Exacerbation of Schizophrenia  
3. NCT00590577 - R092670PSY3007 - 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  
4. NCT00210548 - R092670PSY3003 - 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
What type of data are you looking for?: Individual Participant-Level Data, which includes Full CSR and all supporting documentation

Research Proposal

Project Title

Variability in antipsychotic response

Narrative Summary:

There is a variability in antipsychotic response across individuals with schizophrenia and it has been suggested that this may be due to different responsive and non-responsive subtypes. We intend to examine the variability of antipsychotic response in order to investigate whether there is a greater heterogeneity of response for antipsychotics compared to placebo. We will also look at individual symptoms to see if certain symptoms show greater variability than others.

Scientific Abstract:

Background: Antipsychotics are more effective than placebo in reducing symptoms in schizophrenia. However, response to treatment appears to vary, and as such it has been proposed that different subtypes of schizophrenia...
exist, defined by treatment-response. This has not been formally examined using meta-analysis. If subtypes exist one would expect greater variability of response to active treatment compared to placebo.

Objective: We intend to investigate the variability of response to antipsychotics and placebo across all reported clinical trials. In a subset of trials where individual patient level data is available will investigate variability of response at the level of individual symptoms.

Study Design: Randomised controlled trials comparing placebo and antipsychotics in acute treatment of schizophrenia listed in PubMed, EMBASE and PsycINFO will be examined. Mean change and variance of change in symptoms will be extracted from each study, alongside publication year, participant age and gender, baseline symptom severity, antipsychotic dose, and use of placebo lead-in.

Participants: Individuals with schizophrenia

Outcomes: Relative variability of symptomatic improvement in antipsychotic-treated compared to placebo-treated individuals will be quantified using coefficient of variation ratio (CVR).

Statistical analysis: A random effects meta-analysis will be undertaken. Significance of potential moderating factors will be tested via meta-regression and sensitivity analyses. Where individual symptom level data is available analyses will be performed at this level.

Brief Project Background and Statement of Project Significance:

Schizophrenia is a chronic psychotic illness, and a leading cause of global disease burden(1). The main treatments are antipsychotic drugs, which are all dopamine receptor blockers(2, 3). Meta-analyses of double-blind randomised placebo controlled trials (RCT) have found a significantly greater mean improvement in symptoms in patients treated with antipsychotics compared to those treated with placebo, with medium to large standardised mean differences (SMD)(2).

Response to antipsychotic treatment, is however heterogeneous, and whilst some patients show marked improvements, others appear to show little change with first-line antipsychotic treatment(4, 5). Indeed, in around one third of patients, their illness shows a clinically insignificant response to first-line antipsychotic drugs(6, 7), which has been termed treatment resistant schizophrenia(8). This may be explained by the hypothesis that there are at least two biological subtypes of schizophrenia, one characterised by striatal hyperdopaminergia and a good response to antipsychotics, and a second subtype with a different underlying neurobiological basis that does not respond to antipsychotic treatment(9, 10). A key prediction of this hypothesis is that antipsychotics will have significant benefit only in some patients, who will show improvement beyond non-specific effects seen with a placebo, whereas, in the subtype of non-responsive schizophrenia, drug treatment is non-specific and any symptom change will be similar to that seen in the placebo group. This will lead to greater change in symptoms in the antipsychotic treatment group which includes both the specific effects of treatment and non-specific effects, whereas in the placebo group, which assesses non-specific effects alone, symptom change will be more uniform. Thus, in the context of a RCT, the subtype hypothesis predicts greater variability in response in the antipsychotic treatment group compared to the placebo group.

Determining if there is greater variability in symptom change with active treatment is important as it implies some patients are receiving ineffective treatment, and the need for personalised medicine. The variation in response seen in clinical practice is often taken as support for the subtype hypothesis, however it is important to note that much of this variation can result from within individual variability, in which case the appearance of subtypes may be illusory(11). This is an issue across medicine, but to our knowledge this has not previously been addressed in a systematic synthesis of RCT results.

Specific Aims of the Project:

Advances in meta-analytic techniques mean that in addition to calculating summary SMDs it is now possible to integrate information from multiple studies in order to quantify the magnitude of difference in variability between two treatments(12–14). We intend to apply this approach to test the prediction that there is greater variability in treatment-response in patients receiving antipsychotics compared to those receiving placebo in all suitable RCTS comparing these interventions in schizophrenia. Where data is reported we will look at whether this varies between positive and negative symptom domains. Where individual patient level data is available we will use this to investigate the same questions at an individual symptom level.

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
Summary-level data meta-analysis pooling data from YODA Project with other additional data sources
Participant-level data meta-analysis pooling data from YODA Project with other additional data sources

Research Methods

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

Inclusion criteria consist of: (1) randomised, double blind, placebo-controlled trials, (2) Monotherapy with antipsychotic medications licensed for the treatment of schizophrenia, (3) adults aged 18-65 with an acute exacerbation of schizophrenia or a related disorder (schizoaffective, schizophreniform and delusional disorders). Exclusion criteria include (1) grey literature (with the exception of clinical study reports), (2) relapse prevention studies with no acute treatment phase.

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

The main outcome measure will be the coefficient of variation ratio (CVR). This is a measure of variability in the active treatment arm compared to the variability in the placebo arm, that takes into account the difference in mean change between groups. Please see the statistical analysis plan for a more detailed description of this measure.

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

The primary independent variable is placebo vs antipsychotic treatment.

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

Other variables of interest include year of study, baseline symptom severity, study duration, antipsychotic, antipsychotic dose in olanzapine equivalents(15, 16), participant age, and participant gender. Also of interest is whether studies used a placebo lead-in period to exclude placebo responders, and whether studies attempted to enrich for responders by excluding patients previously found to be non-responsive to antipsychotic treatment.

Statistical Analysis Plan:

The relative variability between an antipsychotic treated group and a placebo treated group of patients can be quantified using the log variability ratio (VR) (See equation 1 in attached file).

In biological systems variance often scales with the mean(17). This can be adjusted for using the log coefficient of variation ratio (CVR) which adjusts the VR for mean differences between groups (see equation 2). The use of CVR to quantify group differences in variability is possible only where data have a true zero point(12). This is not the case for raw change scores which can be positive or negative, and we therefore will convert values of mean change to a ratio scale. A CVR above 1 indicates greater variability in the antipsychotic arm, while a value below 1 indicates greater variability in the placebo arm. We will present CVR as our primary analysis, as otherwise any differences in variability may primarily reflect differences in mean, although the VR results will be presented as a secondary analysis.

All statistical analyses will carried out in the statistical programming language R, primarily using the “metafor” package while custom scripts will be employed for the analysis of individual patient data. For the primary analysis of total symptoms a univariate random effects model will be employed. However, a multivariate meta analytic model will be used to compare CVR individual symptoms because this accounts for the correlation between measures.

Project Timeline:

We intend to start analysis as soon as access is granted to data, analysis will be completed within 6 weeks and manuscript submitted for publication 6 weeks following that.

Dissemination Plan:
The results will be of interest to both clinical and academic psychiatrists. Potential journals include JAMA Psychiatry, Lancet Psychiatry, World Psychiatry

Bibliography:


Supplementary Material:

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