Principal Investigator

First Name: Jose M
Last Name: Rubio
Degree: M.D.
Primary Affiliation: The Zucker Hillside Hospital, Northwell Health
E-mail: lorente01@gmail.com
Phone number: 7184705912
Address: 75-59 263rd st

City: Glen Oaks
State or Province: NY
Zip or Postal Code: 11004
Country: USA
SCOPUS ID: 57193087205

General Information

Key Personnel (in addition to PI):
First Name: Ashkhan
Last name: Davani
Degree: MD
Primary Affiliation: Northwell Health
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?: Other

Conflict of Interest

https://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_2019-1.pdf
https://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_-_ash.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
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. 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

.misc-fixes { display: none; } #admin-region { z-index: 9999999; } #admin-menu { z-index: 99999999; }

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 150 mg eq.) of Paliperidone Palmitate in Subjects With Schizophrenia
5. NCT00101634 - R092670PSY3004 - A Randomized, Double-blind, Placebo-controlled, Parallel-group, Dose-response Study to Evaluate the Efficacy and Safety of 3 Fixed Doses (25 mg eq, 50 mg eq, and 100 mg eq) of Paliperidone Palmitate in Patients With Schizophrenia
6. NCT00397033 - R076477SCA3001 - A Randomized, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy and Safety of Two Dosages of Paliperidone ER in the Treatment of Patients With Schizoaffective Disorder
7. NCT00412373 - R076477SCA3002 - A Randomized, Double-blind, Placebo-controlled, Parallel- Group Study to Evaluate the Efficacy and Safety of Flexible-dose Paliperidone ER in the Treatment of Patients With Schizoaffective Disorder
8. NCT00249132 - RIS-INT-3 - A Canadian multicenter placebo-controlled study of fixed doses of risperidone and haloperidol in the treatment of chronic schizophrenic patients
9. NCT00083668 - R076477-SCH-305 - A Randomized, Double-blind, Placebo- and Active-controlled, Parallel-group, Dose-response Study to Evaluate the Efficacy and Safety of 3 Fixed Dosages of Paliperidone Extended Release (ER) Tablets and Olanzapine, With Open-label Extension, in the Treatment of Patients With Schizophrenia
10. NCT00074477 - R092670-SCH-201 - A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of 50 and 100 Mg-eq of Paliperidone Palmitate in Patients With Schizophrenia
11. NCT00078039 - R076477-SCH-303 - Trial Evaluating Three Fixed Dosages of Paliperidone Extended-Release (ER) Tablets and Olanzapine in the Treatment of Patients With Schizophrenia
12. 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
13. NCT00253136 - RIS-USA-121/CR006055 - Risperidone Depot (Microspheres) vs. Placebo in the Treatment of Subjects With Schizophrenia
14. NCT00524043 - R076477SCH4012 - A Randomized, Double-Blind, Placebo- and Active-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of a Fixed Dosage of 1.5 mg/Day of Paliperidone Extended Release (ER) in the Treatment of Subjects With Schizophrenia
15. NCT01299389 - PALM-JPN-4 - A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Fixed-Dose, Multicenter Study of JNS010 (Paliperidone Palmitate) in 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

Motor side effects and antipsychotic efficacy of antipsychotic drugs: An individual participant meta-analysis

Narrative Summary:

Antipsychotic drugs mitigate psychotic symptoms (i.e., delusions, hallucinations or disorganization), but also may cause motor side effects. It is believed that both phenomena, treatment responsiveness and motor side effects, may be mediated by the effects of antipsychotic drugs in dopaminergic receptors in the striatum. However, to date it is not well known whether there is covariation between these two phenomena. Determining whether treatment response is related to motor side effects may be important to understand the mechanism of action of treatment responsiveness in psychotic disorders.

Scientific Abstract:

Background: Antipsychotic drugs are effective mitigating psychotic symptoms, but also cause motor side effects. Although both phenomena are believed to result from the effects of antipsychotic drugs in striatal dopamine receptors, the relationship between these two phenomena are not understood.

.misc-fixes { display: none; } #admin-region { z-index: 9999999; } #admin-menu { z-index: 99999999; }

Objective: Measure the interaction between change in psychosis and liability to develop motor side effects with antipsychotics.
Study design: We will conduct a systematic search of placebo controlled randomized clinical trials of antipsychotics for the treatment of psychosis in schizophrenia. From those, we will extract data on the change over time of psychotic symptoms in individuals on drug compared to those on placebo, as well as on the development of motor side effects on drug compared to placebo. We will measure the “treatment*time*motor side effects” interaction, to determine whether treatment efficacy changes as a function of liability to develop motor side effects from these drugs.
Participants: Individuals with schizophrenia
Main outcome measure: Psychopathology measurement (i.e., total PANSS or BPRS) and liability to develop parkinsonism (i.e., Simpson scale), akathisia (i.e., Barnes Scale) or tardive dyskinesia (i.e., Abnormal Involuntary Movement Scale).
Statistical analysis: We will conduct a mixed model analysis for repeated measures for each placebo controlled antipsychotic trial, including an interaction term for “time*group*motor side effect liability”. Next, we will pool in a meta-analysis the estimates for such interaction term for each trial included

Brief Project Background and Statement of Project Significance:

Schizophrenia is one of the top 15 causes of disability worldwide (GBD Project Collaborators, 2017). One of the greatest challenges in developing innovative treatments is our limited understanding about its pathophysiology, or the mechanism of action of antipsychotics (Kahn et al., 2015). With the development of clinical neuroscience, the models of pathophysiology and mechanism of action of treatment are becoming increasingly sophisticated (Maia and Frank, 2017). However, these still rely heavily in data collected from non-clinical populations and it is critical to validate them by testing the accuracy of their predictions in clinical populations.
In schizophrenia, it is well established that overall there is aberrant dopaminergic signaling in the striatum (Maia and Frank, 2017). The mitigation of psychotic symptoms by antipsychotic drugs would be theoretically mediated by blunting the phasic dopaminergic response associated with irrelevant stimuli in the associative striatum (Maia and Frank, 2017; McCutcheon et al., 2018). This would also have the unintended consequence of resulting in motor side effects, by affecting the motor division of the striatum. There is converging evidence linking treatment responsiveness to striatal dopamine dysfunction, suggesting that psychotic symptoms in individuals with treatment resistant schizophrenia would be primarily mediated by non-striatal mechanisms (Howes et al., 2012; Jauhar et al., 2018). It has been theorized then that these individuals would be more liable to motor side effects, whereas psychotic symptoms would not be changed by the drug effects in the striatum.
The study of the covariance of antipsychotic and motor effects is an opportunity to empirically validate this theory. Using data from YODA, we found that tardive dyskinesia predicted psychosis relapse, (Rubio et al., 2020), confirming previous similar findings (Lieberman, 1987; Lieberman et al., 1994), although this association was not found for treatment response (Caroff et al., 2011). Parkinsonism has been associated both with treatment response (Yoshida and Takeuchi, 2021) and lack of (Stentebjerg-Olesen et al., 2013), and the results for akathisia are also mixed (Derks et al., 2010; Kane et al., 2010). These mixed results may reflect methodological limitations which need to be overcome in subsequent research.
Our project aims to address this clinical question overcoming three major limitations of the previous literature. First, we plan to obtain large volumes of patient-level data, which will provide sufficient power. Second, most of the previous analyses did not include placebo arms, which is necessary to disentangle antipsychotic effects from other sources of motor signs, which are known to be highly incident in individuals with psychosis even before treatment (Dickson et al., 2012). Finally, most other analyses may have included various sources of bias resulting from lack of randomization, or by running separate statistical tests by group instead of measuring the group interaction in the effects, which is known to lead to inaccurate results (Nieuwenhuis 2011).

Specific Aims of the Project:

Our main study hypothesis makes two assumptions: 1) Antipsychotics are efficacious (i.e,. decrement in symptoms over time is greater for individuals in the antipsychotic condition is greater than in the placebo condition), and 2) Antipsychotics cause motor side effects (i.e,. the incidence of motor side effects in the antipsychotic condition is greater than in the placebo condition). Thus, we aim to test those two assumptions prior to testing the main study hypothesis:
Aim #1: Measure pooled change of psychotic symptoms over time by treatment group (i.e,. treatment response) using a standardized statistical approach across trials. We hypothesize that antipsychotic drugs reduce symptoms over time to a larger extent than placebo.
Aim #2: Measure pooled risk of developing motor side effects with antipsychotic drugs. We anticipate that

.misc-fixes { display: none; } #admin-region { z-index: 9999999; } #admin-menu { z-index: 99999999; }

antipsychotic drugs cause greater degree of motor side effects than placebo.
- Parkinsonism
- Akathisia
- Tardive Dyskinesia

Aim #3: Measure the pooled estimate of the interaction term time * group * liability to motor side effects on psychotic symptoms. We hypothesize that individuals with liability to develop motor side effects (as per below) will have lower treatment response.
- Parkinsonism
- Akathisia
- Tardive Dyskinesia

What is the purpose of the analysis being proposed? Please select all that apply.
Participant-level data meta-analysis
Participant-level data meta-analysis using only data from YODA Project

Research Methods

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

Placebo controlled randomized clinical trials of antipsychotic drugs for acute psychosis

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

Primary: Total psychopathology (total scores of PANSS or BPRS)
Secondary: Psychotic symptoms (Positive symptom score of PANSS or psx subscore of BPRS – conceptual disorganization, grandiosity, hallucinatory behavior, unusual thought content – as in (Robinson et al., 2015)).

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

Liability to experience motor side effects with antipsychotic treatment, defined as presence in at least one study visit of symptoms of moderate severity or worse, as per (Robinson et al., 2015).
Parkinsonism: Moderate symptoms or worse are defined as 2 or more of the Simpson-Angus EPS Scale items gait, rigidity of major joints, tremor, akinesia, and akathisia rated 2, or 1 item rated 3 or higher in any of the study visits
Akathisia: Moderate symptoms or worse defined as the Barnes Akathisia Scale Global score rated 3 or greater in any of the study visits
Tardive dyskinesia: Moderate symptoms or worse defined as the Item 8 (Severity of abnormal movements overall) of the Abnormal Involuntary Movement Scale (AIMS) rated 3 or greater in any of the study visits

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

NA

Statistical Analysis Plan:

We will proceed with a two-step individual participant meta-analysis to analyze the requested data. In a first step, we will conduct a re-analysis of each of the included trials. At this stage, for each trial we will conduct a descriptive analysis of baseline and treatment emergent motor side effects by condition. We will conduct statistical testing to confirm that the randomization was successful and that there were no statistically significant differences in covariates between treatment and placebo group. Trials for which there are differences in baseline motor side effects (Parkinsonism, Akathisia, or Tardive Dyskinesia) will be excluded from the analyses, as we will not be able to confirm that randomization was successful and therefore there is the risk that prognosis might have systematically differed between groups. The next step will be to address Aim #1. To do so, we will first plot the psychopathology scores over time by treatment group, to visualize treatment efficacy. For statistical testing, we will conduct a mixed model regression (R package “lme4”), in which we will measure the “time* treatment” interaction, and derive a Cohen’s d with 95% CIs (R function “lme.dscore” in “lme4”) for the change of psychotic symptoms over time on antipsychotic vs on placebo. Although the efficacy of antipsychotic drugs is well established, this step will confirm our first assumption for Aim#3 in our dataset: that antipsychotic drugs are effective reducing

psychopathology over time. Next, we will proceed to address Aim #2. For this, we will conduct a logistic regression in which the dependent variable will be liability to develop motor side effects (Parkinsonism, Akathisia, and Tardive Dyskinesia) and the independent variable will be treatment group (antipsychotic vs placebo). This will generate odds ratios (ORs) and 95% CIs. Again, although it is well established that antipsychotic drugs cause motor side effects, this will confirm this assumption for Aim#3 in our dataset. Next, we will address Aim #3. Same as in Aim#1, we will first plot symptom severity over time with 95% CIs in: #1) antipsychotic treatment AND no motor side effects, #2) antipsychotic treatment AND motor side effects, #3) placebo treatment AND no motor side effects, and #4) placebo treatment and motor side effects. According to our hypothesis, we anticipate that the magnitude of symptom change will greatest for #1, and lowest for #4. To statistically test these group differences, we will run a mixed model regression in which we will include an interaction term for “time*treatment*motor side effect liability” on psychopathology assessment. After having iterated each one of these steps (i.e., aims 1-3) through each of the included randomized controlled trials, we will proceed to the second stage of the meta-analysis, in which we will pool results across trials. Thus, we will conduct a random effects model meta-analysis (R packages “meta” and “metafor”) of the following outcomes for each one of the included and re-analyzed randomized controlled trials: 1) Cohen’s d of antipsychotic efficacy, 2) Odds Ratios of liability for parkinsonism, 3) Odds Ratios of liability for akathisia, 4) Odds Ratios of liability for Tardive Dyskinesia, 5) Beta estimates of “time*treatment* motor side effects liability” interaction terms. The output of these analyses in the manuscript will be:
1. Baseline and treatment emergent motor side effects
2. Forest plot: Treatment efficacy (pooled Cohen’s d)
3. Forest plot: Motor side effect liability (pooled ORs of developing MSE)
4. Forest plot: Treatment efficacy by liability to develop motor side effects (pooled beta estimates of interaction term).
5. Supplementary materials: Grid with plots for each trial of psychopathology x time for the following groups: #1) treatment AND no motor side effects, #2) treatment AND motor side effects, #3) placebo AND no motor side effects, and #4) placebo and motor side effects
Software Used:
RStudio

Project Timeline:

We anticipate the following milestones:
Start analyses by 3/1/2021
Conclude analyses by 9/1/21
Finalize manuscript by 11/1/21
Have manuscript accepted by 3/1/2022

Dissemination Plan:

We plan to generate a manuscript as a product of the above described analyses. Given the high methodological rigor of the proposed analyses, which overcomes the potential confounders of previous literature, and the significance of the research question addressed by this study, we anticipate that this manuscript will be published in a high tier medical journal, such as Neuropsychopharmacology or Schizophrenia bulletin.

Bibliography:

Caroff, S. N. et al. (2011) ‘Treatment outcomes of patients with tardive dyskinesia and chronic schizophrenia’, The Journal of Clinical Psychiatry, 72(3), pp. 295–303. doi: 10.4088/JCP.09m05793yel.
Derks, E. M. et al. (2010) ‘Antipsychotic drug treatment in first-episode psychosis: should patients be switched to a different antipsychotic drug after 2, 4, or 6 weeks of nonresponse?’, Journal of Clinical Psychopharmacology, 30(2), pp. 176–180. doi: 10.1097/JCP.0b013e3181d2193c.
Dickson, H. et al. (2012) ‘Meta-analyses of cognitive and motor function in youth aged 16 years and younger who subsequently develop schizophrenia’, Psychological Medicine, 42(4), pp. 743–755. doi: 10.1017/S0033291711001693.
Emsley, R., Rabinowitz, J. and Medori, R. (2007) ‘Remission in early psychosis: Rates, predictors, and clinical and functional outcome correlates’, Schizophrenia Research, 89(1–3), pp. 129–139. doi: 10.1016/j.schres.2006.09.013.
Howes, O. D. et al. (2012) ‘The nature of dopamine dysfunction in schizophrenia and what this means for treatment’, Archives of General Psychiatry, 69(8), pp. 776–786. doi: 10.1001/archgenpsychiatry.2012.169.
Howes, O. D. and Kapur, S. (2014) ‘A neurobiological hypothesis for the classification of schizophrenia: type A (hyperdopaminergic) and type B (normodopaminergic)’, The British Journal of Psychiatry: The Journal of Mental Science, 205(1), pp. 1–3. doi: 10.1192/bjp.bp.113.138578.

Jauhar, S. et al. (2018) ‘Determinants of treatment response in first-episode psychosis: an 18F-DOPA PET study’, Molecular Psychiatry. doi: 10.1038/s41380-018-0042-4.
Kahn, R. S. et al. (2015) ‘Schizophrenia’, Nature Reviews. Disease Primers, 1, p. 15067. doi: 10.1038/nrdp.2015.67.
Kane, J. M. et al. (2010) ‘Evaluation of akathisia in patients with schizophrenia, schizoaffective disorder, or bipolar I disorder: a post hoc analysis of pooled data from short- and long-term aripiprazole trials’, Journal of Psychopharmacology, 24(7), pp. 1019–1029. doi: 10.1177/0269881109348157.
Lieberman, J. A. (1987) ‘Prediction of Relapse in Schizophrenia’, Archives of General Psychiatry, 44(7), p. 597. doi: 10.1001/archpsyc.1987.01800190013002.
Lieberman, J. A. et al. (1994) ‘Methylphenidate response, psychopathology and tardive dyskinesia as predictors of relapse in schizophrenia’, Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology, 11(2), pp. 107–118. doi: 10.1038/npp.1994.40.
Maia, T. V. and Frank, M. J. (2017) ‘An Integrative Perspective on the Role of Dopamine in Schizophrenia’, Biological Psychiatry, 81(1), pp. 52–66. doi: 10.1016/j.biopsych.2016.05.021.
McCutcheon, R. et al. (2018) ‘Defining the Locus of Dopaminergic Dysfunction in Schizophrenia: A Meta-analysis and Test of the Mesolimbic Hypothesis’, Schizophrenia Bulletin, 44(6), pp. 1301–1311. doi: 10.1093/schbul/sbx180.
Nieuwenhuis, S., Forstmann, B. U. and Wagenmakers, E.-J. (2011) ‘Erroneous analyses of interactions in neuroscience: a problem of significance’, Nature Neuroscience, 14(9), pp. 1105–1107. doi: 10.1038/nn.2886.
Robinson, D. G. et al. (2015) ‘A Randomized Comparison of Aripiprazole and Risperidone for the Acute Treatment of First-Episode Schizophrenia and Related Disorders: 3-Month Outcomes’, Schizophrenia Bulletin, 41(6), pp. 1227–1236. doi: 10.1093/schbul/sbv125.
Rubio, J. M. et al. (2020) ‘Psychosis relapse during treatment with long-acting injectable antipsychotics in individuals with schizophrenia-spectrum disorders: an individual participant data meta-analysis’, The Lancet Psychiatry, 7(9), pp. 749–761. doi: 10.1016/S2215-0366(20)30264-9.
Stentebjerg-Olesen, M. et al. (2013) ‘Early Nonresponse Determined by the Clinical Global Impressions Scale Predicts Poorer Outcomes in Youth with Schizophrenia Spectrum Disorders Naturalistically Treated with Second-Generation Antipsychotics’, Journal of Child and Adolescent Psychopharmacology, 23(10), pp. 665–675. doi: 10.1089/cap.2013.0007.
Yoshida, K. and Takeuchi, H. (2021) ‘Dose-dependent effects of antipsychotics on efficacy and adverse effects in schizophrenia’, Behavioural Brain Research, p. 113098. doi: 10.1016/j.bbr.2020.113098.

Supplementary Material:

https://yoda.yale.edu/sites/default/files/yoda_project_proposal_-_motor_side_effects_and_ttmt_response_in_schizophrenia.docx