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Requires Data Access? Yes

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

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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. NCT01009047 - R076477PSZ3003 - A Randomized, Multicenter, Double-Blind, Active-Controlled, Flexible-Dose, Parallel-Group Study of the Efficacy and Safety of Prolonged Release Paliperidone for the Treatment of Symptoms of Schizophrenia in Adolescent Subjects, 12 to 17 Years of Age
2. NCT00518323 - R076477PSZ3001 - A Randomized, Multicenter, Double-Blind, Weight-Based, Fixed-Dose, Parallel-Group, Placebo-Controlled Study of the Efficacy and Safety of Extended Release Paliperidone for the Treatment of Schizophrenia in Adolescent Subjects, 12 to 17 Years of Age
3. 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
4. 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
5. 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
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. NCT00077714 - R076477-SCH-304 - A Randomized, Double-blind, Placebo- and Active-controlled, Parallel-group, Dose-response Study to Evaluate the Efficacy and Safety of 2 Fixed Dosages of Paliperidone Extended Release Tablets and Olanzapine, With Open-label Extension, in the Treatment of Patients With Schizophrenia
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. NCT00078039 - R076477-SCH-303 - Trial Evaluating Three Fixed Dosages of Paliperidone Extended-Release (ER) Tablets and Olanzapine in the Treatment of Patients With Schizophrenia
11. 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

12. 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
13. NCT00105326 - R076477-SCH-1010/CR002281 - A Double-blind, Placebo-controlled, Randomized Study Evaluating the Effect of Paliperidone ER Compared With Placebo on Sleep Architecture in Subjects With Schizophrenia
14. NCT03345342 - R092670PSY3015 - A Double-blind, Randomized, Active-controlled, Parallel-group Study of Paliperidone Palmitate 6-Month Formulation
15. NCT00589914 - R092670PSY3006 - A Randomized, Double-Blind, Parallel-Group, Comparative Study of Flexible Doses of Paliperidone Palmitate and Flexible Doses of Risperidone Long-Acting Intramuscular Injection in Subjects With Schizophrenia
16. 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
17. 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
18. 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
19. 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
20. 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
21. NCT01529515 - R092670PSY3012 - A Randomized, Multicenter, Double-Blind, Relapse Prevention Study of Paliperidone Palmitate 3 Month Formulation for the Treatment of Subjects With Schizophrenia
22. NCT01193153 - R092670SCA3004 - A Randomized, Double-Blind, Placebo-Controlled, Parellel-Group Study of Paliperidone Palmitate Evaluating Time to Relapse in Subjects With Schizoaffective Disorder
23. NCT01299389 - PALM-JPN-4 - A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Fixed-Dose, Multicenter Study of JNS010 (Paliperidone Palmitate) in Patients With Schizophrenia
24. NCT01515423 - R092670PSY3011 - A Randomized, Multicenter, Double-Blind, Non-inferiority Study of Paliperidone Palmitate 3 Month and 1 Month Formulations for the Treatment of Subjects With Schizophrenia
25. NCT00249132 - RIS-INT-3 - A Canadian multicenter placebo-controlled study of fixed doses of risperidone and haloperidol in the treatment of chronic schizophrenic patients
26. NCT00088075 - RIS-SCH-302/CR003370 - A Randomized, Double-Blind, Placebo-Controlled Clinical Study of the Efficacy and Safety of Risperidone for the Treatment of Schizophrenia in Adolescents
27. - RIS-USA-72 - The safety and efficacy of risperidone 8 mg qd and 4 mg qd compared to placebo in the treatment of schizophrenia
28. NCT00061802 - RIS-SCP-402 - A Randomized, Double Blind Study to Evaluate the Efficacy and Safety of Two Atypical Antipsychotics vs. Placebo in Patients With an Acute Exacerbation of Either Schizophrenia or Schizoaffective Disorder

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

Research Proposal

Project Title

Understanding treatment effects and symptom dynamics in schizophrenia using network analysis

Narrative Summary:

While antipsychotics can often improve symptoms of schizophrenia, many people still experience difficulties even with treatment. By examining how different symptoms are connected and change over time, we hope to uncover new insights into how treatments drive clinical outcomes. To explore the mechanisms by which specific treatment outcomes occur, we will use symptom network analysis, using data from clinical trials in which schizophrenia patients have been randomly assigned to receive antipsychotic treatment or placebo. Our aim is to better understand the complex relationship between symptom dynamics and treatment outcomes, to improve care for patients with schizophrenia.

Scientific Abstract:

Background: While antipsychotics tend to improve acute symptoms of psychosis, many individuals with schizophrenia-spectrum disorders (SSD) remain symptomatic despite treatment. Treatment effectiveness is typically measured by overall symptom change, leaving the underlying mechanisms unclear. We propose a novel approach using symptom network analysis to elucidate these mechanisms.

Objective: To identify interactions between psychosis symptoms and examine relationships following treatment initiation or discontinuation in individuals with SSD.

Design: We will analyse data from double-blind placebo-controlled trials of antipsychotic medications. Symptom networks will be constructed to explore how treatment initiation and discontinuation impacts symptoms over time. We will also investigate if baseline treatment characteristics can predict treatment response.

Participants: Individuals with SSD who have been randomised to placebo or antipsychotic treatment in a randomised placebo-controlled controlled trial.

Outcome Measures: Symptom severity measured using the PANSS. Other outcome measures will also be utilized depending on availability (e.g., cognition, functional outcome and depression).

Statistical Analysis: PANSS item scores will be used to construct symptom networks examining treatment effects on symptom dynamics over time. Additionally, time-specific symptom networks integrating the treatment condition will explore treatment effects on symptoms at and across timepoints. The impact of sex, illness onset, and their interaction will also be explored.

Brief Project Background and Statement of Project Significance:

Understanding the effectiveness of antipsychotic treatment is crucial for improving outcomes for individuals with schizophrenia-spectrum disorders. Although antipsychotics often effectively improve acute symptoms of psychosis, a significant number of patients remain symptomatic despite treatment.1,2 As clinical trials typically measure treatment effectiveness by focusing on overall symptom change from one timepoint to another, the underlying mechanisms that determine the effectiveness or ineffectiveness of a treatment remain unclear.

Understanding the underlying dynamics of symptom change can elucidate treatment response mechanisms and could thereby enhance our comprehension of why some symptoms improve while others remain unchanged in response to antipsychotic treatment. Similarly, understanding the causal connections between various symptoms can aid in identifying which symptoms might precipitate a relapse upon treatment discontinuation.

An approach to analysing interactions between symptoms over time is network analysis.3--5 This method allows us to understand how symptoms influence each other's development, how changes in one symptom may trigger changes in others, and how these dynamic interactions might explain clinical outcomes.

Specific Aims of the Project:

To identify the interconnectedness among different symptoms of psychosis and examine their relationships following treatment initiation or discontinuation. We intend to examine data from double-blind placebo-controlled trials in which individuals are randomised to receive placebo or active antipsychotic treatment.

Study Design:

Individual trial analysis

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

Other: Individual trial analysis and analysis of multiple trials together where possible.

Research Methods

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

Data sources will be randomised double-blind placebo controlled trials of antipsychotics in the treatment of schizophrenia-spectrum disorders.

Inclusion criteria:
- Randomised double-blind placebo-controlled trials. Trials with a double- and a single-blind/open label phase are also eligible, but only the double-blind phase will be used
- Trials that compared the use of one or more antipsychotics (active treatment) with placebo
- Trials that included male and female patients of any age, diagnosed with a schizophrenia-spectrum disorder
- Symptom severity measured with the Positive and Negative Syndrome Scale (PANSS)

Exclusion criteria:
- Trials with <2 time points at which symptom severity was measured.
- Trials with both double-blind and singe-blind/open label phases will be excluded if they have <2 timepoints of symptom severity assesssment in the double-blind phase.

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

Our main outcome measure is the Positive and Negative Syndrome Scale (PANSS), of which the individual item scores will be used to construct temporal and contemporaneous symptom networks. Other outcome measures include the Brief Assessment of Cognition in Schizophrenia (composite score and raw scores for each subtest), Schizophrenia Quality of Life Scale, Clinical Global Impression (CGI)
Personal and Social Performance Scale (PSP), Hamilton Depression Rating Scale (HAMD), and Calgary Depression Scale for Schizophrenia (CDSS).

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 sex and illness onset (when available) will be examined to see if any associations differ across these variables.

Statistical Analysis Plan:

The PANSS individual item scores at different timepoints will be used to construct symptom networks. We will construct temporal symptom networks examining treatment effects on symptom dynamics over time. Analyses will consider if and when outcome measures for the two randomisation groups differ. Furthermore, we will construct symptom networks integrating the treatment condition to evaluate its effects on symptoms at specific timepoints. These analyses will consider how these symptom networks evolve across the different timepoints of the trial. The impact of sex, illness onset, and their interaction on treatment outcomes will also be explored. In addition we will examine if baseline characteristics can predict outcomes.

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 and presentation at scientific conferences.

Bibliography:

1. Galderisi, S., Mucci, A., Buchanan, R. W. & Arango, C. Negative symptoms of schizophrenia: new developments and unanswered research questions. *The Lancet Psychiatry* **5**, 664--677 (8 2018).
2. Bucci, P. *et al.* Persistent negative symptoms in recent-onset psychosis: Relationship to treatment response and psychosocial functioning. *Eur. Neuropsychopharmacol.* **34**, 76--86 (2020).
3. Epskamp, S. Psychometric network models from time-series and panel data. *Psychometrika* **85**, 206--231 (2020).
4. Blanken, T. F. *et al.* Introducing network intervention analysis to investigate sequential, symptom-specific treatment effects: A demonstration in co-occurring insomnia and depression. *Psychother. Psychosom.* **88**, 52--54 (2019).
5. Boschloo, L. *et al.* The symptom-specific efficacy of antidepressant medication vs. cognitive behavioral therapy in the treatment of depression: results from an individual patient data meta-analysis. *World Psychiatry* **18**, 183--191 (2019).