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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?: Email/Newsletter/Flier

Conflict of Interest

https://yoda.yale.edu/wp-content/uploads/2016/02/radhakrishnan_coi.pdf

https://yoda.yale.edu/wp-content/uploads/2016/10/xin_coi.pdf

https://yoda.yale.edu/wp-content/uploads/2020/06/coi_form_jm.pdf

<https://yoda.yale.edu/wp-content/uploads/2021/08/COI-FORM-ZL.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. [NCT00488319 - A 2-Year, Open-Label, Single-Arm Safety Study of Flexibly Dosed Paliperidone Extended Release \(1.5-12 mg/day\) in the Treatment of Adolescents \(12 to 17 Years of Age\) With Schizophrenia](#)
2. [NCT01009047 - 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](#)
3. [NCT00645099 - A Prospective Randomized Open-label 6-Month Head-To-Head Trial to Compare Metabolic Effects of Paliperidone ER and Olanzapine in Subjects With Schizophrenia](#)
4. [NCT00518323 - 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](#)
5. [NCT00334126 - 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](#)
6. [NCT00086320 - 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](#)
7. [NCT00589914 - 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](#)
8. [NCT00604279 - A Randomized, Open-Label, Parallel Group Comparative Study of Paliperidone Palmitate \(50, 100, 150 mg eq\) and Risperidone LAI \(25, 37.5, or 50 mg\) in Subjects with Schizophrenia](#)
9. [NCT00590577 - 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](#)
10. [NCT00111189 - 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](#)
11. [NCT00210717 - A Randomized, Double-Blind, Parallel Group, Comparative Study of Flexibly Dosed Paliperidone Palmitate \(25, 50, 75, or 100 mg eq.\) Administered Every 4 Weeks and Flexibly Dosed RISPERDAL CONSTA \(25, 37.5, or 50 mg\) Administered Every 2 Weeks in Subjects With Schizophrenia](#)
12. [NCT00119756 - A Randomized, Crossover Study to Evaluate the Overall Safety and Tolerability of Paliperidone Palmitate Injected in the Deltoid or Gluteus Muscle in Patients With Schizophrenia](#)
13. [NCT00210548 - 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](#)
14. [NCT00101634 - 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](#)
15. [NCT00034749 - The Efficacy and Safety of Risperidone in Adolescents With Schizophrenia: a Comparison of Two Dose Ranges of Risperidone](#)
16. [NCT00397033 - 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](#)
17. [NCT00412373 - 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](#)
18. [NCT00236444 - Risperidone in the Prevention of Relapse: a Randomized, Double-blind, Placebo-controlled Trial in Children and Adolescents With Conduct and Other Disruptive Behavior Disorders](#)
19. [NCT00266552 - The Safety And Efficacy Of Risperidone Versus Placebo In Conduct Disorder and Other Disruptive Behavior Disorders In Mild, Moderate And Borderline Mentally Retarded Children Aged 5 To 12 Years](#)

20. [NCT00249132 - A Canadian multicenter placebo-controlled study of fixed doses of risperidone and haloperidol in the treatment of chronic schizophrenic patients](#)
21. [NCT00216476 - CONSTATRE: Risperdal® Consta® Trial of Relapse Prevention and Effectiveness](#)
22. [NCT00216580 - An Open-label Trial of Risperidone Long-acting Injectable in the Treatment of Subjects With Recent Onset Psychosis](#)
23. [NCT00378092 - A Prospective Study of the Clinical Outcome Following Treatment Discontinuation After Remission in First-Episode Schizophrenia](#)
24. [NCT00752427 - 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](#)
25. [NCT00077714 - 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](#)
26. [NCT00083668 - 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](#)
27. [NCT00074477 - 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](#)
28. [NCT00078039 - Trial Evaluating Three Fixed Dosages of Paliperidone Extended-Release \(ER\) Tablets and Olanzapine in the Treatment of Patients With Schizophrenia](#)
29. [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](#)
30. [NCT00249145 - Risperidone in the Treatment of Behavioral Disturbances in Demented Patients: an International, Multicenter, Placebo-controlled, Double-blind, Parallel-group Trial Using Haloperidol as Internal Reference](#)
31. [NCT00088075 - A Randomized, Double-Blind, Placebo-Controlled Clinical Study of the Efficacy and Safety of Risperidone for the Treatment of Schizophrenia in Adolescents](#)
32. [NCT00253136 - Risperidone Depot \(Microspheres\) vs. Placebo in the Treatment of Subjects With Schizophrenia](#)
33. [The safety and efficacy of risperidone 8 mg qd and 4 mg qd compared to placebo in the treatment of schizophrenia](#)
34. [NCT01529515 - A Randomized, Multicenter, Double-Blind, Relapse Prevention Study of Paliperidone Palmitate 3 Month Formulation for the Treatment of Subjects With Schizophrenia](#)
35. [NCT01193153 - A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study of Paliperidone Palmitate Evaluating Time to Relapse in Subjects With Schizoaffective Disorder](#)
36. [NCT01662310 - Paliperidone Extended Release Tablets for the Prevention of Relapse in Subjects With Schizophrenia: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study](#)
37. [NCT00524043 - 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](#)
38. [NCT00105326 - A Double-blind, Placebo-controlled, Randomized Study Evaluating the Effect of Paliperidone ER Compared With Placebo on Sleep Architecture in Subjects With Schizophrenia](#)
39. [NCT00044681 - A Study to Evaluate the Efficacy, Safety and Maintenance Effect of Risperidone Augmentation of SSRI Monotherapy in Young and Older Adult Patients With Unipolar Treatment-Resistant Depression](#)
40. [NCT00249223 - Risperidone Depot \(Microspheres\) vs. Risperidone Tablets - a Non-inferiority, Efficacy Trial in Subjects With Schizophrenia](#)
41. [NCT01157351 - A Fifteen-month, Prospective, Randomized, Active-controlled, Open-label, Flexible Dose Study of Paliperidone Palmitate Compared With Oral Antipsychotic Treatment in](#)

[Delaying Time to Treatment Failure in Adults With Schizophrenia Who Have Been Incarcerated](#)

42. [NCT01081769 - A 24-month, Prospective, Randomized, Active-Controlled, Open-Label, Rater-Blinded, Multicenter, International Study of the Prevention of Relapse Comparing Long-Acting Injectable Paliperidone Palmitate to Treatment as Usual With Oral Antipsychotic Monotherapy in Adults With Schizophrenia](#)
43. [NCT01281527 - A 6-month, Open Label, Prospective, Multicenter, International, Exploratory Study of a Transition to Flexibly Dosed Paliperidone Palmitate in Patients With Schizophrenia Previously Unsuccessfully Treated With Oral or Long-acting Injectable Antipsychotics](#)
44. [NCT01051531 - Safety, Tolerability, and Treatment Response of Paliperidone Palmitate in Subjects With Schizophrenia When Switching From Oral Antipsychotics](#)
45. [NCT01527305 - An Open-Label, Prospective, Non-Comparative Study to Evaluate the Efficacy and Safety of Paliperidone Palmitate in Subjects With Acute Schizophrenia](#)
46. [NCT01299389 - A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Fixed-Dose, Multicenter Study of JNS010 \(Paliperidone Palmitate\) in Patients With Schizophrenia](#)
47. [NCT01258920 - A Long-Term, Open-Label Study of Flexibly Dosed Paliperidone Palmitate Long-Acting Intramuscular Injection in Japanese Patients With Schizophrenia](#)
48. [NCT00216671 - Early Versus Late Initiation of Treatment With Risperdal Consta in Subjects With Schizophrenia After an Acute Episode](#)
49. [NCT00369239 - Is Premorbid Functioning a Predictor of Outcome in Patients With Early Onset Psychosis Treated With Risperdal Consta?](#)
50. [NCT00216632 - Treatment Success in Patients Requiring Treatment Change From Olanzapine to Risperidone Long Acting Injectable \(TRESOR\)](#)
51. [NCT00236379 - A Six-month, Double-blind, Randomized, International, Multicenter Trial to Evaluate the Glucoregulatory Effects of Risperidone and Olanzapine in Subjects With Schizophrenia or Schizoaffective Disorder](#)
52. [NCT01050582 - Evaluation of Growth, Sexual Maturation, and Prolactin-Related Adverse Events in the Pediatric Population Exposed to Atypical Antipsychotic Drugs](#)
53. [NCT00495118 - Risperidone Depot \(Microspheres\) in the Treatment of Subjects With Schizophrenia or Schizoaffective Disorder - an Open-label Follow-up Trial of RIS-INT-62 and RIS-INT-85](#)
54. [NCT00236457 - Randomized, Multi-center, Open Label Trial Comparing Risperidone Depot \(Microspheres\) and Olanzapine Tablets in Patients With Schizophrenia or Schizoaffective Disorder](#)
55. [NCT00236587 - An Open Label, Long Term Trial of Risperidone Long Acting Microspheres in the Treatment of Patients Diagnosed With Schizophrenia](#)
56. [NCT00297388 - A 52-wk Prospective, Randomized, Double-blind, Multicenter Study of Relapse Following Transition From Oral Antipsychotic Medication to 2 Different Doses \(25 or 50 mg Every 2 Wks\) of Risperidone Long-acting Microspheres \(RISPERDAL CONSTA\) in Adults With Schizophrenia or Schizoaffective Disorder](#)
57. [NCT00821600 - Single-Dose, Open-Label Pilot Study to Explore the Pharmacokinetics, Safety and Tolerability of a Gluteal Intramuscular Injection of a 4-Week Long-Acting Injectable Formulation of Risperidone in Patients With Chronic Stable Schizophrenia](#)
58. [NCT00034775 - Open-Label Trial Exploring A Switching Regimen From Oral Neuroleptics, Other Than Risperidone, To Risperidone Depot Microspheres](#)
59. [NCT00460512 - An Open-label Prospective Trial to Explore the Tolerability, Safety and Efficacy of Flexibly Dosed Paliperidone ER in Subjects With Schizophrenia](#)
60. [NCT00566631 - Tolerability, Safety and Treatment Response of Flexible Doses of Paliperidone ER in Acutely Exacerbated Subjects With Schizophrenia](#)
61. [NCT01515423 - A Randomized, Multicenter, Double-Blind, Non-inferiority Study of Paliperidone Palmitate 3 Month and 1 Month Formulations for the Treatment of Subjects With Schizophrenia](#)
62. [NCT02713282 - A 52-Week, Open-Label, Prospective, Multicenter, International Study of a Transition to the Paliperidone Palmitate 3-Month Formulation In Patients With Schizophrenia Previously Stabilized on the Paliperidone Palmitate 1-Month Formulation](#)

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

Research Proposal

Project Title

Harnessing clinical trial data to inform real-world clinical decision making in the treatment of schizophrenia

Narrative Summary:

Randomized clinical trials (RCT) provide rich data related to safety and efficacy of pharmacological agents. This is often at variance with real-world data since patients in the real-world i.e. (real-world data (RWD)) are not constrained by RCT design. Even when the results of RCT and RWD are consistent, they often do not apply directly to an individual patient who presents before a physician. We attempt to overcome these challenges by use of a novel statistical technique, Desirability of Outcome Ranking (DOOR), to better inform clinical-decision making in the treatment of schizophrenia.

Scientific Abstract:

Background: Randomized clinical trials (RCT) provide rich data related to safety and efficacy of pharmacological agents. This is often at variance with real-world data since patients in the real-world i.e. (real-world data (RWD)) are not constrained by RCT design. Even when the results of RCT and RWD are consistent, they often do not apply directly to an individual patient who presents before a physician.

Objectives: To examine the utility of Desirability of Outcome Ranking (DOOR) in measuring the risk-benefit profile of antipsychotic treatment in schizophrenia.

Study Design: Randomized control trial data will be reanalyzed using Desirability of Outcome Ranking (DOOR), a measure that combines clinically-relevant risks and benefits.

Participants: Subject-level data from randomized, placebo-controlled studies of risperidone and paliperidone in schizophrenia patients.

Main Outcome Measures: Utility of DOOR in characterizing treatment responders/non-responders and overall concordance with results of trial using traditional outcome measures.

Statistical Analysis: We will re-analyze the trial data using DOOR for finer gradations of composite outcomes. DOOR probability, proportion in favor of treatment, and win ratio will be used to compare treatments. Their 95% confidence intervals will be estimated by bootstrap.

Brief Project Background and Statement of Project Significance:

Randomized clinical trials (RCT) provide rich data related to safety and efficacy of pharmacological agents. This is often at variance with real-world data since patients in the real-world i.e. (real-world data (RWD)) are not constrained by RCT design. Even when the results of RCT and RWD are consistent, they often do not apply directly to an individual patient who presents before a physician. We attempt to overcome these challenges by use of a novel statistical technique, Desirability of Outcome Ranking (DOOR), to better inform clinical-decision making in the treatment of schizophrenia. DOOR has proven utility in antimicrobial therapy in conjunction with partial credit scoring to allow for quantitative comparisons of the clinical desirability of treatment decisions (Claeys et al, 2021, Evans et al, 2020). In this proposal, we extend this novel statistical technique to clinical decision making in antipsychotic treatment of schizophrenia.

Specific Aims of the Project:

The specific aims of the project are:

a) Develop a Desirability of Outcome Ranking (DOOR) for schizophrenia trials

b) Examine the utility of DOOR in characterizing treatment responders/non-responders and overall concordance with results of trial using traditional outcome measures

Research Methods

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

Individual-level data from RCTs of risperidone and paliperidone in schizophrenia

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

Desirability of Outcome Ranking (DOOR) will be defined a-priori from input from expert psychiatrists who have experience in treating patients with schizophrenia. The outcome is a composite outcome, combining the efficiency and safety measures together.

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

The predictor / independent variable is the treatment assignment (i.e drug vs placebo). The analysis will include the treatment assignment, age, gender, race/ethnicity, and other potential risk factors.

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

We will evaluate the heterogeneity of the composite outcomes in the subgroups of age, gender and race/ethnicity.

Statistical Analysis Plan:

We will generate tables that summarize the distribution and extent of missingness of potential risk factors, for example, age, gender, and race/ethnicity, overall and by treatment arm to assess for random baseline imbalances for the trial data.

Our interest is to compare the DOOR between two treatments. The DOOR probability, proportion in favor of treatment and win ratio will be estimated by making all possible pairwise comparisons between two treatment arms according to DOOR, and their 95% CI will be constructed using bootstrap.

We will also evaluate heterogeneity of the composite outcome in several pre-specified subgroups, for example, age, gender, and race/ethnicity. These are hypothesis generating analyses. We will use the method described above to evaluate the effect of treatments stratified by subgroup. All subgroup analyses will be clearly reported, including how subgroups will be defined, outcomes examined, and how both the point and interval estimates of treatment effects.

Project Timeline:

Estimation of key milestone dates for the proposed study:

- 1) Anticipated project start date = Nov-2021
- 2) Data analysis completion = May 2022
- 3) Dissemination of results= Nov 2022

Dissemination Plan:

Dissemination plan includes presentation at conferences (such as ASCP Annual conference, ISCTM annual meeting) and publication in peer-reviewed journals (such as Journal of Clinical Psychiatry).

Bibliography:

1. Claeys CK, Hopkins TL, Schlaffer K, Hitchcock S, Jiang Y, Evans S, Johnson JK, Leekha S. Comparing the Clinical Utility of Rapid Diagnostics for Treatment of Bloodstream Infections Using Desirability of Outcome Ranking Approach for the Management of Antibiotic Therapy (DOOR-MAT). *Antimicrob Agents Chemother*. 2021;65(9):e0044121.
2. Evans SR, Knutsson M, Amarenco P, Albers GW, Bath PM, et al. Methodologies for pragmatic and efficient assessment of benefits and harms: Application to the SOCRATES trial. *Clin Trials*. 2020 Dec;17(6):617-626.