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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/seth-signed-dated_coi.pdf
https://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_2019_ajay_dated.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. NCT00391222 - RISBMN3001 - A Randomized, Double Blind, Placebo and Active Controlled Parallel Group Study to Evaluate the Efficacy and Safety of Risperidone Long-acting Injectable (LAI) for the Prevention of Mood Episodes in the Treatment of Subjects With Bipolar I Disorder
2. NCT00034749 - RIS-USA-231 - The Efficacy and Safety of Risperidone in Adolescents With Schizophrenia: a Comparison of Two Dose Ranges of Risperidone
3. NCT00132678 - RISBIM3003 - A Randomized, Double-blind, Placebo-controlled Study to Explore the Efficacy and Safety of Risperidone Long-acting Intramuscular Injectable in the Prevention of Mood Episodes in Bipolar 1 Disorder, With Open-label Extension
4. NCT00094926 - RIS-BIP-302 - A Prospective, Randomized, Double-blind, Placebo-controlled Study of the Effectiveness and Safety of RISPERDAL CONSTA Augmentation in Adult Patients With Frequently-relapsing Bipolar Disorder

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5. NCT00249132 - RIS-INT-3 - A Canadian multicenter placebo-controlled study of fixed doses of risperidone and haloperidol in the treatment of chronic schizophrenic patients
6. NCT00216476 - RISSCH3001 - CONSTATRE: Risperdal® Consta® Trial of Relapse Prevention and Effectiveness
7. NCT00253162 - RIS-INT-69 - The Efficacy And Safety Of Flexible Dose Ranges Of Risperidone Versus Placebo Or Haloperidol In The Treatment Of Manic Episodes Associated With Bipolar I Disorder
8. RIS-INT-83 - Efficacy and safety of a flexible dose of risperidone versus placebo in the treatment of psychosis of Alzheimer's disease. A double-blind, placebo-controlled, parallel-group study.
9. 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
10. RIS-USA-1 (RIS-USA-9001) - Risperidone versus haloperidol versus placebo in the treatment of schizophrenia
11. NCT00253149 - RIS-USA-102/CR006040 - The Safety And Efficacy Of Risperdal (Risperidone) Versus Placebo Versus Haloperidol As Add-On Therapy To Mood Stabilizers In The Treatment Of The Manic Phase Of Bipolar Disorder
12. NCT00253136 - RIS-USA-121/CR006055 - Risperidone Depot (Microspheres) vs. Placebo in the Treatment of Subjects With Schizophrenia
13. RIS-USA-150 - A double-blind, placebo-controlled study of risperidone in children and adolescents with autistic disorder
14. NCT00034762 - RIS-USA-232/CR002764 - Efficacy And Safety Of A Flexible Dose Of Risperidone Versus Placebo In The Treatment Of Psychosis Of Alzheimer's Disease
15. NCT00257075 - RIS-USA-239/CR006052 - The Efficacy And Safety Of Flexible Dosage Ranges Of Risperidone Versus Placebo In The Treatment Of Manic Episodes Associated With Bipolar I Disorder
16. NCT00253123 - RIS-USA-63/CR006022 - A Randomized, Double-Blind, Placebo-Controlled Study of Risperidone for Treatment of Behavioral Disturbances in Subjects With Dementia
17. RIS-USA-72 - The safety and efficacy of risperidone 8 mg qd and 4 mg qd compared to placebo in the treatment of schizophrenia
18. NCT00216671 - RISSCH4045 - Early Versus Late Initiation of Treatment With Risperdal Consta in Subjects With Schizophrenia After an Acute Episode
19. NCT00086112 - RIS-ANX-301 - A Double-blind, Randomized, Prospective Study to Evaluate Adjunctive Risperidone Versus Adjunctive Placebo in Generalized Anxiety Disorder Sub-optimally Responsive to Standard Psychotropic Therapy
20. NCT00236457 - RIS-INT-62 - Randomized, Multi-center, Open Label Trial Comparing Risperidone Depot (Microspheres) and Olanzapine Tablets in Patients With 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

A NOVEL METHOD TO SUMMARIZE SAFETY IN CLINICAL TRIALS USING PHARMACOLOGICAL CLASS-RELATED RISKS IN FAERS

Narrative Summary:

The efficacy of antipsychotic drugs relies on the blockade of dopamine D2 receptors, which results in substantial disruption of motor, metabolic and endocrine systems. The incidences of each individual side effect reported in a clinical trial are low relative to their cumulative burden in real-world use. Therefore, new approaches are needed to facilitate more-accurate reporting of side effects in clinical studies, relative to the pharmacological class-effects seen in real-world use. We have established a query of antipsychotic class-related side effects, and are seeking legacy clinical trial data of risperidone to test the query.

Scientific Abstract:

Background: Use of the antipsychotic drug class results in substantial disruption of motor, metabolic and endocrine systems to produce an array of side effects in schizophrenia, bipolar and depression patient populations. The incidence of each individual side effect reported in a clinical trial is low relative to their cumulative burden in real-world use. We have established a query of antipsychotic class-related side effects, and are seeking legacy clinical trial data with risperidone to test the query.

Objective: Test a query of antipsychotic class-related side effects, developed using a real-world reporting database (FAERS), on legacy clinical trial data with risperidone.

Study Design: Retrospective.

Participants: Subject-level adverse event data collected during randomized, placebo-controlled studies of risperidone in patient populations having psychiatric and neurological disorders.

Main Outcome Measure: Portion of subjects in each clinical study having an Adverse Event Preferred Term as a cumulative function of each Preferred Term's class-related risk in real-world reporting database FAERS.

Statistical Analysis: We have ranked the preferred terms (PTs) for the pool of atypical antipsychotics by relative risk in FAERS defined by each PT's Empirical Bayes Geometric Mean (EBGM), a common statistical measure in Bayesian data mining methods (Dumouchel, 1999). Adverse event data from available risperidone studies will be sorted by preferred term according to their FAERS-EBGM ranking within the antipsychotic class.

Brief Project Background and Statement of Project Significance:

Typically the registration and approval of new drug treatments summarizes safety using a highly specific ontology of adverse event terminology (eg, MedDRA). In the investigation of drug safety issues in pharmacovigilance and clinical development, standardized MedDRA queries (SMQs) are validated, pre-determined sets of MedDRA terms grouped together to support safety analysis and reporting.

Here we developed a method to create a "pharmacological class effect query" that seeks to collect and summarize the class-related impact on overall adverse events in clinical development, accumulated across multiple body systems.

Information gained from this work will help in the development of novel treatments for schizophrenia. The current antipsychotic drug class results in substantial disruption of motor, metabolic and endocrine systems to produce an array of side effects in schizophrenia, bipolar and depression patient populations. Here we seek to develop an objective query to quantify the accumulated burden of real-world side effects in drug-development trials, in order to provide a measurable benchmark for future schizophrenia treatments developed in a novel pharmacological class.

If adopted more broadly, the methods developed and piloted with risperidone in schizophrenia may be applied to other drug classes to spur innovation in other therapy areas.

Testing of these analytical methods will benefit from access to additional clinical trial data sets.

Specific Aims of the Project:

The specific aim of this project is to develop a novel method for summarizing and comparing class-related safety and thus facilitate the development and reporting of new pharmacological classes in future schizophrenia drug development. The study's objective is to create cumulative curves to prototype a novel way to summarize and compare large datasets of clinical trial data. The cumulative curves will describe the portion of subjects in each clinical study having an Adverse Event Preferred Term as a cumulative function of each Preferred Term's class-related risk in real-world reporting database FAERS.

What is the purpose of the analysis being proposed? Please select all that apply.
New research question to examine treatment safety

Research Methods

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

This analysis will include all subjects from the indicated risperidone clinical trials (available in YODA project) who have a minimum of one dose administered. In general, that is all subjects with a safety flag.

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

Portion of subjects in each clinical study having an Adverse Event Preferred Term as a cumulative function of each Preferred Term's class-related risk in real-world reporting database FAERS.

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

Main outcome measure of this analysis is subject frequency measurement categorized by adverse event(s).

Primary measure of this analysis is cumulative percentage of subjects within PTs as a function of each PTs class-related risk in FAERS.

The multiple groups of PTs will be gathered from the latest available FAERS data (accessed by Empirica database from Oracle). All antipsychotics with FAERS data will be used to generate class-related queries. No participant-level clinical trial data from other antipsychotics will be pooled with risperidone data from YODA.

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

Each clinical study will be characterized by the portion of subjects on risperidone, or placebo, having AEs with PTs associated with >=2x and >=5x relative risk (FAERS EBGM), and the fold-risk (FAERS EBGM) values where the portion of subjects reaches 50% of the subjects reporting an AE.

It is hypothesized that if the cumulative AE profiles of risperidone are different from placebo (eg, 95%CI non-overlapping across studies), then the real-world FAERS PTs are a more-objective way to collect class-specific PTs for querying and summarizing safety data for clinical trials.

It is hypothesized that if compounds in future schizophrenia clinical trials report a substantially lower portion of PTs in the FAERS class-effect query (eg, at placebo levels), then the real-world FAERS PTs are a more-objective way to determine whether novel compounds might be retaining the expected AE profile of the existing class, or whether a different safety profile will need to be further characterized.

Statistical Analysis Plan:

Briefly FAERS will be used to collect preferred terms associated with antipsychotics (e.g., aripiprazole, asenapine, brexpiprazole, cariprazine, iloperidone, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, ziprasidone). The preferred terms of the antipsychotic-related adverse events span a variety of ontological categories. In work to date, a total of 9968 adverse event records were generated using 2018 2nd Quarter data deployed into Empirica Signal server.

Statistical analysis plan steps:
1. Create integrated summary of safety of all available risperidone studies in YODA.
2. Create a table with all AE Preferred terms and their EBGM value for antipsychotics
3. Analyze and sort this table
Software Used:
R

Project Timeline:

The duration of this project is expected to be 4 months from start of access to data to completion of data analysis, and 6 more months to manuscript completion.

Dissemination Plan:

Abstract results will be submitted to Schizophrenia International Research Society (SIRS) conference 2022 for

presentation/poster. A target journal is Schizophrenia Research or Drug Safety.

Bibliography:

William Dumouchel (1999). Bayesian Data Mining in Large Frequency Tables, with an Application to the FDA Spontaneous Reporting System. The American Statistician, 53:3, 177-190. doi:10.1080/00031305.1999.10474456