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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/prospero_protocol_hodkinson.pdf
https://yoda.yale.edu/system/files/coi_signed_alex_0.pdf
https://yoda.yale.edu/system/files/coi_signed_maria_0.pdf
https://yoda.yale.edu/system/files/coi_signed_carl.pdf
https://yoda.yale.edu/system/files/coi_signed_kamal.pdf
https://yoda.yale.edu/system/files/coi_signed_evan.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. 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
2. 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. 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
4. 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
5. 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
6. 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
7. 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
8. 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
9. NCT00076115 - RIS-BIM-301 - Research on the Effectiveness of Risperidone in Bipolar Disorder in Adolescents and Children (REACH): A Double-Blind, Randomized, Placebo-Controlled Study of the Efficacy and Safety of Risperidone for the Treatment of Acute Mania in Bipolar I Disorder
10. 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
11. 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
12. 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
13. 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
14. 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

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15. NCT00299715 - R076477-BIM-3001 - A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Dose-Response, Multicenter Study to Evaluate the Efficacy and Safety of Three Fixed Doses of Extended-Release Paliperidone in the Treatment of Subjects With Acute Manic and Mixed Episodes Associated With Bipolar I Disorder
16. NCT00309699 - R076477-BIM-3002 - A Randomized, Double-Blind, Active- and Placebo-Controlled, Parallel-Group, Multicenter Study to Evaluate the Efficacy and Safety of Flexibly-Dosed, Extended-Release Paliperidone Compared With Flexibly-Dosed Quetiapine and Placebo in the Treatment of Acute Manic and Mixed Episodes Associated With Bipolar I Disorder
17. NCT00309686 - R076477-BIM-3003 - A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter Study to Evaluate the Efficacy and Safety of Flexibly-Dosed Extended-Release Paliperidone as Adjunctive Therapy to Mood Stabilizers in the Treatment of Acute Manic and Mixed Episodes Associated With Bipolar I Disorder
18. NCT00752427 - R076477-SCH-702 - 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
19. 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
20. 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
21. 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
22. NCT00078039 - R076477-SCH-303 - Trial Evaluating Three Fixed Dosages of Paliperidone Extended-Release (ER) Tablets and Olanzapine in the Treatment of Patients With Schizophrenia
23. 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
24. 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
25. 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
26. NCT00253136 - RIS-USA-121/CR006055 - Risperidone Depot (Microspheres) vs. Placebo in the Treatment of Subjects With Schizophrenia
27. 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
28. RIS-USA-72 - The safety and efficacy of risperidone 8 mg qd and 4 mg qd compared to placebo in the treatment of schizophrenia
29. NCT01529515 - R092670PSY3012 - A Randomized, Multicenter, Double-Blind, Relapse Prevention Study of Paliperidone Palmitate 3 Month Formulation for the Treatment of Subjects With Schizophrenia
30. NCT01193153 - R092670SCA3004 - A Randomized, Double-Blind, Placebo-Controlled, Parellel-Group Study of Paliperidone Palmitate Evaluating Time to Relapse in Subjects With Schizoaffective Disorder
31. NCT01662310 - R076477-SCH-3041 - Paliperidone Extended Release Tablets for the Prevention of Relapse in Subjects With Schizophrenia: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study
32. NCT00490971 - R076477BIM3004 - A Randomized, Double-Blind, Active- and Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Efficacy and Safety of Extended-Release Paliperidone as Maintenance Treatment After an Acute Manic or Mixed Episode Associated With Bipolar I Disorder
33. 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
34. NCT00645307 - R076477-SCH-701 - A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study With an Open-Label Extension Evaluating Extended Release OROS® Paliperidone in the Prevention of Recurrence in Subjects With Schizophrenia - Open Label Phase
35. NCT01299389 - PALM-JPN-4 - A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Fixed-

Dose, Multicenter Study of JNS010 (Paliperidone Palmitate) in Patients With Schizophrenia
36. NCT00236379 - RIS-USA-275 - 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
37. NCT00992407 - RISSCH4178 - A Randomized, Open-label, Active-controlled Study to Evaluate Social Functioning of Long Acting Injectable Risperidone and Oral Risperidone in the Treatment of Subjects With Schizophrenia or Schizoaffective Disorder
38. NCT00236457 - RIS-INT-62 - Randomized, Multi-center, Open Label Trial Comparing Risperidone Depot (Microspheres) and Olanzapine Tablets in Patients With Schizophrenia or Schizoaffective Disorder
39. 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

Safety of Risperidone and Paliperdone in schizophrenia and bipolar disorder diagnosed patients - a systematic review and meta-analysis

Narrative Summary:

Risperidone and Paliperdone are antipsychotic-drugs approved for the treatment of schizophrenia in adults and adolescents, and for the short-term treatment of manic or mixed episodes of bipolar disorder. However, over the last decade there have been a rising number of cases of hormonal imbalances leading to breast tissue development and infertility in boys and girls. To date, meta-analysis of both drugs in schizophrenic patients have solely been based on published RCTs, involving adults, and analyzed using standard methods of meta-analysis. We propose a more robust assessment of the safety of both drugs, using more innovative methodologies involving Clinical Study Reports (CSRs).

Scientific Abstract:

Background: Risperidone and Paliperidone are two mainstay anti-psychotic drugs for treating schizophrenia and other mental health problems like bipolar disorder. However, among the research community, there is rising concerns about serious adverse events such as 'gynecomastia' and rare muscle related side-effects ‘extrapyramidal effects’.

Objective: As existing evidence about the safety of both drugs is based upon data from journal publications, which likely to lead to under reporting of harms. We aim to do a more robust meta-analysis using CSRs.

Study Design: We will carry out a robust and exhaustive systematic review including a large meta-analysis of RCTs to evaluate the safety of risperidone and paliperidone for use in patients with schizophrenia or bipolar disorder.

Participants: Participants of RCTs of risperidone or paliperidone irrespective of dose, age or gender and involving patient populations with schizophrenia and bipolar disorder.

Main Outcome Measures: Serious adverse events or adverse events and death related incidences. Patient safety narratives and listings will be used to assess causality.

Statistical Analysis: Relative risks, risk differences and their 95% confidence intervals will be calculated and combined in traditional pairwise meta-analysis. Sensitivity analysis will also be performed using Peto-OR, and more advance methods such as the beta-binomial model and Bayesian meta-analysis which are considered better for handling heterogeneity when the event rate is rare.

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Please find attached PROSPERO protocol (CRD42019140556)

Brief Project Background and Statement of Project Significance:

Risperidone and Paliperdone are mainstay treatment for people with schizophrenia and bipolar disorder. However, amongst the research community, there have been rising concerns about serious adverse events such as 'gynecomastia' and 'extrapyramidal effects' that have been linked with the use of Risperidone and Paliperdone. The current evidence on the safety of both drugs is based upon data from journal publications, which are susceptible to high levels of reporting bias and publication bias. Clinical study reports offer an untapped source of data and are far better suited to assess the safety profiles of pharmacological interventions. Therefore, to reach a level of precision and confidence about these serious adverse events and rare outcomes, a more robust meta-analysis using CSRs is required. We plan to achieve this goal by using the data from CSRs on Risperidone and Paliperdone trials available at YODA, and by making additional freedom of information requests at the European medicines agency (EMA).

Specific Aims of the Project:

The aims of the project are to examine whether the antipsychotic drugs Risperidone and Paliperdone increase the risk of SAEs for patients suffering from schizophrenia and other mental health problems like bipolar disorder, and to determine whether treatment-related factors are associated with their occurrence.

Main hypothesis: There is an overall significant difference in serious adverse events in the Risperidone or Paliperdone group compared to placebo group.

The same hypothesis test will be used for all identified serious adverse events.

Subgroup analysis will include diagnostic subgroup, age (under 18s), gender, drug combination, dosage from the patient safety listings.

Please find attached PROSPERO protocol (CRD42019140556) for further information.

What is the purpose of the analysis being proposed? Please select all that apply.
New research question to examine treatment safety
Summary-level data meta-analysis
Summary-level data meta-analysis pooling data from YODA Project with other additional data sources
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:

Study design: Systematic review and meta-analysis of RCTs.

Search strategy: We ran extensive searches in the electronic databases Cochrane Schizophrenia Groups Trials Register and CENTRAL, MEDLINE, EMBASE, BIOSIS, CINAHL, LILACS and PsycINFO. Additionally, we contacted all risperidone and paliperdone-marketing pharma companies for missing relevant data. The ‘ClinicalTrials.gov’ and ‘OpenTrials.net’ will be searched to identify any potential unpublished trials. Medical Reviews at the Drugs@FDA and European Public Assessment Reports were checked for any further missing data. For trials that were not accessible via YODA, the CSRs were request via the EMA.

Inclusion criteria: Participants of randomised controlled trials of risperidone or paliperdone treated for schizophrenia and bipolar disorder.

Please find attached PROSPERO protocol (CRD42019140556) for further information.

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

The main outcome measure is the number(s) of serious adverse events in the treatment group and placebo group. The effect size measure will be the odd ratio, relative risk, risk difference and its 95% confidence intervals. We will calculate the number needed to treat to provide benefit/to induce harm, and its 95% CIs. All serious adverse events of interest will be assessed in the meta-analysis. In addition, rare adverse events will be analyzed in a sensitivity analysis involving more advanced methods including Peto-odds ratio, and more advanced methods like the beta-binomial model and Bayesian meta-analysis.

Longer-term outcomes will be assessed in a sensitivity analysis with the trials that had greater length of follow-up. Incidence rates will be calculated if the mean times are available.

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

The state of the treatment (risperidone, paliperdone or placebo) will be the main predictor.

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

Other potential predictors that will be addressed in the subgroup analysis include diagnostic subgroup (schizophrenia/bipolar), age (younger children or adolescents), gender, risperidone vs. paliperdone, combination of other drugs and dosage.

Statistical Analysis Plan:

Because of the novelty and size of clinical study reports (including appendices listing data) we subdivided the extraction, appraisal, and analysis of the data into a two stage exercise. We included trials meeting our inclusion criteria (that is, had an appropriate study design) in stage 1. Trials not meeting our inclusion criteria (for example, open label studies) were not included in stage 1. In stage 1 we assessed the reliability and completeness of the identified trial data. This allowed us to identify missing important text or data. To aid us in determining completeness of the relevant parts of clinical study reports we constructed an extraction form based on the CONSORT-harms statement checklist and expert opinion from the research team.

We decided to only include data in stage 2 of the review (full analysis following standard Cochrane methods) if they satisfied the following three criteria:
1. Completeness: clinical study reports include identifiable CONSORT harms statement specified methods to enable replication of the study. Identifiable CONSORT harms statement specified results (safety results in the core report, tables of adverse and serious adverse events, appendices with serious adverse event narratives (E3 sections 12.3.1, 12.3.2 & 14.3.3) and individual participant safety listings (E3 section 16.2.7) and CRFs for SAEs and withdrawals for AEs (E3 Section 16.3.1)) should be available. A comparison table checklist will be used to support this decision.
2. Internal consistency: all parts (for example, denominators) of the same clinical study reports or unpublished reports are consistent.
3. External consistency: consistency of data as reported in regulatory documents, other versions of the same clinical study reports or unpublished reports, and other references, established by cross-checking.

The analysis will become clearer after stage 1 when we have assessed the state of the reports. An initial plan is outlined below:

Adverse events and Serious adverse events will be assessed by pooling the relative risk (RR) across trials. Effect estimates will be pooled across trials using Mantel-Haenszel fixed or random-effect meta-analysis dependent upon the number of studies reporting the outcome of interest. If there are less than five trials reporting the outcome, then we will use the fixed-effect approach as recommended in the Cochrane handbook. Initial sensitivity analysis was also performed pooling the relative difference instead of RR for rare events (Bradburn et al 2007, Sweating et al 2002). However, because adverse events are likely to be sparse, we will include the peto-odds ratio approach as this has been found to be more effective method for analysing rare event outcomes. We will also calculate the number needed to treat to provide benefit/to induce harm, and its 95% CIs.

Heterogeneity was assessed visually in the forest plots and the I^2 statistics will be compared between the CSR-based and the journal publication-based analyses to determine the magnitude of heterogeneity. I^2 values greater

than 50% we interpreted as considerable levels of heterogeneity. Publication bias will be examined with funnel-plots (trim-and-fill), and the Cochrane risk of bias and GRADE assessment tool will be used to assess the quality of the studies.
Software Used:
RStudio
Project Timeline:

Start of project: 05/2019
First contact of data holders: 06/2019
Actual state of project: Identification of included RCTs from literature search and reported SAEs.

It is planned, that the data extraction and statistical analysis will start by 04/2020

Conference presentations and publication drafts are planned for the preceding months.

Dissemination Plan:

We are performing a very large systematic review involving over 60,000 participants with a robust meta-analysis incorporating CSRs, narratives, patient safety listings and CRFs. The research question is a priory for patients with schizophrenia and bipolar indications and is in line with recent NIHR health technology assessment funding calls to research the safety of anti-psychotic interventions. https://www.nihr.ac.uk/funding-and-support/funding-opportunities/1941-cl... . Therefore, we anticipate that we would look to publish our results in a leading medical journal such as the BMJ or the Lancet in which collaborators with this study have already published. Furthermore, we expect our findings would be translated and implemented into national and international treatment guidelines and through policy involvement with mental health (with specific focus on schizophrenia and bipolar disorder).

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• Methodological references when using clinical study reports:

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Supplementary Material:

https://yoda.yale.edu/sites/default/files/prospero_protocol_hodkinson_0.pdf
https://yoda.yale.edu/sites/default/files/yoda_project_protocol_2019-3978_updates.docx