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Requires Data Access? Yes

Are external grants or funds being used to support this research?: External grants or funds are being used to support this research.
Project Funding Source: German ministry of education and research(January 2024 Now under application)
How did you learn about the YODA Project?: Colleague

Conflict of Interest

https://yoda.yale.edu/wp-content/uploads/2024/01/Stefan-COI-YODA-2024.pdf
https://yoda.yale.edu/wp-content/uploads/2024/01/SV_57KskaKADT3U9Aq-R_2GqedOvNEHeVbO6.pdf
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https://yoda.yale.edu/wp-content/uploads/2024/01/YODA_COI_Schneider-Thoma.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. NCT01559272 - A Single-Dose, Open-Label, Randomized, Parallel-Group Study to Assess the Pharmacokinetics, Safety, and Tolerability of a Paliperidone Palmitate 3-Month Formulation in Subjects With Schizophrenia
2. NCT00034749 - The Efficacy and Safety of Risperidone in Adolescents With Schizophrenia: a Comparison of Two Dose Ranges of Risperidone
3. NCT00236457 - Randomized, Multi-center, Open Label Trial Comparing Risperidone Depot (Microspheres) and Olanzapine Tablets in Patients With Schizophrenia or Schizoaffective Disorder
4. 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
5. NCT01662310 - Paliperidone Extended Release Tablets for the Prevention of Relapse in Subjects With Schizophrenia: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study
6. NCT00061802 - 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
7. 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
8. 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
9. NCT00078039 - Trial Evaluating Three Fixed Dosages of Paliperidone Extended-Release (ER) Tablets and Olanzapine in the Treatment of Patients With Schizophrenia
10. 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
11. 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
12. 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
13. NCT00088075 - A Randomized, Double-Blind, Placebo-Controlled Clinical Study of the Efficacy and Safety of Risperidone for the Treatment of Schizophrenia in Adolescents
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. NCT00105326 - A Double-blind, Placebo-controlled, Randomized Study Evaluating the Effect of Paliperidone ER Compared With Placebo on Sleep Architecture in Subjects With Schizophrenia
16. 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
17. 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

18. 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
19. 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
20. NCT00216476 - CONSTATRE: Risperdal® Consta® Trial of Relapse Prevention and Effectiveness
21. NCT00216671 - Early Versus Late Initiation of Treatment With Risperdal Consta in Subjects With Schizophrenia After an Acute Episode
22. 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
23. NCT00249132 - A Canadian multicenter placebo-controlled study of fixed doses of risperidone and haloperidol in the treatment of chronic schizophrenic patients
24. NCT00249223 - Risperidone Depot (Microspheres) vs. Risperidone Tablets - a Non-inferiority, Efficacy Trial in Subjects With Schizophrenia
25. NCT00253136 - Risperidone Depot (Microspheres) vs. Placebo in the Treatment of Subjects With Schizophrenia
26. NCT00299702 - A 2-year, Prospective, Blinded-rater, Open-label, Active-controlled, Multicenter, Randomized Study of Long-term Efficacy and Effectiveness Comparing Risperdal® Consta® and Abilify® (Aripiprazole) in Adults With Schizophrenia
27. 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
28. 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
29. 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
30. 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
31. 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
32. 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
33. NCT00526877 - Evaluation of Efficacy and Safety of Long-acting Risperidone Microspheres in Patients With Schizophrenia or Schizoaffective Disorders, Who is Receiving Psychiatric Home-care Treatment, When Switching From Typical Depot or Oral Antipsychotics to Long-acting Risperidone Microspheres
34. 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
35. 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
36. 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
37. 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

38. NCT00645307 - 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
39. NCT00650793 - 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
40. NCT00668837 - Open Label Extension to R076477-SCH-305 to Evaluate the Safety and Tolerability of Paliperidone ER in Subjects With Schizophrenia
41. NCT00992407 - 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
42. 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
43. NCT01193153 - A Randomized, Double-Blind, Placebo-Controlled, Parellel-Group Study of Paliperidone Palmitate Evaluating Time to Relapse in Subjects With Schizoaffective Disorder
44. NCT01299389 - A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Fixed-Dose, Multicenter Study of JNS010 (Paliperidone Palmitate) in Patients With Schizophrenia
45. 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
46. NCT01529515 - A Randomized, Multicenter, Double-Blind, Relapse Prevention Study of Paliperidone Palmitate 3 Month Formulation for the Treatment of Subjects With Schizophrenia
47. NCT03345342 - A Double-blind, Randomized, Active-controlled, Parallel-group Study of Paliperidone Palmitate 6-Month Formulation
48. Risperidone versus haloperidol versus placebo in the treatment of schizophrenia
49. The safety and efficacy of risperidone 8 mg qd and 4 mg qd compared to placebo in the treatment of 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

Sex differences in antipsychotic efficacy and side-effects in adults with acute exacerbations of schizophrenia: an individual-participant network meta-analysis

Narrative Summary:

Our research focuses on examining sex differences in the efficacy and side effects of antipsychotic drugs in adults with acute exacerbations of schizophrenia. This individual-participant data network meta-analysis (IPD-NMA) aims to provide detailed insights into how treatment effects vary between men and women. This study emphasizes the importance of considering sex as a crucial factor in the treatment decision-making process. By analyzing individual participant data, we will be able to identify more nuanced differences in drug responses, aiding in the development of more personalized treatment plans. This research is crucial for addressing the significant gap in current treatment guidelines, which often overlook sex-specific recommendations.

Scientific Abstract:

Background: Despite the wide use of antipsychotic drugs in treating schizophrenia, there is a lack of

detailed understanding of how their efficacy and side effects differ between men and women. Current treatment guidelines offer limited sex-specific recommendations.
Objective: To evaluate sex differences in the efficacy and side effects of antipsychotics in adults with acute exacerbations of schizophrenia.
Study Design: This study will be conducted as an IPD-NMA of randomized controlled trials (RCTs), providing a comprehensive comparison of antipsychotic drugs in terms of efficacy and side effects, considering the sex of participants.
Participants: Adults with acute exacerbations of schizophrenia.
Main Outcome Measures: Differences in the efficacy and side effects of antipsychotic drugs between sexes.
Statistical Analysis: The analysis will employ a network meta-analytic approach to combine individual participant data from multiple RCTs. This method allows for a robust comparison and detailed understanding of sex-specific treatment effects.

Brief Project Background and Statement of Project Significance:

Antipsychotic drugs are central to managing acute exacerbations of schizophrenia, but there is an evident gap in understanding the role of sex in influencing drug efficacy and side effects. This research aims to fill this gap by conducting a thorough IPD-NMA, which will provide valuable insights into sex-specific drug responses. The findings are expected to contribute significantly to clinical practice by informing more personalized treatment strategies and potentially influencing future updates of treatment guidelines for schizophrenia. This study not only addresses a critical area of clinical uncertainty but also sets a precedent for considering sex as a fundamental factor in psychiatric research and treatment planning.

Specific Aims of the Project:

To examine the comparative efficacy, acceptability, and tolerability of antipsychotics as monotherapy in the treatment of acute exacerbations in adult men and women with schizophrenia by investigating sex as a potential prognostic factor and effect modifier.
Our main objective is to investigate sex differences, while also adjusting our findings by accounting for additional variables that may act as potential prognostic factors, effect modifiers, or other factors with an impact on the outcomes. Please note that we have compiled an extensive list of variables, as we aim to examine factors beyond the typical ones, including contextual factors, if available.

Study Design:

Meta-analysis (analysis of multiple trials together)

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

Confirm or validate previously conducted research on treatment effectiveness

Confirm or validate previously conducted research on treatment safety

Participant-level data meta-analysis

Meta-analysis using data from the YODA Project and other data sources

Research Methods

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

Data Source
We will include IPD only from studies provided by the YODA Project database and studies in Vivli. Additionally, we will consider aggregated data from previously published network meta-analysis

(NMA) and other relevant meta-analysis of our group (2, 6) to examine potential data availability biases. IPD analysis will be conducted on the secure data platform provided by Vivli.

Selection criteria are:
1.Population: We will include adult patients experiencing an acute episode of schizophrenia, schizophreniform disorder, or schizoaffective disorder (adult and acute illness as defined by the study authors, with no additional restrictions in terms of setting, gender, ethnicity). There is no definitive evidence suggesting that the latter schizophrenia-like psychoses are the result of fundamentally different disease processes or require distinct treatment approaches. Our inclusion criteria for trials are irrespective of the diagnostic criteria used. It is a general strategy of the Cochrane Schizophrenia Group (CSG) (1) to include not only studies that used specific diagnostic criteria such as ICD-10 or DSM-5, as they are not consistently used in clinical practice. Nevertheless, we will exclude studies that did not use operationalized criteria in a sensitivity analysis. Studies where less than 20% of participants have a mental health condition other than schizophrenia-like will be considered acceptable. All participants with schizophrenia-like conditions within the included trials will be eligible for the IPD-analysis. We will exclude studies focusing on specific subgroups of patients, such as children, those of advanced age, with comorbid somatic illnesses or substance use, first episodes, exhibiting treatment resistance, predominant negative symptoms, or in a clinically stable condition at baseline. This decision mirrors the approach of a previous comprehensive NMA based on aggregated data (2), and it will help to avoid potential study effects among different designs that could not be controlled otherwise, even with an IPD-analysis, and could violate the transitivity assumption of the NMA. Moreover, we will exclude studies focusing only on women or men in order again to exclude potential study effects that cannot be well controlled.
2. Intervention: We will examin second-generation antipsychotics (e.g., paliperidone, risperidone), three first-generation antipsychotics (chlorpromazine, haloperidol, perphenazine), and placebo as monotherapy in any form (i.e., oral or long acting injectables□LAI□). We will consider oral and LAI forms as distinct interventions in the primary analysis and the same in a sensitivity analysis. Oral and injectable placebo will be considered as the same node to allow a better-connected network. In fixed-dose studies, we will only include target to maximum doses according to the Second International Consensus Study on Antipsychotic Dose (3) in the primary analysis. We will include all flexible-dose studies.
3. Comparator(s): All interventions are compared in the NMA, with placebo as the reference in forest plots.
4. Outcomes: See the section below.
5. Design of primary studies: We will include open and blinded RCTs comparing one antipsychotic drug with another antipsychotic agent or placebo (see “2. Intervention”). Exclusions include augmentation/combination strategies, crossover studies beyond the first phase, trials with high bias risk in randomization, and cluster randomized trials. Minimum follow-up is 3 weeks, with preference for 6-week data, mirroring previous NMA (2). There will be no other restrictions in terms of publication year and status, sponsorship, or country of origin.

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

We will conduct individual-participant-data network meta-analysis (IPD-NMA) of randomized controlled trials (RCTs) comparing antipsychotics with each other or placebo as monotherapy in the treatment of acute exacerbations of schizophrenia.
We will consider
- Overall symptoms of schizophrenia (primary outcome) measured by validated rating scales such as the Positive and Negative Syndrome Scale (PANSS) or the Brief Psychiatric Rating Scale (BPRS).
- Positive symptoms of schizophrenia measured by validated (sub)scales such as the PANSS positive symptoms subscale.
- Negative symptoms of schizophrenia measured by validated (sub)scales such as the PANSS negative symptoms subscale.
- Depressive symptoms as measured by validated (sub)scales, such as the Calgary Depression Scale for Schizophrenia (CDSS).
- Clinical global impression of disease severity and improvement measured by the CGI-Improvement and CGI-Severity scales.

- Response to treatment measured as the number of patients with at least 50% and at least 20% reduction from baseline in overall symptoms rating scale.
- Quality of life measured by validated rating scales such as Heinrichs Quality of Life scale.
- Overall functioning measured by validated rating scales such as Global Assessment of Functioning or the Psychosocial Performance Scale.
- Treatment discontinuation measured as the number of patients discontinuing the study prematurely due to any cause, inefficacy or side effects.
- Side effects commonly observed with antipsychotics include akathisia, extrapyramidal side effects (such as parkinsonism and dystonia), anticholinergic side effects (such as blurred vision and dry mouth), sedation, QTc prolongation, weight increase, prolactin elevation and relevant endocrinological side-effects (e.g., disturbances of menstruation). These are measured as the number of patients experiencing an adverse event (e.g. reported using the MedDRA terminology or as use of antiparkinsonian medications as proxy for extrapyramidal side-effects), measured by validated rating scales (e.g., Barnes Akathisia Rating Scale, BARS, for akathisia and the Simpson Agnus Scale, SAS, for extrapyramidal side effects and Abnormal Involuntary Movement Scale, AIMS, for dyskinesia), and laboratory measures (e.g., body weight in kg, QTc interval in msec, and prolactin levels in ng/ml).

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

Our main objective is to investigate sex differences, while also adjusting our findings by accounting for additional variables that may act as potential prognostic factors, effect modifiers, or other factors with an impact on the outcomes. Please note that we have compiled an extensive list of variables, as we aim to examine factors beyond the typical ones, including contextual factors, if available. The first 10 are our core set. Importantly, the conduct of the project does not depend on the availability of these variables; however, they can improve statistical modelling.
- Baseline scores of the different outcome measures (see above section)
- Duration of illness (schizophrenia) before study (age at illness onset allows to calculate it).
- Antipsychotic dose used during the trial.
- Antipsychotic formulation.
- Age at baseline.
- Sex and gender.
- Height and body weight at baseline.
- Ethnicity.
- Smoking status.
- Plasma levels of antipsychotic drug used during the study.

- Diagnosis of schizophrenia or schizoaffective disorder.
- Menstruation and menopause status (in women)
- Duration of the current episode before study.
- Number of previous psychotic episodes.
- Number, type, and maximum dose of previous antipsychotics.
- Current living situation (living independently or in an environment with assistance).
- Relationship level (having a partner yes or no).
- Number of children (having children or not)
- Employment status (patient employed yes or no).
- Family history of mental illness (if yes, which diagnoses).
- History or current alcohol/substance abuse.
- History of trauma/witnessing a trauma.
- Country the participant is living.

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

This study would aim to examine sex differences of antipsychotic effects. Moreover, the following variables will be used to perform further subgroup and sensitivity analyses:
- Age.

- Duration of illness.
- Ethnicity.
- Diagnosis.
- Baseline severity.
- Plasma concentration.
- Blinding status (blinded or open).
- Risk of bias (high risk of bias or low risk/some concerns)

Statistical Analysis Plan:

1. The effect size for continuous outcomes will be the mean difference or the standardized mean difference (when various scales are used, and for dichotomous outcomes will be the odds ratio. Treatments will be ranked in network meta-analysis using the surface-under-the-cumulative-ranking-curve (SUCRA), and consider differences in the rankings between men and women.
2. We will analyze the data “as-randomized”. We will use a one-stage IPD network meta-regression models (NMR) within a Bayesian framework (4). The independent variables will include relevant participant-, intervention- and study-level varaibles (see predictors-section in the Research Proposal part). The specification of the regression models will aim to examine differences between men and women, and the final specification will be determined a posteriori based on the available data across studies and its clinical relevance. Heterogeneity will be quantified using the between-study variance (τ^2) and the 95%PI of the treatment effects, assuming a common heterogeneity variance across the treatment comparisons. We will use minimally informative priors for location parameters, and a half-normal distribution for τ.
Our primary time-point will be recorded as close to 6 weeks as possible, and we will explore the timing of outcome assessment as an effect modifier. We will also consider models for repeated measures in case of multiple measurements.
Missing outcome and co-variate data will be imputed in the Bayesian model, by taking into consideration the stratification of patients in trials and the missingness mechanism (assuming missing at random in the absence of contradictory evidence). NMR will be performed with the R package crossnma 2023 (5) and self-programmed routines in JAGS.
3. The transitivity assumption will be examined with the distribution of potential effect-modifiers across treatment comparisons. Incoherence will be examined using the separating-indirect-from-direct-evidence approach, and a design-by-treatment interaction test (7).
4. We will examine potential differences between men and women for all outcomes using NMR models. Moreover, we will examine factors that could explain the potential sex differences: a) age, b) duration of illness, c) ethnicity, d) diagnosis, e) baseline severity, and f) plasma concentrations (or proxy variables). Other variables will also be considered in the meta-regression models if the data permits (see predictors-section).
5. We plan the following sensitivity analyses for the primary outcome, i.e., a) exclusion of open studies, and b) exclusion of studies with an overall high risk of bias.
6. Small-study effects will be examined for the primary outcome using contour-enhanced funnel plot if more than 10 studies are available for a pairwise comparison, and fitting a meta-regression model by including study precision as a covariate. Data availability bias will be examined by comparing studies available in Vivli or not using their aggregated data, which should already be available from our previous meta-analyses (2, 6).
7. We will assess confidence in the evidence on sex-specific treatment effects using the Confidence in Network Meta-Analysis (CINeMA) framework (8) for overall symptoms, dropouts due to any reason, sedation, weight gain, prolactin elevation, QTc prolongation, akathisia, extrapyramidal side effects, and anticholinergic side effects.

Software Used:

RStudio

Project Timeline:

Start of project: The study will start immediately after the data is available, and the funding agency approves the project.

The actual state of the project: it is planned to finish data extraction and start data analysis by 11/2024. The manuscript will be made and submitted in six months (6/2025). The publication is planned for the following six months(12/2025).

Dissemination Plan:

The anticipated product is a publication in a peer-reviewed scientific journal in the field of psychiatry (target audience are clinicians and researchers in psychiatry) with a high impact factor such as "The Lancet Psychiatry", "The American Journal of Psychiatry", or "JAMA Psychiatry". Several previous systematic reviews of our group have been published in those major journals with wide visibility. It can be expected that our findings will be rapidly implemented in national and international treatment guidelines.

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