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How did you learn about the YODA Project?: Colleague

Conflict of Interest

https://yoda.yale.edu/system/files/funding_prof._leucht.pdf
https://yoda.yale.edu/system/files/funding_johannes_schneiderthoma.pdf
https://yoda.yale.edu/system/files/funding_angelika_kapfhammer_0.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

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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. NCT00645099 - R076477SCH3020 - A Prospective Randomized Open-label 6-Month Head-To-Head Trial to Compare Metabolic Effects of Paliperidone ER and Olanzapine in Subjects With 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. 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
5. NCT00210717 - R092670PSY3002 - 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
6. NCT00216476 - RISSCH3001 - CONSTATRE: Risperdal® Consta® Trial of Relapse Prevention and Effectiveness
7. NCT01529515 - R092670PSY3012 - A Randomized, Multicenter, Double-Blind, Relapse Prevention Study of Paliperidone Palmitate 3 Month Formulation for the Treatment of Subjects With Schizophrenia
8. NCT01193153 - R092670SCA3004 - A Randomized, Double-Blind, Placebo-Controlled, Parellel-Group Study of Paliperidone Palmitate Evaluating Time to Relapse in Subjects With Schizoaffective Disorder
9. 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
10. 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
11. 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
12. NCT00236457 - RIS-INT-62 - Randomized, Multi-center, Open Label Trial Comparing Risperidone Depot (Microspheres) and Olanzapine Tablets in Patients With Schizophrenia or Schizoaffective Disorder
13. NCT00299702 - RISSCH4060 - 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

What type of data are you looking for?: Full CSR

Research Proposal

Project Title

Metabolic side effects of antipsychotic drugs during medium- to long-term treatment in schizophrenia: Systematic review and network meta-analysis

Narrative Summary:

Antipsychotic drugs differ little in efficacy but in the occurrence of side effects. Beside extrapyramidal motor disorders and prolactin increase, metabolic disorders are the most important side effects: Weight gain and changes in lipid and glucose metabolism increase cardiovascular risk and can lead to severe somatic diseases (e.g. diabetes, stroke and myocardial infarction). To date a comprehensive comparison of the metabolic side effects of the antipsychotic drugs during medium- to long-term treatment of individuals with schizophrenia is still missing. We will conduct a systematic review and network meta-analysis to fill this gap.

Scientific Abstract:

Background: Antipsychotic drugs are the mainstay for the treatment of schizophrenia. Important known side effects are weight gain and disturbances in lipid and glucose metabolism (metabolic side effects). To date a comprehensive comparison of the propensity of the different antipsychotic drugs to cause metabolic side effects is still missing.
Objective: To estimate to which degree antipsychotic drugs differ in metabolic side effects during medium- to long-term treatment of individuals with schizophrenia.
Study Design: Systematic review and network meta-analysis
Participants: Individuals with a diagnosis of schizophrenia or related disorders who participated in randomized controlled trials which compared antipsychotic drugs head-to-head or versus placebo without restrictions in terms of age, gender, ethnicity or setting.
Main Outcome Measures: Parameters describing weight gain and changes in the glucose and lipid metabolism.
Statistical Analysis: Network meta-analysis of mean differences (MD) for continous outcomes and odds ratio (OR) for dichotomous outcomes.

Please find attached the PROSPERO protocol for further information.

Brief Project Background and Statement of Project Significance:

Standardized mortality ratios (SMRs) show a significantly higher all-cause mortality of individuals with schizophrenia compared to the general population [1], and the life-span of people with schizophrenia has been estimated to be 14.5 years shorter [2]. Approximately 40% of the excess mortality is explained by suicides (and accidents). The remaining 60% are due to a variety of natural causes [3]. Particularly metabolic side effects of antipsychotics are thought to increase natural-cause-mortality because they are associated with increased cardiovascular mortality and morbidity [4,5,6].
Moreover, metabolic side effects, and weight gain in particular, reduce patients' quality of life and lead to drug-non-adherence [7]. Drug-non-adherence often results in poor treatment outcome and psychotic relapse, thus leading to further hospitalisations and adding to the loss of productivity.
We will conduct a systematic review and network meta-analysis of randomized controlled trials to summarize the existing evidence of differences between antipsychotic drugs in metabolic side effects. These findings could help physicians and patients to choose the best drug for the individual.

Please find attached the PROSPERO protocol for further information.

Specific Aims of the Project:

The aim of this project is to examine the differences of antipsychotic drugs in propensity to cause metabolic side effects (weight gain and changes in the lipid and glucose metabolism) in the medium- to long-term treatment of individuals with schizophrenia.

Main hypothesis: Antipsychotic drugs differ in their propensities to cause metabolic side effects.

Subgroup analysis will explore effects of baseline metabolic parameters, age, sex, ethnicity, life-time exposure to antipsychotics (if not available duration of illness will be used as a proxy), antipsychotic dose, pharmaceutical sponsorship, study duration.

Please find attached the PROSPERO protocol for further information.

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

Research Methods

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

Search strategy: We ran a search in the Cochrane Schizophrenia Group's Study-Based Register of Trials with no

date/time, language, document type, and publication status limitations [8-11]. This register is compiled inter alia of regular searches in multiple electronic databases (including MEDLINE, Embase, PsycINFO, PubMed, ClinicalTrials.gov). Additionally, we will contact pharma companies for missing relevant data.

Included antipsychotic drugs are Amisulpride, Aripiprazole, Asenapine, Benperidol, Brexpiprazole, Cariprazine, Chlorpromazine, Clopenthixol, Clozapine, Flupentixol, Fluphenazine, Fluspirilene, Haloperidol, Iloperidone, Levomepromazine, Loxapine, Lumateperone, Lurasidone, Molindone, Olanzapine, Paliperidone, Penfluridol, Perazine, Perphenazine, Pimozide, Quetiapine, Risperidone, Sertindole, Sulpiride, Thioridazine, Tiotixene, Trifluoperazine, Ziprasidone, Zotepine, Zuclopenthixol.

Inclusion criteria:
Individuals with a diagnosis of schizophrenia or related disorders who participated in randomized controlled trials which compared antipsychotic drugs head-to-head or versus placebo.

Please find attached the PROSPERO protocol for further information.

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

The main outcome measure is the continuous measure of body weight.
The effect size measure will be mean differences (MD) and its 95% credibility intervals (CrIs). We will prefer change data over endpoint data. Estimates based on imputation methods to handle missing data (used by the original authors) will be preferred over completers' data. Imputed data based on mixed-models of repeated measurement (MMRM) will be preferred over last-observation carried forward (LOCF), if available. We will estimate missing standard deviations (SDs) as described in the Cochrane Handbook [12].

Please find attached the PROSPERO protocol for further information.

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

We expect the different antipsychotic drugs to be the main predictor.
Other potential predictors (baseline metabolic parameters, age, gender, ethnicity, life-time exposure to antipsychotics, antipsychotic dose, pharmaceutical sponsorship and study duration) will be adressed in subgroup analyses.

Please find attached the PROSPERO protocol for further information.

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

We plan to analyse for each domain the parameter with the most data available:
1.Glucose metabolism: Continuous measures of fastening glucose, HbA1c, HOMA-IR and insulin. Dichotomous measures of number of patients with impaired fastening glucose and increased HbA1c.
2.Disturbances in total cholesterol metabolism: Continuous measures of total cholesterol. Dichotomous measures of number of patients with hypercholesterinemia.
3.Disturbances in LDL cholesterol metabolism: Continuous measures of LDL cholesterol. Dichotomous measures of number of patients with increased LDL cholesterol.
4.Disturbances in HDL cholesterol metabolism: Continuous measures of HDL cholesterol. Dichotomous measures of number of patients with reduced HDL cholesterol.
5.Disturbances in triglyceride metabolism: Continuous measures of triglycerides. Dichotomous measures of number of patients with hypertriglyceridemia.

Addtitionally we will extract BMI, waist circumference, and number of patients overweight, obese, and with clinically significant weight gain.

Please find attached the PROSPERO protocol for further information.

Statistical Analysis Plan:

Primarily, we will perform random effects network meta-analysis fitted in a Bayesian environment in JAGS. A

common heterogeneity parameter will be used in the model.
We will estimate the probability for the ranking of each intervention using SUCRA (surface under the cumulative ranking curve) [13].
We will assess transitivity of the network first epidemiologically by comparing the distribution of potential effect modifiers across studies grouped by comparison. Potential effect modifiers are listed under “Main Predictor" above. Statistical evaluation of the transitivity (consistency) will be performed using the design-by-treatment test [14], and the SIDE (Separating Indirect from Direct Evidence) approach [15]. In case of significant inconsistency, we will investigate possible sources of it (mistakes in data entry, clear differences in study characteristics). Small or moderate amounts of inconsistency will be further explored by subgroup analyses of the potential effect modifiers.

We will explore the association between study size and effect size with a comparison-adjusted funnel plot and a contour enhanced funnel plot of all active drugs versus placebo (assuming that at least 10 studies are available per outcome). Any asymmetry observed can be attributed to systematic differences between small and large studies, true heterogeneity or publication bias.
We will evaluate the confidence in estimates of the primary outcome with the framework Confidence in Network Meta-Analysis (CINeMA) [16].

If the requirements of network meta-analysis are not met (low likelihood of transitivity and/or large unexplained inconsistency) we will use pairwise meta-analysis for data synthesis. We will perform frequentist pairwise meta-analysis in R using the package “meta”. Heterogeneity will be investigated by visual inspection of forest plots, by estimating the between studies variance tau^2 and with the I^2 statistic.

Please find attached the PROSPERO protocol for further information.
Software Used:
I am not analyzing participant-level data / I will not be using these software for analyses in the secure platform
Project Timeline:

Start of project: 10/2019
First contact of data holders: 11/2020
Actual state of the project: Identification of included RCTs from literature search and data extraction.

It is planned to finish data extraction and to start data analysis by 06/2021.

First data presentations and publications are planned for the following months.

According to the framework of our grant, there is a deadline for data presentation in 11/2021.

Dissemination Plan:

Findings of this systematic review will be published in peer-reviewed scientific journals (such as Lancet Psychiatry, JAMA Psychiatry, Schizophrenia Bulletin or Schizophrenia Research) and it is likely that they will contribute to treatment guidelines.

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Supplementary Material:

https://yoda.yale.edu/sites/default/files/prospero.pdf
https://yoda.yale.edu/sites/default/files/not_listed_studies_that_we_would_like_to_include_in_our_request.pdf