Metabolic side effects of antipsychotic drugs in individuals with schizophrenia during medium- to long-term treatment: A systematic review and network meta-analysis of randomized controlled trials

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To enable PROSPERO to focus on COVID-19 registrations during the 2020 pandemic, this registration record was automatically published exactly as submitted. The PROSPERO team has not checked eligibility.

Citation

Review question
How do antipsychotic drugs differ in their propensity to cause metabolic side effects, i.e. weight gain and disturbances in lipid and glucose metabolism in individuals with schizophrenia during medium- to long-term treatment?

Searches
The search strategy will be developed by Farhad Shokraneh, information specialist of the Cochrane Schizophrenia Group, Nottingham, UK.

1. Electronic databases:
We will search the Cochrane Schizophrenia Group’s Study-Based Register of Trials with no date/time, language, document type, and publication status limitations. The only exception is exclusion of trials from mainland China because of serious quality concerns (Woodhead 2016; Tong et al. 2018; Parry 2017). This register is compiled of regular searches in multiple electronic databases. The broad search strategy will combine terms for the various antipsychotics, schizophrenia and randomization. Details of the search strategy can be found in the attachment.

2. Hand searching:
The Cochrane Schizophrenia Group’s Study-Based Register of Trials also includes hand searches. We will additionally check the included studies in the previously published relevant systematic reviews.

3. Contacting the researchers/drug companies:
We will contact via email the corresponding authors and the responsible drug companies of each included study published in the last 20 years for missing information about their studies.

Search strategy
Types of study to be included
We will include only randomized trials (RCTs) in which participants received either a placebo or an antipsychotic (i.e. placebo-controlled trials and head-to-head comparisons of drugs). Studies whose sequence generation for randomization was at high risk of bias (e.g. randomization by day of the week) will be excluded. We will accept open and blinded RCTs, but open and single-blind RCTs will be excluded in a sensitivity analysis. The minimum duration of studies will be more than 3 months. In the case of cross-over studies we will use only the first cross-over phase in order to avoid the problem of carry-over effects which are very likely in schizophrenia (Elbourne et al. 2002). We will exclude cluster randomized trials due to the unit-of-analysis-problems associated with this design.

Condition or domain being studied
Schizophrenia.

Participants/population
We will include trials in people with schizophrenia or related disorders (such as schizophreniform or schizoaffective disorders). There is no clear evidence that the latter schizophrenia-like psychoses are caused by fundamentally different disease processes or require different treatment approaches. We will include trials irrespective of the diagnostic criteria used. Here we follow the strategy of the Cochrane Schizophrenia Group to include not only studies that used specific diagnostic criteria such as ICD-10 or DSM-IV, because these criteria are not meticulously used in clinical routine either. There will be no restrictions in terms of gender, ethnicity, age, or setting. Also, we will include patients irrespective of the stage of the disease (acute episode; maintenance phase) because occurrence of side effects can be considered largely independent of psychopathology at study start.

Intervention(s), exposure(s)
We will include a broad collection of antipsychotic drugs, comprising all newer antipsychotics developed in the last decades (formerly called second-generation antipsychotics, SGAs) and the clinically most important older antipsychotics (formerly called first-generation antipsychotics, FGAs) based on a survey of international schizophrenia experts. We will include all compounds in any oral form of administration or as intramuscular depot formulations. If an antipsychotic is available in both, oral and depot form, both formulations will be used as separate interventions in the network. Only short-acting intramuscular antipsychotics will be excluded because these are exclusively used in emergency situations nowadays. In fixed-dose studies we will only include target to maximum doses according to the International Consensus Study on Antipsychotic Dosing (Gardner et al. 2010). All flexible-dose treatment regimens will be included, because these allow the investigators to titrate to the adequate dose for the individual patient.

Comparator(s)/control
In network meta-analysis there is no formal comparator as all antipsychotic drugs and placebo will be compared with each other. However, we will use placebo as comparator for presentation of the results.

Main outcome(s)
The primary outcome will be the continuous measure of body weight.

We will extract also all other outcomes related to body weight namely continuous measures of body mass index (BMI) and waist circumference, and dichotomous measures such as number of patients overweight, obese, with clinically significant weight gain, and increased waist circumference. We plan to analyse these parameters only when sufficient data is available.

* Measures of effect
For continuous outcomes, we will use 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 (Higgins et al. 2019, chapter 6.5.2). For dichotomous outcomes we will use odds ratio (OR) and its 95% credibility intervals (CrIs). Estimates based on imputation methods (used by the original authors) will be preferred over crude numbers of patients with the event. In case of crude numbers of patients with the event (the typical reporting of side effects) we will prefer data of all patients randomized (whether they completed or not) over data of patients who completed the trial.

Additional outcome(s)
Because reporting of metabolic side effects is not standardized in trials of schizophrenia, we will extract different parameters for the other domains of the metabolic syndrome and plan to analyse for each domain the parameter with the most data available:

1. Glucose metabolism:
   Continuous measures of fastening glucose, glycated hemoglobin (HbA1c), homeostatic model assessment of insulin resistance (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 low density lipoprotein (LDL) cholesterol metabolism:
   Continuous measures of LDL cholesterol.
   Dichotomous measures of number of patients with increased LDL cholesterol.

4. Disturbances in high density lipoprotein (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.

The pathological thresholds of these parameters (relevant for the dichotomous outcome measures) will be used as defined by the original study authors. Different units will be transformed to each other.

Timing of outcome measurement:
We will analyse the outcomes at more than 3 months, which is medium/long-term according to the Cochrane Schizophrenia Group.

* Measures of effect
See above 24. Main outcome(s), Measures of effect.

Data extraction (selection and coding)
1. Selection of trials: Two reviewers will independently inspect all abstracts identified in the literature searches. Disagreement will be resolved by discussion, and where doubt remains, we will acquire the full article for further inspection. Once the full articles are obtained, at least two reviewers will independently decide whether the studies meet the review criteria. If disagreement cannot be clarified by discussion, we will resolve it with a third reviewer or seek further information from the study authors.
2. Data extraction: At least two reviewers will independently extract data from all selected trials on
We a priori plan the following sensitivity analyses of the primary outcome:

2. Sensitivity analyses: their effects can be subject to aggregation bias.

We are aware that subgroup/meta-regression analyses are observational by nature and therefore consider the results to be exploratory and not explanatory, in particular for patient-level covariates (as their effects can be subject to aggregation bias).

1. Subgroup or meta-regression analyses:
We a priori plan to address the following potential treatment effect moderators in subgroup/meta-regression analyses of the primary outcome:
   a) Baseline weight;
   b) Age;
   c) Sex (percentage women);
   d) Ethnicity;
   e) Life-time exposure to antipsychotics (if not available duration of illness will be used as a proxy);
   f) Antipsychotic dose;
   g) Pharmaceutical sponsorship;
   h) Study duration.
We are aware that subgroup/meta-regression analyses are observational by nature and therefore consider the results to be exploratory and not explanatory, in particular for patient-level covariates (as their effects can be subject to aggregation bias).

2. Sensitivity analyses:
We a priori plan the following sensitivity analyses of the primary outcome:

Risk of bias (quality) assessment
Again working independently, two reviewers will assess risk of bias using the Cochrane Risk of bias tool II.

Strategy for data synthesis
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).

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 “Analysis of subgroups or subsets” below. Statistical evaluation of the transitivity (consistency) will be performed using the design-by-treatment test, and the SIDE (Separating Indirect from Direct Evidence) approach. 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 network meta-regression and subgroup analyses.

We will explore the association between study size and effect size with a comparison-adjusted funnel plot and for 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).

If the requirements of network meta-analysis are not met (low likelihood of transitivity and/or large unexplained inconsistency) we will use frequentist 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.

Analysis of subgroups or subsets
For the primary outcome (if enough studies per comparison are available) we will explore the role of the following variables:

1. Subgroup or meta-regression analyses:
   a) Baseline weight;
   b) Age;
   c) Sex (percentage women);
   d) Ethnicity;
   e) Life-time exposure to antipsychotics (if not available duration of illness will be used as a proxy);
   f) Antipsychotic dose;
   g) Pharmaceutical sponsorship;
   h) Study duration.
We are aware that subgroup/meta-regression analyses are observational by nature and therefore consider the results to be exploratory and not explanatory, in particular for patient-level covariates (as their effects can be subject to aggregation bias).

2. Sensitivity analyses:
We a priori plan the following sensitivity analyses of the primary outcome:
a) Exclusion of non-double-blind studies (open and single-blind studies);
b) Analysis of only data of observed cases;
c) Exclusion of studies that did not use operationalized criteria to diagnose schizophrenia;
d) Exclusion of studies with an overall assessment of high risk of bias;
e) Exclusion of studies in patients with minimal prior exposure to antipsychotics, in particular trials in first-episode patients and most studies in children;
f) Exclusion of enriched design studies. In enriched design studies, patients are first stabilized on one compound and then randomized to either staying on the same compound or to switching to another compound.

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**Conflicts of interest**
In the last 3 years, Stefan Leucht has received honoraria as a consultant/advisor and/or for lectures from LB Pharma, Otsuka, Lundbeck, Boehringer Ingelheim, LTS Lohmann, Janssen, Johnson&Johnson, TEVA, MSD, Sandoz, SanofiAventis, Angelini, Recordati, Sunovion, Geodon Richter.

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The record owner confirms that they will update the status of the review when it is completed and will add publication details in due course.

Versions

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