








BMJ Open Efficacy of clozapine compared with other second-generation antipsychotic drugs in patients with treatment-resistant schizophrenia: protocol for a systematic review and individual patient data meta-analysis of randomised controlled trials

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ABSTRACT

Introduction Guidelines recommend clozapine for treatment-resistant schizophrenia. However, meta-analysis of aggregate data (AD) did not demonstrate higher efficacy of clozapine compared with other second-generation antipsychotics but found substantial heterogeneity between trials and variation between participants in treatment effects. Therefore, we will conduct an individual participant data (IPD) meta-analysis to estimate the efficacy of clozapine compared with other second-generation antipsychotics while accounting for potentially important effect modifiers.

Methods and analysis In a systematic review, two reviewers will independently search Cochrane Schizophrenia Group's trial register (without restrictions in date, language or state of publication) and related reviews. We will include randomised controlled trials (RCTs) in participants with treatment-resistant schizophrenia comparing clozapine with other second-generation antipsychotics for at least 6 weeks. We will apply no restrictions in age, gender, origin, ethnicity or setting, but exclude open-label studies, studies from China, experimental studies and phase II of cross-over trials. IPD will be requested from trial authors and cross-check against published results. AD will be extracted in duplicate. Risk of bias will be assessed using Cochrane's Risk of Bias 2 tool.

The primary outcome will be overall symptoms of schizophrenia.

We will synthesise results using random-effects meta-analysis and meta-regression methods in a 3-level Bayesian model. The model combines IPD with AD when IPD is not available for all studies, and include participant, intervention and study design characteristics as potential effect modifiers. The effect size measures will be mean difference (or standardised mean difference when different scales were used). Confidence in the evidence will be assessed using GRADE.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ To our knowledge, this is the first meta-analysis of the efficacy of clozapine compared with other antipsychotics based on individual patient data (IPD). The use of IPD is a strength of the review because it allows more fine-grained analyses of moderators of treatment effects.
- ⇒ The resulting review may be limited because IPD may not be available for all studies (eg, because data sets were deleted or because study authors might not be reached). In this case, we combine IPD and aggregate data (of studies for which no IPD is available) in a hierarchical model.
- ⇒ As a further possible limitation, not all potentially clinically relevant moderators may be available to be included in the analysis (eg, because they have not been measured in the original studies).
- ⇒ Premature study discontinuation of participants is a known limitation of randomised controlled trials (RCTs) in schizophrenia and therefore also in meta-analysis of these RCTs. IPD will allow to impute missing observations and thus mitigate this problem to a certain extent.
- ⇒ Moreover, our review may be limited because criteria to diagnose schizophrenia and to define treatment resistance may vary between the original RCTs. Primarily, we will include all RCTs, but heterogeneity introduced thereby will be investigated in additional analyses.

Ethics and dissemination This project has been approved by the ethics commission of the Technical University of Munich (#612/21 S-NP). The results will be published open-access in a peer-review journal and a plain-language version of the results will be disseminated.

If we need to amend this protocol, we will describe the change and give the rationale in a specific section in the resulting publication 'Changes with respect to the protocol'.

Systematic review registration PROSPERO (#CRD42021254986)

INTRODUCTION

Schizophrenia is a frequent and serious mental disorder¹ characterised by delusions, hallucinations, cognitive impairments and loss of emotions.² The main treatment is antipsychotic drugs,³ but up to one-third of individuals afflicted do not respond adequately to antipsychotics and are treatment resistant.⁴ Clozapine is considered to be more efficacious than other antipsychotics for treatment-resistant schizophrenia and thus recommended by clinical guidelines.^{3,5,6}

However, in previous meta-analyses on this topic,^{7–10} clozapine was mainly superior to the first-generation antipsychotics haloperidol and chlorpromazine. Superiority to other second generation was not demonstrated as the overall effect was mostly around no difference (in network meta-analysis) or even in favour of the other second-generation antipsychotics (in pairwise meta-analysis), although with uncertainty in any case. Particularly, it needs to be noted that there was substantial heterogeneity between trials of the same comparison (with mean estimates in favour of clozapine in some studies and in favour of other SGAs in other studies) and high variation in the effects between participants (reflected by wide 95% CIs in the results of individual studies). This indicates that there are factors modifying the treatment effects, which are possibly related to differences between patients (eg, illness severity, chronicity) and treatment regimens (eg, type, dose, duration). A recent analysis of the variability of effects¹¹ observed a numerical increase in variation with clozapine compared with other first-generation and second-generation antipsychotics in patients with treatment-resistant schizophrenia (which could in principle indicate a subgroup of patients specifically responsive to clozapine) but with very high uncertainty which prevented firm conclusions. Consequently, it is currently unclear whether clozapine can be superior to other second-generation antipsychotics for treatment-resistant schizophrenia and if yes, under which circumstances—a question of high clinical relevance because other antipsychotics have more benign side effect profiles than clozapine.¹²

Of note, the existing meta-analyses are based on aggregate data, that is, summary results for each study group. Data for each individual patient (IPD) allow to incorporate patient and treatment characteristics on the participant level (such as the individual illness severity or the drug dosage used by the individual patient). This can increase statistical power and allows more fine-grained analyses of moderators of treatment effects.

Therefore, summarised following the PICO(S) scheme, we will conduct a systematic review with individual patient data meta-analysis of randomised controlled trials (Study design) to investigate how patient and treatment characteristics modify the efficacy to reduce psychotic symptoms after treatment over 6–8 weeks (Outcome) of clozapine

(Intervention) compared with other second-generation antipsychotics (Comparator) in individuals with treatment-resistant schizophrenia (Population).

The use of IPD to provide more precise and individualised estimates, the update of the existing reviews from 2016 or older using newer standards (eg, in terms of risk of bias), and the importance of the review question which can impact on clinicians prescribing practices and clinical guidelines (which are currently based on imprecise evidence) justify the conduct of the review.^{13,14}

METHODS AND ANALYSIS

This review is registered with PROSPERO (https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=254986). We report this protocol according to the Preferred Reporting Items for Systematic review and Meta-analysis protocols (PRISMA-P) 2015 statement¹³ (checklist in online supplemental appendix 1). We will conduct IPD meta-analysis following the statistical recommendations for conduct and planning of IPD meta-analysis examining interactions between treatment effect and participant-level covariates by Riley *et al.*¹⁵

Criteria for considering studies for this review

Study designs

We will only include blinded (at least single-blind) randomised controlled trials (RCTs). We will exclude non-randomised studies, quasi-randomised studies and open-label studies. Moreover, we will exclude trials with an experimental focus and design component, like neuroimaging, trials from mainland China (due to serious quality concerns which are difficult to rule out^{16,17}) and the second phase of cross-over trials (due to possible carry-over effects).¹⁸

Participants

We will include studies with participants with a treatment-resistant form of schizophrenia, schizophreniform disorder or schizoaffective disorder. Primarily, we will include studies irrespective of the criteria used to diagnose the disorder (because those are not meticulously used in clinical practice either) and the definition of treatment resistance (because a consensus about it has only been reached recently,¹⁹ before the conduct of most relevant studies), but we will address differences in the diagnostic accuracy, as well as differences between diagnoses, in the analytical approach (see methods below and discussion). There will be no restrictions in age, gender or ethnicity of the study participants.

Setting

Studies in inpatients or outpatients are eligible.

Interventions

Eligible studies need to investigate clozapine used as antipsychotic monotherapy, that is, we will exclude clozapine as add-on to other antipsychotics.

Comparators

Comparators will be any other second-generation antipsychotics, in monotherapy, in any form of administration. Second-generation antipsychotic drugs listed by WHO are amisulpride, aripiprazole, asenapine, brexpiprazole, cariprazine, clozapine, iloperidone, lumateperone, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, sertindole, ziprasidone and zotepine.

Outcomes

The *primary outcome* will be overall symptoms of schizophrenia as measured by validated scales such as the Positive and Negative Syndrome Scale (PANSS)²⁰ or the Brief Psychiatric Rating Scale (BPRS).²¹

As additional measures of efficacy, when sufficient data are available from the original studies, we plan to investigate the *secondary outcomes* positive symptoms of schizophrenia, negative symptoms of schizophrenia, clinical global impression of severity and improvement, quality of life and social functioning as measured by rating scales, and the number of participants leaving the study early due to inefficacy and the number of participants experiencing clinical improvement (ie, response), defined as at least a 20% reduction of PANSS/BPRS (which corresponds to 'minimally improved on the clinical global impression of improvement scale'²²; we opt for this threshold because we feel that even minimal improvement can be clinically important in the context of treatment-resistant schizophrenia). For the calculation of PANSS/BPRS percentage reduction from baseline, the minimum score will be subtracted.

Moreover, we plan to investigate the number of participants leaving the study early due to adverse events and due to any reason, respectively. These shall parallel efficacy findings as measures of overall tolerability and acceptability. We do not conduct a comprehensive analysis of side effects because there is less uncertainty in this regard and because it requires a review on its own.

Timing

The time point of outcome measurement will be 6–8 weeks (8 weeks preferred) or the closest time point to it available because this is the typical time frame used in studies investigating efficacy of antipsychotics for psychotic symptoms²³ and differences between antipsychotics have been observed for treatment-resistant schizophrenia at this time point (eg, in the pivotal 6-week study by Kane *et al.*²⁴). Accordingly, only studies with a follow-up of at least 6 weeks will be included.

Search strategy

Electronic searches

We will search the Cochrane Schizophrenia Group's Study-Based Register of Trials—a specialised register for clinical trials of interventions for schizophrenia^{25–28}—without date, language, document type and publication status limitations. Following the methods from Cochrane,²⁹ this register is compiled of monthly searches in multiple

electronic databases of scientific articles (MEDLINE, Embase, Allied and Complementary Medicine, Cumulative Index to Nursing and Allied Health Literature, PsycINFO, PubMed), *clinical trial registries* (US National Institute of Health Ongoing Trials Register (ClinicalTrials.gov), WHO International Clinical Trials Registry Platform (www.who.int/ictrp)), databases for *thesis and dissertations* (ProQuest Dissertations and Theses A&I), Chinese databases (Chinese Biomedical Literature Database, China Knowledge Resource Integrated Database and Wanfang, until the end of 2016) and *hand searches* of conference books and other grey literature. In addition to the comprehensive searches used to compile this register, it has the practical advantages of being pre-selected to contain only records related to studies in schizophrenia (ie, it does not contain clearly irrelevant references) and of being study based (meaning that multiple references belonging to the same study are tagged).

The strategy to search Cochrane Schizophrenia Group's register, developed by Farhad Shokrane, ^{25–28} the former information specialist of the Cochrane Schizophrenia Group, Nottingham, UK, will be broad and include the names of all second-generation antipsychotics specified above in 'Interventions' and 'Comparators', as well as the names of several first-generation antipsychotics. The reason to include these first-generation antipsychotics in the search strategy is that we will use this broad search for different projects of our group, some of which address also first-generation antipsychotics. Studies with first-generation antipsychotics are, however, not relevant for this review and will be excluded during screening. Specifically, the information specialist will search in the Intervention Field of STUDYfor (*Amisulpride* OR *Aripiprazole* OR *Asenapine* OR *Benperidol* OR *Brexipiprazole* OR *Cariprazine* OR *Chlorpromazine* OR *Clopenthixol* OR *Clozapine* OR *Flupentixol* OR *Fluphenazine* OR *Fluspirilene* OR *Haloperidol* OR *Iloperidone* OR *Levomepromazine* OR *Loxapine* OR *Lumateperone* OR *Lurasidone* OR *Molindone* OR *Olanzapine* OR *Paliperidone* OR *Penfluridol* OR *Perazine* OR *Perphenazine* OR *Pimozide* OR *Quetiapine* OR *Risperidone* OR *Sertindole* OR *Sulpiride* OR *Thioridazine* OR *Tiotixene* OR *Trifluoperazine* OR *Ziprasidone* OR *Zotepine* OR *Zucloperthixol*).

The specific search strategies for the multiple databases used to compile the register are provided in online supplemental appendix 2.

During the conduct of the review, we will update the literature search by searching updated versions of the Cochrane Schizophrenia Group's register and when eventually the last months before submission of the resulting publication are not covered by a search in PubMed.

Reference lists and other sources

Moreover, we will search previous reviews on clozapine for treatment-resistant schizophrenia or comparing clozapine with second-generation antipsychotics^{7–9} as well

as all articles citing these reviews (using Google Scholar for citation index).

In case of articles published in languages other than English, we will reach out to our international network of researchers (mainly systematic reviewers and trial-list in the field of psychiatry and thus familiar with the topic) and the network of the Cochrane Schizophrenia Group for help with data extraction or seek professional translation.

Identification and selection of studies

Two reviewers will independently inspect titles, abstracts and, if needed, full publications of references identified in the literature search to decide whether the studies match the eligibility criteria. In case of disagreement, a decision will be reached by discussion, by consulting a third reviewer or by contacting study authors for clarification.

The selection process will be managed using the reference software Citavi (Swiss Academic Software, Zurich, Switzerland).

Data extraction

We will contact the investigators and the sponsoring pharmaceutical industries of eligible trials and request de-identified individual patient data (IPD). In addition, we will request IPD from data-sharing portals (such as vivli.org or yoda.yale.edu). We will convert IPD received in different formats (different files, structures and outcome names) to a common format using 'R'³⁰ (particularly the packages 'haven'³¹ and 'tidyverse'³²).

When IPD is not obtained, two reviewers will extract independently aggregate data (AD) from the references identified in the literature search. AD will be managed in a Microsoft Access database with specifically customised data-entry forms (see online supplemental appendix 3) and an algorithm to check for differences between independent extractions. Emerging differences will be solved by discussion (among the extracting reviewers or with a third reviewer) or by seeking clarification from original authors.

Data extraction for analysis from IPD and AD will start after submission of the protocol.

IPD integrity

IPD integrity of each study will be evaluated, including checking for missing data, duplicates, extreme outliers or unusual values. Moreover, we will cross-check the IPD used for analysis against the summary statistics from the published reports. Therefore, we will recalculate the summary statistics from the IPD. Moreover, we will examine the pattern of group allocation over time and the distribution of baseline characteristics between groups which will then be used for the assessment of risk of bias arising from the randomisation process (see below).

Data items

From IPD and AD we will seek information on

- ▶ Criteria used to diagnose schizophrenia and related disorders.
- ▶ Diagnoses of participants (in terms of schizophrenia and related disorders and psychiatric comorbidities).
- ▶ Definition of treatment resistance.
- ▶ Sponsorship.
- ▶ Number of participants.
- ▶ Age.
- ▶ Gender.
- ▶ Weight.
- ▶ Smoking status.
- ▶ Current use of illicit drugs.
- ▶ History of substance abuse.
- ▶ Duration of illness.
- ▶ Duration of current episode.
- ▶ Number of previous episodes.
- ▶ Number of previous hospitalisations.
- ▶ Previous antipsychotic medications.
- ▶ Type (compound, administration) and dose of antipsychotic use in the study.
- ▶ Plasma level of antipsychotic used in the study.
- ▶ Outcomes (see above) together with the time point of outcome measurement and the baseline value of the scales used.

For the primary outcome 'overall symptoms of schizophrenia', we will transform BPRS values to PANSS results by a validated method of equipercenile linking.³³ If other scales apart from PANSS and BPRS were used, results will be standardised into z-scores, similar to other IPD meta-analyses.³⁴ This method will also be used in other outcomes when data from different scales are available, and a more appropriate method is not stated.

For the secondary outcomes 'positive symptoms' and 'negative symptoms', no such linking method exists. Moreover, there are different ways to construct positive and negative subscores in PANSS and BPRS. Therefore, in order to use the same outcome measures across trials, in IPD, positive and negative subscores will be expressed as BPRS subscores (BPRS items 4, 11, 12 and 15 for positive and 3, 13 and 16 for negative subscore) for which all required items are available even when a patient was assessed by PANSS (PANSS items 2, 3, 6 and 23 for positive and 8, 9 and 21 for negative subscore).³⁵

Risk-of-bias assessment

Two independent reviewers will evaluate risk of bias of individual studies using the Cochrane Risk of Bias 2 tool.³⁶ This tool assessed the risk of bias on the outcome level for biases 1) arising from the randomisation process, 2) due to deviations from intended interventions, 3) due to missing outcome data, 4) in the measurement of the outcome and 5) in the selection of reported results with the judgement options 'High risk', 'Some concerns' and 'Low risk'. The assessment will be performed independently by two reviewers with experience in systematic reviews and with this tool, but not blinded to the studies (which is practically almost impossible). Disagreements between reviewers will be solved by discussion, if needed

involving a third even more experienced reviewer (but no specific evaluation of inter-rater agreement is planned for the expected small sample of studies). Studies with inadequate randomisation (which we will additionally examine using IPD; see 'IPD integrity' above) will be excluded from the review, as well as open-label studies which may have a high risk of deviations from the intended interventions and in the measurement of the outcome. Moreover, studies with an overall judgement of high risk of bias will be excluded in sensitivity analysis.

Data analysis

Synthesis

We will conduct Bayesian IPD meta-analysis. The primary outcome as well as the secondary outcomes measured by rating scales (see 'Outcomes' above) will be analysed by a linear regression where the mean difference (MD) will be used to measure the effect size (provided that all results are from the same scale; when the outcome was measured on different scales, the standardised mean difference (SMD) will be used). The secondary outcomes based on number of participants with an event will be analysed by a logistic regression model where the OR will be used to measure the effect size because of its better mathematical properties for statistical modelling as compared with risk ratios (RRs). However, for presentation of results, we will transform ORs to RRs to increase interpretability and prevent misinterpretation of the magnitude of effects.

These regression models will be used to estimate how the treatment effect changes with different participant and treatment characteristics. Potential covariates will be the participant-level characteristics baseline severity, duration of current episode and illness, number of previous episodes and hospitalisations, previous antipsychotics, specific diagnoses, age, sex, weight, antipsychotic dose, smoking status, current or previous substance abuse, plasma level of antipsychotic and duration of follow-up. Because not all clinically relevant characteristics may be available in all studies, we will decide on a final set of covariates based on clinical relevance and availability across studies balancing statistical power and the aim to inform about as much clinically relevant aspects as possible.

We will consider Bayesian and non-Bayesian imputation methods to address missing observations. Considering that with Bayesian models with IPD computation time is an issue, we will choose a pragmatic approach that is feasible and scientifically sound, depending on the amount of missing observations.

The effect sizes and covariate effects will be combined across studies using a Bayesian random-effects meta-analysis model. Minimally informative priors will be assumed for all location parameters (effect sizes and regression coefficients), and for heterogeneity, we will use a half-normal prior on the heterogeneity SD.

When IPD is not obtained for all trials, we will combine IPD and AD studies using the three-level hierarchical model as described by Sutton *et al.*³⁷ The model

separately analyses IPD and AD studies, then their results are combined across studies using standard meta-analysis methods. To assess the impact of including AD studies, we will perform a sensitivity analysis with IPD studies only and compare that with the results from the combined IPD-AD model.

For the primary outcome, we will additionally perform sensitivity analyses by excluding studies that did not use operationalised criteria to diagnose schizophrenia, single-blind studies (ie, studies in which participants knew their assigned treatment, but raters did not) and studies judged at high risk of bias (if substantially different results arise, we will consider this approach for the primary analysis).

Subgroup analyses of the primary outcome will address 1) the definition of treatment resistance applied in the study, 2) sponsoring of pharmaceutical industry, 3) the specific second-generation antipsychotic drugs used as comparator and 4) covariates for which the meta-regression analysis suggests a moderating effect.

We will summarise the estimates of treatment effects and of interaction effects between covariates and treatment effects in forest plots, and we will measure the heterogeneity by estimating the between-study variance in treatment effect (τ^2).

The statistical model will be implemented in 'R'³⁰ by performing Bayesian analyses using self-programmed routines in 'JAGS'.³⁸

Meta-bias(es)/risk of bias across studies

We will present the association between study sample size and treatment effect in funnel plots, which can be an indication of publication bias. Moreover, we will report for which studies IPD was available and compare the meta-analysis estimates based on IPD trials with the estimates from an analysis that combines IPD and AD (if not all trials provide the IPD) (see sensitivity analysis above).

Confidence in cumulative evidence

We will assess the confidence in the cumulative evidence using the Grading of Recommendations Assessment, Development and Evaluation working group (GRADE) methodology.³⁹ This framework considers domains of risk of bias, consistency, directness, precision and publication bias to judge the quality of the evidence for specific outcomes as high, moderate, low or very low. Methods to assess risk of bias, inconsistency (=heterogeneity) and publication bias are described above. Directness will be assessed using the inclusion criteria of the individual trials, particularly the definitions concerning treatment resistance. To assess precision of an estimate, we consider effect sizes larger than SMD 0.1/1 step in CGI-S or CGI-I (or the corresponding MDs) for continuous outcomes and ORs smaller than 0.8 and larger than 1.25 for binary outcomes as appreciable benefit/harm.

Patient and public involvement

This project was recognised as having a high relevance in a meeting that we held with a group of patients and

relatives to identify patient-relevant research questions. They will be also involved as consultants during the process of the project. Particularly, they are involved in identifying patient-relevant outcomes and moderators during the protocol stage (WPH agreed to become a coauthor) and in interpreting the results from a patients' and relatives' perspective. Moreover, they will help to prepare a 'plain-language' version of the results for dissemination to patients, relatives and non-academic audiences.

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