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TABLE OF CONTENTS

HEADER 1
ABSTRACT 1
BACKGROUND 2
OBJECTIVES 3
METHODS 3
ACKNOWLEDGEMENTS 10
REFERENCES 11
HISTORY 14
CONTRIBUTIONS OF AUTHORS 14
DECLARATIONS OF INTEREST 14
SOURCES OF SUPPORT 14

[Intervention Protocol]

Antipsychotic polypharmacy reduction versus polypharmacy continuation for people with schizophrenia

Irene Bighelli[1], Myrto T Samara[1], Alessandro Rodolico[2], Wulf-Peter Hansen[3], Stefan Leucht[4]

[1]Klinik und Poliklinik für Psychiatrie und Psychotherapie, Technische Universität München Klinikum rechts der Isar, München, Germany. [2]Department of Clinical and Experimental Medicine, Psychiatry Unit, University of Catania, Catania, Italy. [3]BASTA - Bündnis für psychisch erkrankte Menschen, München, Germany. [4]Department of Psychiatry and Psychotherapy, School of Medicine, Munich, Germany

Contact address: Stefan Leucht, stefan.leucht@tum.de.

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ABSTRACT

Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

To examine the effects and safety of reducing antipsychotic polypharmacy compared to maintaining people with schizophrenia on the same number of antipsychotics.

To examine factors of reduction of polypharmacy such as the number of antipsychotics that are withdrawn and whether the reduction of polypharmacy was compensated by increasing the dose of the remaining antipsychotics.

BACKGROUND

Antipsychotic drugs are effective for the acute treatment and relapse prevention of schizophrenia (Leucht 2012; Leucht 2013), but they have important adverse effects such as movement disorders and weight gain including associated metabolic problems, which are likely to contribute to a well-documented excess mortality (Hjorthoj 2017). Controversial data suggest that antipsychotics are likely to be associated with brain volume loss in a dose-related manner (Ho 2011). However, in clinical practice, acutely ill patients are frequently treated with high doses or combinations of antipsychotics; this is due to various pressures, such as risk for suicide or aggressive behaviour, lack of hospital beds and cost issues leading to shorter durations of hospitalisation and high rates of non-response (Samara 2016; Samara 2019). For example, one systematic review of 147 studies showed that 20% of people with schizophrenia received several antipsychotics (Gallego 2012), and 10% received doses above the officially approved labels (Patel 2014). Therefore, the critical question the clinician must address is whether high dose and antipsychotic polypharmacy can be carefully reduced while continuing to maintain the relapse prevention benefit once the acute phase of the illness has been treated and the patient is in a maintenance phase. This could include a complete withdrawal of antipsychotics in up to 20% of patients who do not experience a second episode of schizophrenia within five years (Robinson 1999). Evidently, there will always be a difficult trade-off, because if the dose is too low or if the antipsychotic is stopped, there could be a high risk for relapse that can have adverse consequences for patients (Leucht 2013). In the current Cochrane Review, we will summarise all randomised controlled trials (RCTs) that compare reducing antipsychotic polypharmacy with remaining on the same number of antipsychotics. A companion review will address the related question of reducing antipsychotic doses.

Description of the condition

Schizophrenia is a chronic and disabling psychiatric disorder with a lifetime prevalence of approximately 1% of the population worldwide (McGrath 2008; Moreno-Küstner 2018). Onset is usually in early adulthood and the symptoms can be severe (Carpenter 1994). Its typical manifestations are 'positive' symptoms such as fixed, false beliefs (delusions) and perceptions without a stimulus (hallucinations); 'negative' symptoms such as apathy and lack of drive, disorganisation of behaviour and thought; and catatonic symptoms such as mannerisms and bizarre posturing (Carpenter 1994).

It is one of the leading causes worldwide of long-term disability, with devastating impact for patients and their families (GBD 2018). The degree of distress and impairment is considerable; employment rates vary between 4.5% and 50% (Bouwmans 2015), and lifetime suicide prevalence is estimated around 4% to 10%, with rates that are highest among males in the early course of the disorder (Palmer 2005; Popovic 2014; Tanskanen 2018). Quality of life for people with schizophrenia can be poor and it is likely to deteriorate during the course of the disease; overall lifespan is described to be about 15 years shorter than average (Hjorthoj 2017).

The course of the illness can be divided into three stages. In the onset or prodromal phase, initial changes such as subtle modifications in the person's behaviour, feelings and cognition can occur, which then develop into clear psychotic symptoms during the acute phase. The acute episode, frequently treated with high doses of antipsychotics, is followed by a remission phase, in which the florid symptoms recede (Andreasen 2005); however, in this phase most individuals will still require maintenance treatment to prevent relapses (Leucht 2012). Remission is a necessary, but not sufficient, step towards recovery that is intended as "the ability to function in the community, socially and vocationally, as well as being relatively free of disease-related psychopathology" (Andreasen 2005).

Description of the intervention

Antipsychotic medication is the current mainstay of treatment in schizophrenia. Due to the chronic nature of the disease, long-term treatment with antipsychotics is usually needed to prevent the risk of relapse (Leucht 2012). Unfortunately, these medications have many adverse effects that make their use complicated (Leucht 2013), including movement disorder, weight gain, metabolic problems and sexual dysfunction (Leucht 2013); possible brain volume loss (Ho 2011); and increased risk of mortality (McGrath 2008).

Moreover, there are high rates of non-response, with 40% to 50% of patients taking antipsychotics not reaching even a minimal response (Leucht 2017; Samara 2019), so that often clinicians try to combine several antipsychotics (polypharmacy) to increase efficacy (Gallego 2012). However, the exact rates of non-response are difficult to measure, because of the potential confounding derived from the poor adherence to medication.

One review of 147 studies found an overall prevalence of antipsychotic polypharmacy of approximately 20% (Gallego 2012).

Polypharmacy includes augmentation strategies, combining different antipsychotics because of their difference in targeted receptor sites (e.g. combining clozapine and amisulpride) or combining different antipsychotics in order to minimise adverse effects (e.g. clozapine and aripiprazole) (Hiemke 2018).

The intervention will be the reduction of the number of antipsychotics prescribed to the patient during the maintenance phase. We will define reducing antipsychotic polypharmacy as the process of withdrawing a person with schizophrenia from one or more of their prescribed antipsychotics. Reduction of polypharmacy can also mean that, even if the number of antipsychotics is reduced, this reduction is compensated by increasing the dose of the remaining compounds, so that the overall dose of antipsychotics received by the patient might not change. However, there is a difficult trade-off, because if the overall dose of antipsychotics becomes too low there is a risk for relapse (Leucht 2012).

How the intervention might work

Combinations of antipsychotic drugs can lead to drug–drug interactions resulting in unexpectedly high or low plasma levels, for example by the inhibition or induction of cytochrome P450 enzymes in the liver, which are responsible for the metabolism of most psychotropic drugs (Hiemke 2011). Under these circumstances, the drug–drug interactions of haloperidol and olanzapine need to be monitored (Hiemke 2018).

This is a potentially dangerous situation and, if applied, plasma level monitoring should be performed, but such monitoring is expensive and not available in all settings (Hiemke 2011). Moreover, if two or more antipsychotics are combined, patients may receive overall too high doses. It has been shown, mainly for first-generation antipsychotics, that relatively low doses are needed to achieve at least 65% blockade of dopamine receptors that is thought to be sufficient for antipsychotic efficacy (Kapur 2000).

Reducing polypharmacy by withdrawing one or more antipsychotics should theoretically decrease the problems in terms of drug–drug interactions; it also has the potential to reduce the overall antipsychotic load and the adverse-effect burden for people with schizophrenia (Misawa 2011; Ray 2009; Uchida 2009). Reducing polypharmacy can also increase adherence and reduce treatment costs. However, there are potential harms; the risk is that patients need the drug combinations that they receive or that the overall dose becomes too low after withdrawal of one or several antipsychotics so that people relapse (Leucht 2012). The aim of this review is to examine the evidence and give information on potential benefits and pitfalls of this strategy.

Why it is important to do this review

Antipsychotic drugs are effective for the acute treatment and relapse prevention of schizophrenia (Leucht 2012; Leucht 2013), but they have important adverse effects such as movement disorders and weight gain including associated metabolic problems, which are likely to contribute to a well-documented excess mortality (Hjorthoj 2017). Controversial data suggest that antipsychotics could cause brain volume loss in a dose-related manner (Andreasen 2013; Ho 2011), even if it is difficult to differentiate this volume change from the one that could derive from the illness or other confounding factors such as cannabis use (Van Haren 2013).

Due to various pressures, such as a risk for suicide or aggressive behaviour, but also shorter duration of hospitalisation and high rates of non-response (Samara 2016; Samara 2019), acutely ill patients are frequently treated with combinations of antipsychotics (Gallego 2012). However, guidelines recommend against combining antipsychotics, because this can lead to drug–drug interactions, and because there is limited evidence for the effectiveness of this strategy (Galling 2017). Therefore, can polypharmacy be carefully reduced during the maintenance phase (Essock 2011). This review will systematically summarise data from all relevant RCTs to provide high-quality evidence for the effects reducing antipsychotic polypharmacy compared to maintaining polypharmacy for people with schizophrenia who are stabilised on antipsychotic treatment. The results are also potentially important for guidelines and policy makers given the high rates of disability and thus costs of schizophrenia for society (Vos 2012).

A companion review will address the related question of reducing antipsychotic doses (Bighelli in press).

OBJECTIVES

To examine the effects and safety of reducing antipsychotic polypharmacy compared to maintaining people with schizophrenia on the same number of antipsychotics.

To examine factors of reduction of polypharmacy such as the number of antipsychotics that are withdrawn and whether the reduction of polypharmacy was compensated by increasing the dose of the remaining antipsychotics.

METHODS

Criteria for considering studies for this review

Types of studies

All relevant RCTs. If a trial was described as 'double blind' but randomisation was implied, we will include such trials and examine the effect of their inclusion by excluding them in a sensitivity analysis (see Sensitivity analysis). If their inclusion does not result in a substantive difference, they will remain in the analyses. If their inclusion results in important clinically significant but not necessarily statistically significant differences, we will not add the data from these lower-quality studies to the results of the high-quality trials, but will present such data within a subcategory. We will exclude quasi-RCTs, such as those allocating by alternate days of the week.

Where studies have multiple publications, we will collate the reports of the same study so that each study, rather than each report, is the unit of interest for the review, and such studies have a single identifier with multiple references.

Types of participants

Adults, however defined, with schizophrenia or related disorders, including schizophreniform disorder, schizoaffective disorder and delusional disorder, by any means of diagnosis (irrespectively of the diagnostic criteria used), who are receiving more than one antipsychotic and are stabilised on their current antipsychotic treatment, irrespective of age, gender, race or country. We will accept any definition of stability used in the individual studies. We will exclude studies that compare antipsychotic polypharmacy with monotherapy for acutely ill people with schizophrenia.

We are interested in ensuring that information is relevant to the current care of people with schizophrenia. Therefore, we will highlight the current clinical state clearly (early postacute, partial remission, remission), as well as the stage (first episode, early illness, persistent), and whether the studies primarily focused on people with particular problems (e.g. negative symptoms, treatment-resistant illnesses).

See Subgroup analysis and investigation of heterogeneity.

Types of interventions

1. Antipsychotic polypharmacy reduction

Any reduction in the number of antipsychotics (considering antipsychotics licensed in at least one country) from a starting point of at least two antipsychotics, irrespectively of which combinations patients were originally on, which antipsychotics were withdrawn, how many antipsychotics were withdrawn and how fast the withdrawal was undertaken.

2. Antipsychotic polypharmacy continuation

Continuation of the current number of antipsychotics.

Types of outcome measures

We will divide all outcomes into short term (up to six months), medium term (up to one year, i.e. seven to 12 months) and long term (more than 12 months). Up to one year will be the primary time point of interest.

Primary outcomes

1. Quality of life

1.1. Clinically important change in quality of life

Number of patients with a clinically important change in quality of life, as defined in each study.

2. Service use

2.1. Readmission to hospital

Number of patients that were readmitted to hospital.

3. Adverse effect

3.1. Leaving the study early due to adverse effects – overall tolerability

Number of patients that discontinued their participation from the study due to adverse effects.

Secondary outcomes

1. Quality of life

1.1. Mean endpoint or change score on quality-of-life scale

We will accept any published quality of life scales (e.g. Heinrich-Carpenter Quality of Life Scale, or "Subjective well-being under neuroleptics scale (SWUN)").

2. Service use

2.1. Days in hospital

3. Functioning

3.1. Clinically important change in functioning

Number of participants with a clinically important change in functioning, as defined in each study.

3.2. Mean endpoint or change score on functioning scale

We will accept any published rating scales such as the Global Assessment of Functioning or the Psychosocial Performance Scale.

4. Global state

4.1. Relapse/exacerbations of psychosis

We will accept any definitions of the original authors of each study.

4.2. Mean endpoint or change score on global state scale

We will accept any published rating scale.

5. Leaving the study early

5.1. Due to any reason – overall acceptability

Number of patients that prematurely discontinued due to any reason.

5.2. Due to inefficacy – overall efficacy

Number of patients that prematurely discontinued due to inefficacy.

6. Mental state

6.1. General

6.1.1. Clinically important change in general mental state

Number of patients with a clinically important change - as defined by the individual studies (for example, mental state much improved, or less than 50% reduction on a specified rating scale).

6.1.2. Mean endpoint or change score on general mental state scale

6.2. Specific

6.2.1. Clinically important change in positive symptoms

6.2.2. Mean endpoint or change score on positive symptom scale

We will examine the positive symptoms of schizophrenia according to the positive subscale of the PANSS, the "Scale for Assessment of Positive Symptoms" (SAPS) or any other validated positive symptom scale.

6.2.3. Clinically important change in negative symptoms

6.2.4. Mean endpoint or change score on in negative symptom scale

We will investigate the negative symptoms of schizophrenia according to the negative subscale of the PANSS or the "Scale for the Assessment of Negative Symptoms" (SANS) or any other validated negative symptom scale.

6.2.5. Clinically important change in depressive symptoms

6.2.6. Mean endpoint or change score on depressive symptom scale

We will investigate depressive symptoms according to the Calgary Depression Scale, the Hamilton Depression Scale, the Montgomery Asberg Depression scale or or any other validated depression scales.

7. Behaviour

7.1. Clinically important change in behaviour (including aggression)

7.2. Mean endpoint or change score on behaviour scale

We will accept any published rating scale.

8. Satisfaction with care

8.1. Clinically important change in satisfaction with care

8.2. Mean endpoint or change score on satisfaction with care scale

We will accept any published rating scale.

9. Adverse effect/events

9.1. Effects

9.1.1. At least one adverse effect

9.1.2. Weight gain: clinically important change

9.1.3. Incidence of various specific adverse effects

9.2. Event: mortality

9.2.1. Overall mortality

9.2.2. Due to natural causes

9.2.3. Due to suicide

10. Medication – mean antipsychotic dose at endpoint

We will examine whether reduction of polypharmacy also led to a reduction of antipsychotic doses. We will convert antipsychotic doses to olanzapine equivalents for this procedure (Gardner 2010).

Search methods for identification of studies

We will apply no language restrictions within the search.

Electronic searches

Cochrane Schizophrenia Group's Study-based Register of Trials

The Information Specialist will search the register using the following search strategy:

Polypharmacy in Intervention Field of STUDY

In such a study-based register, searching the major concept retrieves all the synonyms and relevant studies. This is because the studies have already been organised, based on their interventions, and linked to the relevant topics (Shokraneh 2017). This allows rapid and accurate searches that reduce waste in the next steps of systematic reviewing (Shokraneh 2019).

Following Cochrane methods (Lefebvre 2019), the Information Specialist compiles this register from systematic searches of major resources and their monthly updates (unless otherwise specified):

- Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library;
- MEDLINE;
- Embase;
- Allied and Complementary Medicine (AMED);
- BIOSIS;
- Cumulative Index to Nursing and Allied Health Literature (CINAHL);
- PsycINFO;
- PubMed;
- US National Institute of Health Ongoing Trials Register ClinicalTrials.gov;
- World Health Organization International Clinical Trials Registry Platform (www.who.int/ictrp);
- ProQuest Dissertations and Theses A&I and its quarterly update;
- Chinese databases (Chinese Biomedical Literature Database, China Knowledge Resource Integrated Database, and Wanfang) and their annual updates.

The register also includes handsearches and conference proceedings (see Groups' website; schizophrenia.cochrane.org/register-trials). It places no limitations on language, date, document type or publication status.

Searching other resources

1. Reference searching

We will inspect references of all included studies, previous relevant systematic and narrative reviews, and guidelines for further relevant studies.

2. Personal contact

We will contact the first author of each included study with a request for further studies and for missing information on their studies. We will note the outcome of this contact in the 'Characteristics of included studies' or 'Classification of studies awaiting classification' tables. We will contact pharmaceutical companies of second-generation antipsychotics for further studies, if we find in our literature search that at least one has conducted such studies. However, it is unlikely that companies will have conducted such studies.

Data collection and analysis

Selection of studies

After removing duplicates, at least two review authors (of IB, MS and AR) will independently inspect citations from the searches and identify potentially relevant abstracts using Covidence (www.covidence.org/) software that has been produced to improve the quality of the study selection and data extraction process, and remove duplicates. Where disputes arise, we will acquire the full report for more detailed scrutiny. At least two review authors (of IB, MS or AR) will independently obtain and inspect full reports of the abstracts meeting the review criteria. We will resolve disagreements by discussion with another review author (SL). Where it is not possible to resolve disagreement by discussion, we will attempt to contact the authors of the study for clarification. We will list studies excluded at this stage in the 'Characteristics of excluded studies' table.

Data extraction and management

1. Data extraction

Two review authors (of IB, MS or AR) will independently extract data from all included studies. We will discuss any disagreement, eventually with another review author (SL), and, if necessary, we will contact authors of studies through an open-ended request to obtain missing information or for clarification. We will document these final decisions.

We will extract data presented only in graphs and figures, but we will include them only if two review authors independently obtain the same result.

For each included study we will also extract the following Study characteristics, and provide them in 'Characteristics of included studies' tables: Methods (Allocation, Blinding, Duration, Design, Location, Setting), Participants (Diagnosis, N, Gender, Age, History of illness), Interventions (Dose, Administration, Rescue medication), Outcomes, Notes.

2. Management

2.1. Forms

We will extract data using the Covidence Software, after piloting the form with a sample of 5 studies (www.covidence.org/).

2.2. Scale-derived data

We will include continuous data from rating scales only if:

- the psychometric properties of the measuring instrument have been described in a peer-reviewed journal (Marshall 2000); and
- the measuring instrument has not been written or modified by one of the trialists for that particular trial.

2.3. Endpoint versus change data

There are advantages of both endpoint and change data: change data can remove a component of between-person variability from the analysis; however, calculation of change needs two assessments (baseline and endpoint) that can be difficult to obtain in unstable and difficult-to-measure conditions such as schizophrenia. We have decided primarily to use endpoint data, and only use change data if the endpoint data are not available.

2.4. Skewed data

Continuous data on clinical and social outcomes are often not normally distributed. To avoid the pitfall of applying parametric tests to non-parametric data, we will apply the following standards to relevant continuous data before inclusion.

For endpoint data from studies including fewer than 200 participants:

- when a scale starts from the finite number zero, we will subtract the lowest possible value from the mean, and divide this by the standard deviation (SD). If this value is less than one, it strongly suggests that the data are skewed and we will exclude these data and report them in separate tables. If this ratio is greater than one but less than two, there is suggestion that the data are skewed: we will enter these data and test whether their inclusion or exclusion would change the results substantially (Sensitivity analysis). Finally, if the ratio is larger than two, we will include these data, because it is less likely that they are skewed (Altman 1996; Higgins 2021);
- if a scale starts from a positive value (such as the Positive and Negative Syndrome Scale (PANSS), which can have values from 30 to 210 (Kay 1986)), we will modify the calculation described above to take the scale starting point into account. In these cases, skewed data are present if 2 SD > (S − Smin), where S is the mean score and 'Smin' is the minimum score.

Note: we will enter all relevant data from studies of more than 200 participants in the analysis irrespective of the above rules, because skewed data pose less of a problem in large studies. We will also enter all relevant change data, as when continuous data are presented on a scale that includes a possibility of negative values (such as change data), it is difficult to determine whether data are skewed.

2.5. Common measurement

To facilitate comparison between trials, we will, where relevant, convert variables that can be reported in different metrics, such as days in hospital (mean days per year, per week or per month) to a common metric (e.g. mean days per month).

2.6. Conversion of continuous to binary

Where possible, we will attempt to convert continuous outcome measures to dichotomous data. This can be done by identifying cut-off points on rating scales and dividing participants accordingly into 'clinically improved' or 'not clinically improved'. It is generally assumed that if there is a 50% reduction in a scale-derived score such as the Brief Psychiatric Rating Scale (BPRS) (Overall 1962), or the PANSS (Kay 1986), this could be considered a clinically significant response (Leucht 2005a; Leucht 2005b). If data based on these thresholds are not available, we will use the primary cut-off presented by the original authors.

2.7. Direction of graphs

Where possible, we will enter data so that the area to the left of the line of no effect indicates a favourable outcome for the intervention under investigation (reduction of polypharmacy). Where keeping to this makes it impossible to avoid outcome titles with clumsy double-negatives (e.g. 'not unimproved'), we will report data where the left of the line indicates an unfavourable outcome and note this in the graphs.

Assessment of risk of bias in included studies

Two review authors (of IB, MS and AR) will independently assess risk of bias by using the RoB 2 tool (Sterne 2019), and referring to the criteria described in the *Cochrane Handbook for Systematic Reviews of Interventions* to assess trial quality (Higgins 2021). This set of criteria is based on the judgement of the following domains:

- bias arising from the randomisation process;
- bias due to deviations from intended interventions;
- bias due to missing outcome data;
- bias in measurement of the outcome; and
- bias in selection of the reported result.

For each domain, we will rate the available 'signalling questions' to reach a judgement (high, some concerns, low) following the tool algorithms implemented in the RoB 2 Excel tool (available on the riskofbiasinfo.org website).

The effect of interest in performing ratings with the tool will be the effect of assignment to the interventions at baseline, regardless of whether the interventions are received as intended (the 'intention-to-treat' (ITT) effect) (Section 8.2.2; Higgins 2021).

We will perform an evaluation with the RoB 2 tool for the following outcomes.

- Quality of life: clinically important change
- Service use: readmission to hospital
- Adverse effect: leaving the study early due to adverse events – overall tolerability
- Functioning: clinically important change
- Global state: relapse/exacerbations of psychosis
- Leaving the study early: due to any reason – overall acceptability
- Adverse effects/events: at least one adverse effect.

For cluster trials, we will use the additional domain specific for cluster RCTs from the archived version of the tool (Domain 1b – 'Bias arising from the timing of identification and recruitment of participants') and use the signalling questions from the archived version).

For cross-over trials, we will only use data from the first phase (see Measures of treatment effect), and we will use the standard version of the RoB 2.

If the raters disagree, we will make the final rating by consensus, if necessary, with another review author (SL). Where studies provide inadequate details of randomisation and other characteristics, we will attempt to contact study authors to request further information. We will report non-concurrence in quality assessment, but if disputes arise regarding the category to which a trial is to be allocated, we will resolve this by discussion.

We will note the level of risk of bias in the text of the review, the 'Risk of bias' table, 'Risk of bias' graph, 'Risk of bias' summary and the 'Summary of findings' table.

Measures of treatment effect

1. Binary data

For binary outcomes, we will calculate a standard estimation of the risk ratio (RR) and its 95% confidence interval (CI), as it has been shown that RR is more intuitive than odds ratios (Boissel 1999), and that odds ratios tend to be interpreted as RR by clinicians (Deeks 2000).

Although the number needed to treat for an additional beneficial outcome (NNTB) and the number needed to treat for an additional harmful outcome (NNTH), with their CIs, are intuitively attractive to clinicians, they are problematic to calculate and interpret in meta-analyses (Hutton 2009). For binary data presented in the 'Summary of findings' table, we will, where possible, calculate illustrative comparative risks.

2. Continuous data

If scales of reasonable similarity are used for an outcome, we will calculate mean differences (MDs) as the effect size measure, and we will transform the effect back to the units of one or more of the specific instruments. If the scales are not similar enough, we will estimate standardised mean differences (SMDs) between groups.

Unit of analysis issues

1. Cluster trials

Studies increasingly employ 'cluster randomisation' (such as randomisation by clinician or practice), but analysis and pooling of clustered data poses problems. First, authors often fail to account for intraclass correlation in clustered studies, leading to a unit-of-analysis error whereby P values are spuriously low, CIs unduly narrow and statistical significance overestimated (Divine 1992). This causes type I errors (Bland 1997; Gulliford 1999).

Where clustering has been incorporated into the analysis of primary studies, we will present these data as if from a non-cluster randomised study, but adjust for the clustering effect.

Where clustering is not accounted for in primary studies, we will present data in a table, with a (*) symbol to indicate the presence of a probable unit of analysis error. We will seek to contact first authors of studies to obtain intraclass correlation coefficients for their clustered data and to adjust for this by using accepted methods (Gulliford 1999).

We have sought statistical advice and have been advised that the binary data from cluster trials presented in a report should be divided by a 'design effect'. This is calculated using the mean number of participants per cluster (m) and the intraclass correlation coefficient (ICC): thus design effect = 1 + (m − 1) × ICC (Donner 2002). If the ICC is not reported, we will assume it to be 0.1 (Ukoumunne 1999).

If cluster studies have been appropriately analysed and taken ICCs and relevant data documented in the report into account, synthesis with other studies will be possible using the generic inverse variance technique.

2. Cross-over trials

A major concern of cross-over trials is the carry-over effect. This occurs if an effect (e.g. pharmacological, physiological or psychological) of the treatment in the first phase is carried over to the second phase. As a consequence, participants can differ significantly from their initial state at entry to the second phase, despite a washout phase. For the same reason, cross-over trials are not appropriate if the condition of interest is unstable (Elbourne 2002). As both carry-over and unstable conditions are very likely in severe mental illness, we will only use data from the first phase of cross-over studies.

3. Studies with multiple treatment groups

Where a study involves more than two treatment arms, if relevant, we will present the additional treatment arms in comparisons. If data are binary, we will simply add these and combine within the 2×2 table.

If data are continuous, we will combine data using the formula in Section 7.7.3.8 (Combining groups) of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021). Where additional treatment arms are not relevant, we will not reproduce these data. However, we will list all treatment arms in the 'Characteristics of included studies' table.

Dealing with missing data

1. Overall loss of credibility

We share the concern that at some degree of loss to follow-up, data lose credibility (Xia 2009). However, it is unclear at which point this becomes a problem. Therefore, we will not exclude studies based on degree of attrition, but we will account for attrition in the 'Risk of bias' assessment.

2. Binary

We will present data in an ITT analysis. We will assume participants leaving the study early will have the same rates of outcome as participants who complete.

3. Continuous

3.1. Assumptions about participants who leave the trials early or are lost to follow-up

There are various methods to account for participants who leave the trials early or are lost to follow-up. Some trials just present the results of study completers; other trials use the method of last observation carried forward (LOCF); while methods such as multiple imputation or mixed-effects models for repeated measurements (MMRM) have become more of a standard. While the MMRMs seem to be somewhat better than LOCF (Leon 2006), we consider that the high percentage of participants leaving the studies early and differences between groups in their reasons for doing so is often the core problem in RCTs of people with schizophrenia. Therefore, we will not exclude studies based on the statistical approach used. However, by preference we will use the more sophisticated approaches (i.e. we will prefer to use MMRM or multiple-imputation to LOCF), and we will only present completer analyses if some type of ITT data are not available. We will exclude studies presenting only completer data in sensitivity analyses.

3.2. Standard deviations

If SDs are not reported, we will try to obtain the missing values from the authors. If these are not available, where there are missing measures of variance for continuous data, but an exact standard error (SE) and CIs available for group means, and either P value or t value available for differences in mean, we will calculate SDs according to the rules described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021). When only the SE is reported, SDs are calculated by the formula SD = SE × √(n). Sections 7.7.3 and 16.1.3 of the *Cochrane Handbook for Systematic Reviews of Interventions* present detailed formulae for estimating SDs from P, t or F values; CIs; ranges or other statistics (Higgins 2021). If these formulae do not apply, we will calculate the SDs according to a validated imputation method based on the SDs of the other included studies (Furukawa 2006). Although some of these imputation strategies can introduce error, the alternative would be to exclude a given study's outcome and thus to lose information. Nevertheless, we will examine the validity of the imputations in a sensitivity analysis that excludes imputed values.

Assessment of heterogeneity

1. Clinical heterogeneity

We will consider all included studies initially, without seeing comparison data, to judge clinical heterogeneity. We will inspect all studies for participants who are clearly outliers or situations that we had not predicted would arise and, where found, discuss such situations or participant groups.

2. Methodological heterogeneity

We will consider all included studies initially, without seeing comparison data, to judge methodological heterogeneity. We will inspect all studies for clearly outlying methods that we had not predicted would arise and discuss any such methodological outliers.

3. Statistical heterogeneity

3.1. Visual inspection

We will inspect graphs visually to investigate the possibility of statistical heterogeneity.

3.2. Employing the I^2 statistic

We will investigate heterogeneity between studies by considering the I^2 statistic alongside the Chi^2 P value. The I^2 statistic provides an estimate of the percentage of inconsistency thought to be due to chance (Higgins 2003). The importance of the observed value of the I^2 statistic depends on the magnitude and direction of effects as well as the strength of evidence for heterogeneity (e.g. P value from Chi^2 test, or a CI for the I^2 statistic). We will interpret an I^2 statistic estimate of 50% or greater and accompanied by a statistically significant Chi^2 statistic as evidence of substantial heterogeneity (Section 9.5.2, *Cochrane Handbook for Systematic Reviews of Interventions*) (Higgins 2021). When there are substantial levels of heterogeneity in the primary outcomes, we will explore reasons for heterogeneity (Subgroup analysis and investigation of heterogeneity).

Assessment of reporting biases

Reporting biases arise when the dissemination of research findings is influenced by the nature and direction of results (Egger 1997). These are described in Section 10 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021). We are aware that funnel plots may be useful in investigating reporting biases, but are of limited power to detect small-study effects. We will not use funnel plots for outcomes where there are 10 or fewer studies, or where all studies are of similar size. In other cases, where funnel plots are possible, we will seek statistical advice in their interpretation and produce a contour enhanced funnel-plot (Peters 2008).

Data synthesis

We understand that there is no closed argument for preference for use of fixed-effect or random-effects models. The random-effects method incorporates an assumption that the different studies are estimating different, yet related, intervention effects. This often seems to be true to us and the random-effects model takes into account differences between studies, even if there is no statistically significant heterogeneity. However, there is a disadvantage to the random-effects model: it puts added weight onto small studies, which often are the most biased type. Depending on the direction of effect, these studies can either inflate or deflate the effect size. We will use a random-effects model for all analyses.

Subgroup analysis and investigation of heterogeneity

1. Subgroup analyses

Subgroup analyses will only be conducted on the primary outcomes. We are aware that subgroup analyses are observational by nature and, therefore, consider the results to be exploratory and not explanatory. If the moderators in question are continuous, we will either dichotomise them by a median split or we will conduct meta-regression analyses in R.

1.1. Degree of antipsychotic polypharmacy reduction

We will perform subgroup analyses based on the how many antipsychotics are withdrawn in the selected studies. The greater the number of drugs withdrawn, the higher the chances to have fewer adverse effects and better quality of life, but also the risk for major relapses leading to rehospitalisation should be higher.

1.2. Speed of antipsychotic polypharmacy reduction

Too fast a reduction of the number of antipsychotics may increase the risk for major relapses in terms of rehospitalisation. Therefore, we will categorise the studies into abrupt and gradual reduction.

1.3. Initial number of antipsychotics

Results may differ based upon whether participants were originally on two or more antipsychotics.

1.4. Severity of illness

It may be easier to reduce polypharmacy in people with less severe schizophrenia than in people with more severe schizophrenia.

1.5. Clinical state, stage or problem

We will provide an overview of the effects of polypharmacy reduction versus antipsychotic number maintenance for people with schizophrenia in general. In addition, however, we will try to report data on subgroups of people in the same clinical state, stage and with similar problems. The following groups appear to be especially pertinent.

1.5.1. Participants with first episode versus participants with multiple episodes

Up to 20% of first-episode patients may not have a second episode (Robinson 1999). Therefore, reducing polypharmacy may be particularly useful in this subgroup.

1.5.2. Participants in remission versus other participants

Reductions of polypharmacy may be more meaningful in participants in remission (if available according to Andreasen 2005) than in participants who are stable but not symptom free.

2. Investigation of heterogeneity

We will report if inconsistency is high. First, we will investigate whether data have been entered correctly. Second, if data are correct, we will inspect the graph visually and remove outlying studies successively to see if homogeneity is restored. Decisions as to whether single studies should be excluded from the analysis or whether a formal meta-analysis should not be undertaken will depend on issues such as whether the heterogeneity was due to differences in direction of effect or only to the degree of the difference between intervention and control (Higgins 2021). When unanticipated clinical or methodological heterogeneity is obvious, we will simply state hypotheses regarding these for future reviews or updates of this review. We do not anticipate undertaking analyses relating to these.

Sensitivity analysis

We plan to carry out sensitivity analyses, for primary outcomes only, to explore the influence of the factors listed below. We will exclude the studies identified in each sensitivity analysis, and discuss the difference with the main analysis.

1. Risk of bias

We will analyse the effects of excluding trials that are judged to be at overall high risk of bias for the primary outcome (see Assessment of risk of bias in included studies).

2. Imputed values

We will analyse the effects of excluding data from trials where we use imputed values for ICC to calculate the design effect in cluster-RCTs (see Unit of analysis issues), or where SDs were imputed.

3. Operationalised criteria to diagnose schizophrenia

We will analyse the effects of excluding data from trials that did not use operational criteria to diagnose schizophrenia.

4. Fixed-effect and random-effects models

In the main analyses, we will synthesise data using a random-effects model; however, in this sensitivity analysis we will also synthesise data for the primary outcomes using a fixed-effect model to evaluate whether this alters the significance of the results.

5. Suggestion of skewed data

We will analyse the effects of excluding data from trials where there is a suggestion that data are skewed (see Data extraction and management).

6. Chinese studies

Studies from mainland China often use other randomisation methods than the internationally approved ones, the reports are very short and the methods are often not described in details (Woodhead 2016). To account for these potential differences we will exclude these studies from a sensitivity analysis.

7. Reduction of polypharmacy is compensated by an increase in dose in the remaining antipsychotics

In some trials reduction of polypharmacy may be compensated by the increase of the dose of the remaining antipsychotics. This procedure might still be superior to keeping the same number of antipsychotics due to fewer drug–drug interactions. We will carry out a sensitivity analysis excluding these trials.

Summary of findings and assessment of the certainty of the evidence

We will use the GRADE approach to interpret findings (Schünemann 2011); and will use GRADE profiler to import data from RevMan Web to create a 'Summary of findings' table (GRADEpro GDT; RevMan Web) for the comparison of polypharmacy reduction compared to polypharmacy continuation. This table will provide outcome-specific information concerning the overall certainty of evidence from each included study in the comparison, the magnitude of effect of the interventions examined and the sum of available data on all outcomes we rate as important to patient care and decision making. The overall RoB 2 judgements will be used to feed into the GRADE assessment. We aim to select the following main outcomes for inclusion in the 'Summary of findings' table.

- Quality of life: clinically important change
- Service use: readmission to hospital
- Adverse effect: leaving the study early due to adverse events – overall tolerability
- Functioning: clinically important change
- Global state: relapse/exacerbations of psychosis
- Leaving the study early: due to any reason – overall acceptability
- Adverse effects/events: at least one adverse effect

We will justify all decisions to downgrade the certainty of studies using footnotes and we will make comments to aid reader's understanding of the review where necessary.

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CONTRIBUTIONS OF AUTHORS

IB: protocol development.

MS: protocol development.

AR: protocol development.

WPH: protocol development, patient perspective.

SL: protocol development.

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IB: none.

MS: none.

AR: none.

WPH: none.

SL: In the past 3 years, SL has received honoraria for service as a consultant or adviser and/or for lectures from Angelini, Böhringer Ingelheim, Geodon&Richter, Janssen, Johnson&Johnson, Lundbeck, LTS Lohmann, MSD, Otsuka, Recordati, SanofiAventis, Sandoz, Sunovion, TEVA, ROVI and EISAI.

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