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Chlorpromazine versus lithium for people with schizophrenia (Protocol)

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Chlorpromazine versus lithium for people with schizophrenia

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ABSTRACT

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

To investigate the effects of chlorpromazine alone versus lithium alone in the treatment of schizophrenia, schizophrenia-like psychoses and schizoaffective psychoses.

It is expected that the implementation of several subgroup analyses may be possible (see Subgroup analysis and investigation of heterogeneity).

BACKGROUND

Description of the condition

One per cent of the global population has schizophrenia (WHO 2016). Schizophrenia can be a debilitating and chronic mental illness. It is characterised by so-called 'positive symptoms' such as hallucinations, and delusions, and 'negative symptoms' such as poor psychomotor skills, diminished emotional expression and avolition, these problems may be substantial and generalised (Schaefer 2013) and can worsen over time (Agnew-Blais 2015; Cannon 2000).

The potentially debilitating and deteriorating nature of schizophrenia means it can lead to the development of a range of physical, psychological, and socioeconomic problems. For example, people living with the illness often experience depression, anxiety, poor quality social relationships and reduced educational and occupational performance (Shamsi 2011; Tandberg 2013;

Thornicroft 2004). These factors may lead to poor physical health and increased suicide rate (Palmer 2005; Saha 2007). As a result, people with schizophrenia have a reduced lifespan and are 2 to 2.5 times more likely to experience early death when compared to the rest of the population (McGrath 2008). Schizophrenia is associated with substantial economic costs and societal burden (Awad 2008; Knapp 2004). Over half of those living with schizophrenia do not receive adequate care, and over 80% of these people come from low- and middle-income countries (WHO 2016). Identifying interventions which are both clinically and cost-effective is crucial.

Description of the intervention

Chlorpromazine, originally developed to treat allergic reactions, was utilised to aid anaesthesia and stabilise patients during surgical procedures (Dripps 1955). Since discovering chlorpromazine's sedative influence, its efficacy in improving symptoms of

schizophrenia has been investigated widely (Delay 1952). The beneficial influence of chlorpromazine upon symptoms of schizophrenia has led to its universal employment as an antipsychotic medication for over 50 years (Ban 2007) and chlorpromazine is still listed by the World Health Organization (WHO) as an essential drug for the treatment of psychotic disorders (WHO 2015). Use of this so-called 'benchmark' drug for schizophrenia is supported by research indicating its efficacy in reducing relapse and improving global functioning (Adams 2014).

Lithium is a medication that is often prescribed to treat severe mood disturbances associated with affective psychoses (Cipriani 2005). It has been found to effectively treat symptoms of mania in bipolar disorder, alleviate symptoms of depression for people who are resistant to other forms of treatment, and reduce self-harming and aggressive behaviours (NICE 2016). Lithium can be prescribed as an adjunctive drug treatment with antipsychotics in the treatment of schizophrenia (Leucht 2015). By reducing the residual symptoms not addressed by antipsychotics, or the adverse effects produced by taking antipsychotic medication, lithium might improve antipsychotic medication adherence and achieve a satisfactory treatment response (Barkhof 2012). We know of no reviews of the efficacy of using lithium alone to treat symptoms of schizophrenia.

How the intervention might work

The antipsychotic effect of chlorpromazine is frequently associated with action upon receptors within the brain (Sedvall 1996). Specifically, chlorpromazine is suggested to block sites primarily at dopamine receptors (D1 and D2); however its action results from its role as an antagonist of D2 receptor of the mesolimbic pathway (Saha 2016). Adverse side effects associated with typical antipsychotics include, but are not limited to, abnormal blood pressure, dry mouth and sedation (Leucht 2008). In addition, more serious extrapyramidal side effects, such as tardive dyskinesia are possible, but are less likely than anticholinergic side effects (Arana 2000). The efficacy of lithium cannot be attributed to its action on any specific biochemical mechanism, as it acts on nearly every neurotransmitter system in the brain (Jope 1999). Lithium can influence neurotransmitter and receptor-mediated signalling by altering signal transduction cascades, ion transport, hormonal and circadian regulation, and mechanisms of gene expression (Lenox 2003). When used as an adjunctive treatment of schizophrenia, lithium may reduce the residual symptoms not addressed by antipsychotics, or the adverse effects produced by taking antipsychotic medication (Barkhof 2012; Manji 2000).

Why it is important to do this review

Lithium is widely used as a mood stabiliser, but is rarely used alone for the treatment of schizophrenia and is more commonly prescribed as an adjunct therapy (Lehman 1998). However, both lithium and chlorpromazine are widely accessible. We know of no reviews of the use of lithium as a sole treatment for people with schizophrenia, and the purpose of this review is to summarise investigations of the comparative effectiveness of chlorpromazine and lithium, two old drugs included in the WHO Model List of Essential Medicines (WHO 2015). Should lithium be shown to have some effect, this could have important treatment implications. This review is one of a series on the effects of chlorpromazine (Table 1).

OBJECTIVES

To investigate the effects of chlorpromazine alone versus lithium alone in the treatment of schizophrenia, schizophrenia-like psychoses and schizoaffective psychoses.

It is expected that the implementation of several subgroup analyses may be possible (see Subgroup analysis and investigation of heterogeneity).

METHODS

Criteria for considering studies for this review

Types of studies

All relevant randomised controlled trials. We will include trials described as 'double-blind' - in which randomisation is implied - in a Sensitivity analysis. We will exclude quasi-randomised studies, such as those that allocate intervention by alternate days of the week. Where people are given additional treatments as well as chlorpromazine or lithium, we will only include data if the adjunct treatment is evenly distributed between groups and it is only the chlorpromazine or lithium that is randomised.

Types of participants

We will included studies if at least 80% of their participants are adults aged 18 to 65 years old with schizophrenia or related disorders, including schizophreniform, schizoaffective disorder and delusional disorder, by any means of diagnosis. For studies with a range of diagnoses, we will only include studies where the majority of people have schizophrenia or related disorders.

We are interested in making sure that information is as relevant as possible to the current care of people with schizophrenia, so aim to highlight the current clinical state clearly (acute, early post-acute, partial remission, remission), as well as the stage (prodromal, first

episode, early illness, persistent), and whether the studies primarily focus upon people with particular problems (for example, negative symptoms, treatment-resistant illnesses).

Types of interventions

1. Chlorpromazine
Any dose or mode of administration.

2. Lithium
Any dose or mode of administration.

Types of outcome measures
We aim, where possible, to categorise outcomes into short term (up to six weeks), medium term (six weeks to six months) and long term (over six months).
We will endeavour to report binary outcomes recording clear and clinically meaningful degrees of change (e.g. global impression of much improved, or more than 50% improvement on a rating scale - as defined within the trials) before any others. Thereafter, we will list other binary outcomes and then those that are continuous.

Primary outcomes

1. Global state
1.1 Clinically important overall change

2. Mental state
2.1 General symptoms - clinically important overall changes

3. Adverse effects
3.1 Specific - movement disorders (extrapyramidal side effects, specifically tardive dyskinesia and neuroleptic malignant syndrome) - clinically important overall change

Secondary outcomes

1. Global state
1.1 Any change in global state
1.2 Re-admission
1.3 Relapse
1.4 Severity of illness
1.5 Average endpoint/change score global state scale
1.6 Duration of hospital stay

2. Mental state

2.1 General symptoms
2.1.1 Any change in mental state
2.1.2 Average endpoint/change score general mental state scale

2.2 Specific symptoms
2.2.1 Mood - depression
2.2.2 Negative symptoms (avolition, poor self-care, blunted affect)
2.2.3 Positive symptoms (delusions, hallucinations, disordered thinking)
2.2.4 Average endpoint/change score specific mental state scale

3. Adverse effects

3.1 General adverse effects
3.1.1 At least one adverse effect
3.1.2 Clinically important adverse effects
3.1.3 Average endpoint/change scores adverse-effect scales

3.2 Specific adverse effects - clinically important - as defined by each of the studies
3.2.1 Anticholinergic
3.2.2 Central nervous system
3.2.3 Movement disorders
3.2.4 Various other
3.2.5 Average endpoint or change score on specific adverse effect scale

4. Quality of life (recipient or informal carers or professional carers)
4.1 Clinically important change in quality of life - as defined by each of the studies
4.2 Any change in quality of life - as defined by each of the studies
4.3 Average endpoint or change score on quality of life scale

5. Behaviour

5.1 General behaviour
5.1.1 Clinically important change in behaviour

5.1.2 Any change in behaviour
5.1.3 Average endpoint/change score general behaviour scale

5.2 Specific behaviour

5.2.1 Aggressive or violent behaviour
5.2.2 Average endpoint/change score specific behaviour scale

6. Social functioning

6.1 Clinically important change in social functioning
6.2 Any change in social functioning
6.3 Average endpoint/change score social functioning scale
6.4 Employment status during trial

7. Leaving the study early

7.1 For any reason
7.2 For specific reason

8. Satisfaction with treatment - carer or participant

8.1 Clinically important change
8.2 Any change
8.3 Average endpoint/change score satisfaction scale

9. Economic

9.1 Cost of care - direct and indirect

'Summary of findings' table

We will use the GRADE approach to interpret findings (
Schünemann 2011); and will use GRADEpro to export data from
this review to create 'Summary of findings' tables. These tables
provide outcome-specific information concerning the overall qual-
ity 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. We aim to select the following main
outcomes for inclusion in the 'Summary of findings' table:
   1. Global state - clinically important change
   2. Mental state - general symptoms - clinically important
change
   3. Behaviour - specific - aggressive or violent behaviour
   4. Adverse effects - specific - movement disorders - clinically
important change
   5. Leaving the study early - for any reason
   6. Satisfaction with treatment - participant/carer - clinically
important change
   7. Cost of care - direct or indirect

If data are not available for these pre-specified outcomes but are
available for ones that are similar, we will present the closest out-
come to the pre-specified one in the table but take this into ac-
count when grading the finding.

Search methods for identification of studies

Electronic searches

Cochrane Schizophrenia Group's Study-Based Register of Trials

The information specialist will search the register using the fol-
lowing search strategy:
(*Chlorpromazine* AND *Lithium*) in Intervention Field of
STUDY
In such a study-based register, searching the major concept re-
trieves all the synonyms and relevant studies because all the stud-
ies have already been organised based on their interventions and
linked to the relevant topics.
This register is compiled by systematic searches of major re-
sources (including AMED, BIOSIS, CINAHL, Embase, MED-
LINE, PsycINFO, PubMed, and registries of clinical trials) and
their monthly updates, handsearches, grey literature, and confer-
ence proceedings (see Group's Module). There is no language,
date, document type, or publication status limitations for inclu-
sion of records into the register.

Searching other resources

1. Reference searching

We will inspect references of all included studies for further rele-
vant studies.

Data collection and analysis

Selection of studies

All review authors will independently inspect citations from the
searches and identify relevant abstracts, and satisfactory risk of
bias assessment. CMG, KT, and SR will independently re inspect
a random 20% sample to ensure reliability. DC will re-inspect all
the samples. We will then obtain and inspect full reports of the
abstracts or reports meeting the review criteria. DC will re-inspect
a random 20% of these full reports in order to ensure reliability
of selection. Where it is not possible to resolve disagreement by
discussion, we will attempt to contact the authors of the study
concerned for clarification. We will include studies meeting our
inclusion criteria and reporting useable data.

Data extraction and management

1. Extraction

Review authors (DC, CMG, KT, SR) will extract data from all included studies. In addition, to ensure reliability, all authors will independently extract data from a random sample of these studies, using a standardised form. We will discuss disagreements, and document decisions. We will attempt to extract data presented only in graphs and figures whenever possible. If studies are multi-centre, where possible, we will extract data relevant to each component centre separately.

2. Management

2.1 Forms

We will extract data onto standard, pre-designed, simple forms.

2.2 Scale-derived data

We will include continuous data from rating scales only if:

a) the psychometric properties of the measuring instrument have been described in a peer-reviewed journal (Marshall 2000); and
b) the measuring instrument has not been written or modified by one of the trials for that particular trial;
c) the instrument should be a global assessment of an area of functioning and not sub-scores which are not, in themselves, validated or shown to be reliable; however there are exceptions, and we will include sub-scores from mental state scales measuring positive and negative symptoms of schizophrenia.

Ideally, the measuring instrument should either be i. a self-report or ii. completed by an independent rater or relative (not the therapist). We realise that this is not often reported clearly; in 'Description of studies' we will note if this is the case or not.

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), which 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 former are not available. If necessary, we will combine endpoint and change data in the analysis, as we prefer to use mean differences (MDs) rather than standardised mean differences (SMDs) throughout (Higgins 2011).

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:

a) 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 lower than one, it strongly suggests that the data are skewed and we will exclude these data. If this ratio is higher 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. If these data do change results, we will enter them as 'other data'. 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 2011).

b) 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 $2 SD > (S - S min)$, where S is the mean score and 'S min' is the minimum score. We will enter skewed data as 'other data'.

Please 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 tell whether or not data are skewed.

2.5 Common measurement

To facilitate comparison between trials we aim, where relevant, to 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 make efforts to convert 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 as 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 in such a way that the area to the left of the line of no effect indicates a favourable outcome for chlorpromazine or lithium. Where keeping to this makes it impossible to avoid outcome titles with clumsy double-negatives (e.g. 'not un- improved') we will report data where the left of the line indicates an unfavourable outcome. We will note this in the relevant graphs.

Assessment of risk of bias in included studies

Again, all review authors will work independently to assess risk of bias by using the criteria described in the *Cochrane Handbook for Systematic Reviews of Interventions* to assess trial quality (Higgins 2011a). This set of criteria is based on evidence of associations between overestimate of effect and high risk of bias of the article such as sequence generation, allocation concealment, blinding, incomplete outcome data and selective reporting.

If the raters disagree, we will make the final rating by consensus, with the involvement of another member of the review group. Where inadequate details of randomisation and other characteristics of trials are provided, we will contact the authors of the studies in order to obtain further information. We will report non-concurrence in quality assessment. If disputes arise as to which category a trial is to be allocated, again we will resolve this by discussion.

We will note the level of risk of bias in both the text of the review and in 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/s we will, where possible, calculate illustrative comparative risks.

2. Continuous data

For continuous outcomes we will estimate MD between groups. We prefer not to calculate effect size measures (SMD). However if scales of very considerable similarity are used, we will presume there is a small difference in measurement, and we will calculate

effect size and transform the effect back to the units of one or more of the specific instruments.

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. Firstly, authors often fail to account for intra-class 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 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 intra-class correlation coefficients (ICCs) 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 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 wash-out 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 two-by-two table. If data are continuous, we will combine data following the formula in section 7.7.3.8 (Combining groups) of the *Cochrane Handbook for Systematic Reviews of Interventions*

(Higgins 2011). Where additional treatment arms are not relevant, we will not reproduce these data.

Dealing with missing data

1. Overall loss of credibility

At some degree of loss of follow-up, data must lose credibility (Xia 2009). We choose that, for any particular outcome, should more than 50% of data be unaccounted for we will not reproduce these data or use them within analyses. If, however, more than 50% of those in one arm of a study are lost, but the total loss is less than 50%, we will address this within the 'Summary of findings' table/s by down-rating quality. Finally, we will also downgrade quality within the 'Summary of findings' table/s should the loss be 25% to 50% in total.

2. Binary

In the case where attrition for a binary outcome is between 0% and 50% and where these data are not clearly described, we will present data on a 'once-randomised-always-analyse' basis (an intention-to-treat (ITT) analysis). Those leaving the study early are all assumed to have the same rates of negative outcome as those who completed. We will use the rate of those who stay in the study - in that particular arm of the trial - and apply this also to those who did not. We will undertake a sensitivity analysis to test how prone the primary outcomes are to change when data only from people who complete the study to that point are compared to the ITT analysis using the above assumptions.

3. Continuous

3.1 Attrition

We will use data where attrition for a continuous outcome is between 0% and 50%, and data only from people who complete the study to that point are reported.

3.2 Standard deviations

If standard deviations (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 can calculate SDs according to the rules described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011). When only the SE is reported, SDs are calculated by the formula $SD = SE * \sqrt{(n)}$. Chapters 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 (Deeks 2011). If these formulae do not apply, we will calculate the SDs according to a validated imputation method which is 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.

3.3 Assumptions about participants who left the trials early or were lost to follow-up

Various methods are available to account for participants who left the trials early or were lost to follow-up. Some trials just present the results of study completers; others use the method of last observation carried forward (LOCF); while more recently, methods such as multiple imputation or mixed-effects models for repeated measurements (MMRM) have become more of a standard. While the latter methods seem to be somewhat better than LOCF (Leon 2006), we feel 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 randomised schizophrenia trials. We will therefore 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 kind of ITT data are not available at all. Moreover, we will address this issue in the item 'Incomplete outcome data' of the 'Risk of bias' tool.

Assessment of heterogeneity

1. Clinical heterogeneity

We will consider all included studies initially, without seeing comparison data, to judge clinical heterogeneity. We will simply 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 simply inspect all studies for clearly outlying methods which 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 I² statistic

We will investigate heterogeneity between studies by considering the I² statistic alongside the Chi² P value. The I² statistic provides an estimate of the percentage of inconsistency thought to be due to chance (Higgins 2003). The importance of the observed value of I² depends on the magnitude and direction of effects as well as the strength of evidence for heterogeneity (e.g. P value from Chi² test, or a confidence interval for I²). We will interpret an I² estimate greater than or equal to 50% and accompanied by a statistically significant Chi² statistic as evidence of substantial heterogeneity (Section 9.5.2 *Cochrane Handbook for Systematic Reviews of Interventions*) (Higgins 2011, Deeks 2011). When substantial levels of heterogeneity are found in the primary outcome, 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 10.1 of the *Cochrane Handbook for Systematic reviews of Interventions* (Sterne 2011).

1. Protocol versus full study

We will try to locate protocols of included randomised trials. If the protocol is available, we will compare outcomes in the protocol and in the published report . If the protocol is not available, we will compare outcomes listed in the methods section of the trial report with actually reported results.

2. Funnel plot

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.

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. There is, however, a disadvantage to the random-effects model: it puts added weight onto small studies, which often are the most biased ones. Depending on the direction of effect, these studies can either inflate or deflate the effect size. We choose random-effects models for all analyses.

Subgroup analysis and investigation of heterogeneity

1. Subgroup analyses

1.1 Primary outcomes

We will aim to provide an overview of the effects of chlorpromazine and lithium for people with schizophrenia in general. In addition, we will try to report data on subgroups of people in the same clinical state, stage and with similar problems. We will also, if possible, undertake subgroup analyses to compare the results for the following: participants with or without schizoaffective or prominent affective symptoms and participants with or without treatment-resistant schizophrenia.

2. Investigation of heterogeneity

We will report if inconsistency is high. Firstly, we will investigate whether data have been entered correctly. Secondly, if data are correct, we will inspect the graph visually and remove outlying studies successively to see if homogeneity is restored. For this review we have decided that should this occur with data contributing to the summary finding of no more than 10% of the total weighting, we will present data. If not, we will not pool these data and will discuss any issues. We know of no supporting research for this 10% cut-off but are investigating use of prediction intervals as an alternative to this unsatisfactory state.

When unanticipated clinical or methodological heterogeneity is obvious, we will simply state hypotheses regarding these for future reviews or versions of this review. We do not anticipate undertaking analyses relating to these.

Sensitivity analysis

If there are substantial differences in the direction or precision of effect estimates in any of the sensitivity analyses listed below, we will not add data from the lower-quality studies to the results of

the higher-quality trials, but will present these data within a sub-category. If their inclusion does not result in a substantive difference, they will remain in the analyses.

1. Implication of randomisation

If trials are described in some way as to imply randomisation, for the primary outcomes, we will pool data from the implied trials with trials that are randomised.

2. Assumptions for lost binary data

Where assumptions have to be made regarding people lost to follow-up (see Dealing with missing data), we will compare the findings of the primary outcomes when we use our assumption compared with completer data only. If there is a substantial difference, we will report results and discuss them but continue to employ our assumption.

Where assumptions have to be made regarding missing SDs (see Dealing with missing data), we will compare the findings on primary outcomes when we use our assumption compared with completer data only. We will undertake a sensitivity analysis testing how prone results are to change when 'completer' data only are compared to the imputed data using the above assumption. If there is a substantial difference, we will report results and discuss them but continue to employ our assumption.

3. Risk of bias

We will analyse the effects of excluding trials that are at high risk of bias across one or more of the domains (see Assessment of risk of bias in included studies) for the meta-analysis of the primary outcome.

4. Imputed values

We will also undertake a sensitivity analysis to assess the effects of including data from trials where we use imputed values for ICC in calculating the design effect in cluster-randomised trials.

5. Fixed- and random-effects

We will synthesise data using a random-effects model; however, we will also synthesise data for the primary outcome using a fixed-effect model to evaluate whether this alters the significance of the results.

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* *Indicates the major publication for the study*

ADDITIONAL TABLES

Table 1.   Cochrane reviews of chlorpromazine

Title	Stage
Chlorpromazine versus acetophenazine	Protocol
Chlorpromazine versus aripiprazole	Protocol
Chlorpromazine versus clotiapine	Full review
Chlorpromazine versus haloperidol	Full review
Chlorpromazine versus metiapine	Full review
Chlorpromazine versus penfluridol	Protocol
Chlorpromazine versus piperacetazine	Protocol
Chlorpromazine versus placebo	Full review
Chlorpromazine versus reserpine	Full review
Chlorpromazine versus pimozide	Registered title
Chlorpromazine cessation	Full review
Chlorpromazine versus atypical antipsychotic drugs	Full review
Chlorpromazine dose for schizophrenia	Full review
Chlorpromazine for psychosis induced aggression or agitation	Full review
Chlorpromazine versus thiothixene	Registered title

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DC: protocol development.

SR: protocol development.

CMG: protocol development.

KT: protocol development.

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External sources

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