Trifluoperazine versus placebo for schizophrenia (Protocol)

Koch K, Mansi K, Haynes E, Adams CE

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[Intervention Protocol]

Trifluoperazine versus placebo for schizophrenia

Kai Koch[1], Kamel Mansi[2], Euan Haynes[2], Clive E Adams[2]

[1]Department of Medicine, The University of Nottingham, Nottingham, UK. [2]Cochrane Schizophrenia Group, The University of Nottingham, Nottingham, UK

Contact address: Kai Koch, Department of Medicine, The University of Nottingham, Medical School, Queens Medical School, Nottingham, NG7 2UH, UK. mzydkuk@nottingham.ac.uk.

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To determine the absolute effects of trifluoperazine for schizophrenia and schizophrenia-like illnesses when compared with placebo.

BACKGROUND

Description of the condition

Schizophrenia is a term used for a major group of psychiatric disorders characterised by psychotic symptoms involving a change in a person's thoughts, emotions, behaviour and perception of reality (NICE 2009). It has an incidence of 1% worldwide with a prevalence of 15.2/100,000 distributed with a ratio of 4:1 of men:women (McGrath 2004). Onset is commonly during adolescence or in young adults (Saha 2005) but can occur at any age, often at a time during a transition to independency (NICE 2009). Symptoms are divided into positive and negative symptoms; positive encompassing hallucinations, delusions and difficulty thinking whilst negative symptoms consist of social withdrawal and a loss of interest, energy and emotion (NICE 2009; RCPSYCH 2010). Although it is common to have a negative prodrome (early symptom indicating the onset of a disease/condition) preceding positive symptoms, the course, duration and severity of schizophrenia varies considerably and is usually unique to each person (NICE 2009; Lankappa 2012). People with schizophrenia have higher-risk mortality than the general population due to increased rates of death through suicide and accidents as well as organic diseases such as cardiovascular, renal and respiratory disease (Saha 2007; Tiihonen 2009; BNF 2012). Furthermore, people with schizophrenia suffer social problems including exclusion, reduced opportunities with jobs and relationships and a lack of public understanding of the disorder creating a harmful stigma (NICE 2009). Key treatment for this illness is medication. This has been shown to be of benefit for at least 'positive symptoms' but effectiveness relies on adherence and is plagued with adverse side effects, highlighting the importance of drug profiles and their selection.

Description of the intervention

Trifluoperazine, trade name Stelazine, is a long established antipsychotic that has been used to treat schizophrenia since the 1950's. It is one of the first generation (typical) drugs that have a high potency for treating predominately positive symptoms (Turner 2007). These drugs, trifluoperazine in particular, have large adverse profiles particularly relating to extrapyramidal side effects

(EPS) including pseudo parkinsonism, dystonia (sustained muscle contraction), akathisia (uncontrollable motor restlessness) and tardive dyskinesia (involuntary repetitive body movements). There is no first-line antipsychotic for schizophrenia as efficacy does not vary greatly so the clinical decision regarding which drug to use is made based on the individual patient circumstances (BNF 2012). However, modern generations of so called atypical drugs have become available and are more effective at treating negative symptoms as well as reducing EPS, although they are much more expensive than 'typical' drugs (Kerwin 1994; BNF 2012).

How the intervention might work

Pharmacodynamics of trifluoperazine: it is a high potency derivative of phenothiazine and is chemically related to chlorpromazine. It causes a postsynaptic D2 dopamine receptor blockade in the brain, specifically the mesolimbic, mesocortical centres and the striatum; the latter is responsible for the ESP (Arana 2000). The clinical effects of trifluoperazine are likely due to a decrease in homovallinic acid levels (primary dopamine metabolite) and normally take weeks to occur (Bazire 2000). Trifluoperazine has weak anticholinergic and sedative effects whilst having strong extrapyramidal and antiemetic effects. Trifluoperazine is readily absorbed by the gastrointestinal (GI) tract and levels will peak in the plasma after one and a half to two hours. As trifluoperazine is a protein-binding drug, it will be distributed into breast milk, care must therefore be taken with pregnant or breast feeding mothers. Trifluoperazine has a low potency of cholinergic blockade resulting in parasympatholytic side effects such as confusion, agitation, dry mouth and blurred vision. It weakly acts at histamine and alpha-adrenergic receptors relative to the other typical antipsychotics so causes less sedation and orthostatic hypotension, hence is generally well tolerated (Kaplan 1998).

Why it is important to do this review

Trifluoperazine is a well established antipsychotic drug used to treat schizophrenia. It is inexpensive. The previous trifluoperazine Cochrane review was undertaken nearly a decade ago (Marques 2004) and does include a placebo comparison. Although relative effects of trifluoperazine against other antipsychotic drugs is important, establishing an up-to-date absolute measure of clinical outcomes, efficacy and effects of the drug is needed.

OBJECTIVES

To determine the absolute effects of trifluoperazine for schizophrenia and schizophrenia-like illnesses when compared with placebo.

METHODS

Criteria for considering studies for this review

Types of studies

All relevant randomised controlled trials. If a trial is described as 'double blind' but implies randomisation, we will include such trials 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 does result 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 better trials, but will present such data within a subcategory. We will exclude quasi-randomised studies, such as those allocating by alternate days of the week. Where people are given additional treatments within trifluoperazine, we will only include data if the adjunct treatment is evenly distributed between groups and it is only the trifluoperazine that is randomised.

Types of participants

Participants with schizophrenia or related disorders, including schizophreniform disorder, schizoaffective disorder and delusional disorder, again, by any means of diagnosis.

We are interested in making sure that information is as relevant to the current care of people with schizophrenia as possible so propose to clearly highlight the current clinical state (acute, early post-acute, partial remission, remission) as well as the stage (prodromal, first episode, early illness, persistent) and as to whether the studies primarily focused on people with particular problems (for example, negative symptoms, treatment-resistant illnesses).

Types of interventions

1. Trifluoperazine

Any dose administered by any means. We will try to follow BNF 2012 doses ("initially 5 mg twice daily, increased by 5 mg daily after one week, then at intervals of 3 days, according to the response; elderly reduce initial dose by at least half") and we will consider any dose over 30 mg as very high. Doses outside this range will be further investigated using sensitivity analysis.

2. Placebo

Any form of placebo or no treatment alternative.

Types of outcome measures

All outcomes will be divided into short term (less than three months), medium term (three to six months) and long term (over six months).

Primary outcomes

1. Global state

1.1 Clinically significant response in medium-term global state, as defined by each study

2. Severe adverse effects

2.1 Clinically significant severe short-term adverse effects based on relevant rating scales

3. Behaviour

3.1 Clinically significant agitation or distress as defined by each study

4. Relapse +/- hospitalisation

4.1 Relapse including any hospitalisation of a participant within a study.

Secondary outcomes

1. Global state

1.1 Average score/change in global state - short and long term
1.2 Relapse

2. Mental state

2.1 Clinically significant response in psychotic symptoms
2.2 Average score/change in psychotic symptoms
2.3 Clinically significant response in positive symptoms
2.4 Average score/change in positive symptoms
2.5 Clinically significant response in negative symptoms
2.6 Average score/change in negative symptoms

3. Leaving the study early

4. Extrapyramidal adverse effects

4.1 Use of any antiparkinsonism drugs
4.2 Average score/change in extrapyramidal adverse effects
4.3 Tardive dyskinesia
4.4 Acute dystonia
4.5 Akathisia
4.6 Pseudo parkinsonism

5. Other adverse effects/event, general and specific

5.1 Death

6. Hospital and service utilisation outcomes

6.1 Hospital admission
6.2 Average change in days in hospital
6.3 Improvement in hospital status (for example: change from formal to informal admission status, use of seclusion, level of observation)

7. Economic outcomes

7.1 Average change in total cost of medical and mental health care
7.2 Total indirect and direct costs

8. Quality of life/satisfaction with care for either recipients of are or caregivers

8.1. Significant change in quality of life/satisfaction
8.2 Average score/change in quality of life/satisfaction

9. Behaviour

9.1 Use of adjunctive medication for sedation
9.2 Aggression to self or others

10. Cognitive response

10.1 Clinically important change
10.2 Any change, general and specific

11. Summary of findings table

We will use the GRADE approach to interpret findings (Schünemann 2008) and will use GRADE profiler (GRADEPRO) to import data from RevMan 5.1 (Review Manager) to create 'Summary of findings' tables. These tables provide outcome-specific information concerning the overall quality 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 will 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 significant response in global state - medium term
2. Global state - relapse +/- hospitalisation - medium term

3. Mental state - clinically significant response in psychotic symptoms - medium term
4. Leaving the study early - medium term
5. Severe adverse side effects - short term
6. Behaviour - clinically significant response in behaviour - medium term
7. Economic outcomes

Search methods for identification of studies

Electronic searches

Cochrane Schizophrenia Group trials Register

The Trial Search Co-ordinator will search the Cochrane Schizophrenia Group's trials Register. Using the phrase:
[(*10-[3-(4-methyl-1-piperazinyl)propyl]-2-trifluoromethylpheno thiazine (hydrochloride)* or *terfluzine* or *terfluzinor discimer* or *eskazine foille* or *iremo* or *piero* or *jatroneural* or *modalina* or *oxyperazine* or *sedofren* or *sporalon* or *stelazine* or *stelazina* or *stelium* or *terflurazine* or *terfluoperazine* or *SKF 5019* or *7623 RP* or *trifluoperazine* or *Solazine* in title, abstract, and index terms of REFERENCE) or (*trifluoperazine* in interventions of STUDY)]
The Cochrane Schizophrenia Group's trials Register is compiled by systematic searches of major databases, handsearches and conference proceedings (see group module). Trials identified through the searching activities are each assigned to awaiting classification of relevant review titles.

Searching other resources

1. Reference searching

We will inspect references of all included studies for further relevant studies.

2. Personal contact

We will contact the first author of each included study for information regarding unpublished trials.

Data collection and analysis

Selection of studies

Review author KM will independently inspect citations from the searches and identify relevant abstracts. A random 20% sample will be independently re-inspected by KK and EH to ensure reliability. Where disputes arise, the full report will be acquired for more detailed scrutiny. Full reports of the abstracts meeting the review criteria will be obtained and inspected by KM. Again, a random 20% of reports will be re-inspected by KK and EH. in order to ensure reliable selection. Where it is not possible to resolve disagreement by discussion, we will attempt to contact the authors of the study for clarification.

Data extraction and management

1. Extraction

Review author KM will extract data from all included studies. In addition, to ensure reliability, KK and EH will independently extract data from a random sample of these studies, comprising 10% of the total. Again, any disagreement will be discussed, decisions documented and, if necessary, authors of studies will be contacted for clarification. With remaining problems KM, KK and EH will help clarify issues and these final decisions will be documented. Data presented only in graphs and figures will be extracted whenever possible, but included only if two review authors independently have the same result. We will attempt to contact authors through an open-ended request in order to obtain missing information or for clarification whenever necessary. If studies are multicentre, where possible, we will extract data relevant to each component centre separately.

2. Management

2.1 Forms

We will extract data onto standard, 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 trialists for that particular trial.

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. On the other hand, calculation of change needs two assessments (baseline and endpoint) which can be difficult 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. Endpoint and change data will be combined in the analysis as we will use mean differences (MD) rather than standardised mean differences (SMD) 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 aim to apply the following standards to all data before inclusion:

a) standard deviations (SDs) and means are reported in the paper or obtainable from the authors;
b) when a scale starts from the finite number zero, the SD, when multiplied by two, is less than the mean (as otherwise the mean is unlikely to be an appropriate measure of the centre of the distribution, (Altman 1996);
c) if a scale starts from a positive value (such as the Positive and Negative Syndrome Scale (PANSS), (Kay 1986)) which can have values from 30 to 210), the calculation described above will be modified to take the scale starting point into account. In these cases skew is present if 2 SD > (S-S min), where S is the mean score and 'S min' is the minimum score.
Endpoint scores on scales often have a finite start and end point and these rules can be applied. Skewed data pose less of a problem when looking at means if the sample size is large (> 200) and we will enter these into the syntheses. We will present skewed endpoint data from studies of less than 200 participants in 'Additional tables' rather than enter such data in analyses.

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 data are skewed or not. We will present and enter skewed change data into analyses.

2.5 Common measure

To facilitate comparison between trials, we intend 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, efforts will be made 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 2005; Leucht 2005a). 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 trifluoperazine. Where keeping to this makes it impossible to avoid outcome titles with clumsy double-negatives (e.g. 'Not improved') we will report data where the left of the line indicates an unfavourable outcome. This will be noted in the relevant graphs.

Assessment of risk of bias in included studies

Again, review authors KM, KK and EH will work independently to assess risk of bias by using criteria described in the *Cochrane Handbook for Systemic reviews of Interventions* (Higgins 2011) to assess trial quality. 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, the final rating will be made 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. Non-concurrence in quality assessment will be reported, but if disputes arise as to which category a trial is to be allocated, again, we will resolve by discussion.
The level of risk of bias will be noted 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). It has been shown that RR is more intuitive (Boissel 1999) than odds ratios and that odds ratios tend to be interpreted as RR by clinicians (Deeks 2000). For binary data presented in the Summary of Findings table, where possible, we will calculate illustrative comparative risks as the Number Needed to Treat/Harm (NNT/H)

statistic with its confidence intervals is intuitively attractive to clinicians but is problematic both in its accurate calculation in meta-analyses and interpretation (Hutton 2009).

2. Continuous data

For continuous outcomes, we will estimate mean difference (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 (Divine 1992) whereby P values are spuriously low, confidence intervals unduly narrow and statistical significance overestimated. 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). 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.

We have sought statistical advice and have been advised that the binary data as 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 [Design effect = 1+(m-1)*ICC] (Donner 2002). If the ICC is not reported it will be assumed to be 0.1 (Ukoumunne 1999).

If cluster studies have been appropriately analysed taking into account ICCs and relevant data documented in the report, 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. It 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 on entry to the second phase the participants can differ systematically from their initial state 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 effects are very likely in severe mental illness, we will only use data of the first phase of cross-over studies.

3. Studies with multiple treatment groups

Where a study involves more than two treatment arms, if relevant, the additional treatment arms will be presented in comparisons. If data are binary these will be simply added and combined 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 Systemic reviews of Interventions* (Higgins 2011). Where the additional treatment arms are not relevant, we will not use 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, (except for the outcome 'leaving the study early'). 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 mark such data with (*) to indicate that such a result may well be prone to bias.

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 analysis). Those leaving the study early are all assumed to have the same rates of negative outcome as those who completed, with the exception of the outcomes of death and adverse effects. For these outcomes, the rate of those who stay in the study - in that particular arm of the trial - will be used for 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 intention-to-treat analysis using the above assumptions.

3. Continuous

3.1 Attrition

In the case 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, we will reproduce these.

3.2 Standard deviations

If standard deviations (SDs) are not reported, we will first try to obtain the missing values from the authors. If not available, where there are missing measures of variance for continuous data, but an exact standard error (SE) and confidence intervals available for group means, and either the 'P' value or 't' value are available for differences in mean, we can calculate them according to the rules described in the *Cochrane Handbook for Systemic reviews of Interventions* (Higgins 2011): When only the SE is reported, SDs are calculated by the formula SD = SE * square root (n). Chapters 7.7.3 and 16.1.3 of the *Cochrane Handbook for Systemic reviews of Interventions* (Higgins 2011) present detailed formulae for estimating SDs from P values, t or F values, confidence intervals, ranges or other statistics. 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. We nevertheless will examine the validity of the imputations in a sensitivity analysis excluding imputed values.

3.3 Last observation carried forward

We anticipate that in some studies the method of last observation carried forward (LOCF) will be employed within the study report. As with all methods of imputation to deal with missing data, LOCF introduces uncertainty about the reliability of the results (Leucht 2007). Therefore, where LOCF data have been used in the trial, if less than 50% of the data have been assumed, we will present and use these data and indicate that they are the product of LOCF assumptions.

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 clearly outlying people or situations which we had not predicted would arise. When such situations or participant groups arise, these will be fully discussed.

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. When such methodological outliers arise, these will be fully discussed.

3. Statistical heterogeneity

3.1 Visual inspection

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

3.2 Employing the I^2 statistic

Heterogeneity between studies will be investigated by considering the I^2 method alongside the Chi^2 'P' value. The I^2 provides an estimate of the percentage of inconsistency thought to be due to chance (Higgins 2003). The importance of the observed value of I^2 depends on i. magnitude and direction of effects and ii. strength of evidence for heterogeneity (e.g. 'P' value from Chi^2 test, or a confidence interval for I^2). An I^2 estimate greater than or equal to around 50% accompanied by a statistically significant Chi^2 statistic, will be interpreted as evidence of substantial levels of heterogeneity (Section 9.5.2 - Higgins 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

1. Protocol versus full study

Reporting biases arise when the dissemination of research findings is influenced by the nature and direction of results. These are described in section 10.1 of the *Cochrane Handbook for Systemic reviews of Interventions* (Higgins 2011). We will try to locate protocols of included randomised trials. If the protocol is available, outcomes in the protocol and in the published report will be compared. If the protocol is not available, outcomes listed in the methods section of the trial report will be compared with actually reported results.

2. Funnel plot

Reporting biases arise when the dissemination of research findings is influenced by the nature and direction of results (Egger 1997). These are again described in Section 10 of the *Cochrane Handbook for Systemic reviews of Interventions* (Higgins 2011). 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 ten or fewer studies, or where all studies are of similar sizes. 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 a random-effect model for all analyses. The reader is, however, able to choose to inspect the data using a fixed-effect model.

Subgroup analysis and investigation of heterogeneity

1. Subgroup analyses

We do not anticipate any subgroup analyses.

1.2 Clinical state, stage or problem

We propose to undertake this review and provide an overview of the effects of trifluoperazine 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.

2. Investigation of heterogeneity

If inconsistency is high, this will be reported. First, we will investigate whether data have been entered correctly. Second, if data are correct, we will visually inspect the graph and outlying studies will be successively removed to see if homogeneity is restored. For this review we decided that should this occur with data contributing to the summary finding of no more than around 10% of the total weighting, data will be presented. If not, data are not pooled and issues will be discussed. 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 are 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

1. Implication of randomisation

We aim to include trials in a sensitivity analysis if they are described in some way as to imply randomisation. For the primary outcomes, we will include these studies and if there is no substantive difference when the implied randomised studies are added to those with better description of randomisation, then all data will be employed from these studies.

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/s and when we use data only from people who complete the study to that point. If there is a substantial difference, we will report results and discuss them but will continue to employ our assumption.
Where assumptions have to be made regarding missing SDs data (see Dealing with missing data), we will compare the findings of the primary outcomes when we use our assumption/s and when we use data only from people who complete the study to that point. A sensitivity analysis will be undertaken to test how prone results are to change when completer-only 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 will continue to employ our assumption.

3. Risk of bias

We will analyse the effects of excluding trials that are judged to be at high risk of bias across one or more of the domains of randomisation (implied as randomised with no further details available), allocation concealment, blinding and outcome reporting for the meta-analysis of the primary outcome. If the exclusion of trials at high risk of bias does not substantially alter the direction of effect or the precision of the effect estimates, then data from these trials will be included in the analysis.

4. Imputed values

We will also undertake a sensitivity analysis to assess the effects of including data from trials where we used imputed values for ICC in calculating the design effect in cluster randomised trials.
If substantial differences are noted in the direction or precision of effect estimates in any of the sensitivity analyses listed above, we will not pool data from the excluded trials with the other trials contributing to the outcome, but will present them separately.

5. Fixed and random effects

All data will be synthesised 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.

6. Unusual doses of trifluoperazine

Again, only working with primary outcomes, we will investigate whether doses over 30mg of trifluoperazine do have any different effects than more modest doses.

ACKNOWLEDGEMENTS

The Cochrane Schizophrenia Group Editorial Base in Nottingham produces and maintains standard text for use in the Methods section of their reviews. We have used this text as the basis of what appears here and adapted it as required.

The search term was developed by the Trial Search Co-ordinator of the Cochrane Schizophrenia Group (Samantha Roberts) and the contact author of this protocol.

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* *Indicates the major publication for the study*

HISTORY

Protocol first published: Issue 11, 2012

CONTRIBUTIONS OF AUTHORS

Kai Koch - wrote the protocol.

Kamel Mansi - checked the protocol.

Euan Haynes - checked the protocol.

Clive E Adams - checked the protocol.

DECLARATIONS OF INTEREST

Kai Koch - none.

Kamel Mansi - none.

Euan Haynes - none.

Clive E Adams - none.

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