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Fluphenazine decanoate (timing of administration) for people with schizophrenia (Protocol)

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[Intervention Protocol]

Fluphenazine decanoate (timing of administration) 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 benefits and harm of administering fluphenazine decanoate at different time intervals for people with schizophrenia.

BACKGROUND

Description of the condition

Schizophrenia is a debilitating, severe and often chronic mental disorder with a global lifetime prevalence of about 1% (Dickenson 2013; Zare 2017). It usually starts between ages 16 and 30, and in rare cases during childhood or old age. Slightly more men are diagnosed with schizophrenia than women (in the order of 1.4:1) (Abel 2010), but women tend to be diagnosed later in life than men.

Schizophrenia affects how a person thinks, feels, and behaves. Its characteristics typically include positive symptoms (delusions and hallucinations), negative symptoms (flattening and poverty of speech, social withdrawal, inability to find pleasure in activities normally considered pleasurable, and a lack of drive), disorganisation of behaviour and thought, and catatonic symptoms such as mannerisms and bizarre posturing (Carpenter 1994; Elis 2013). It is commonly associated with impairments in social and occupational functioning. Life expectancy in people with schizophrenia can fall by up to 20% because of an increased risk of suicide and of cardiovascular, metabolic and infectious diseases (Hennekens 2005; NIMH). Individuals are also likely to have other psychiatric co-morbidities, such as panic disorder and depression (Buckley 2009). In addition, stigma, discrimination and violation of human rights of people with schizophrenia are common (WHO 2016).

Schizophrenia is one of 25 leading causes of disability worldwide (Global Burden of Disease Study 2013) and people with schizophrenia are more likely to be single and unemployed (Dickenson 2013; Messias 2007). It also ranks among the top seven causes for loss of years of life due to disability (Dold 2015), and the health, social and economic impact has been tremendous,

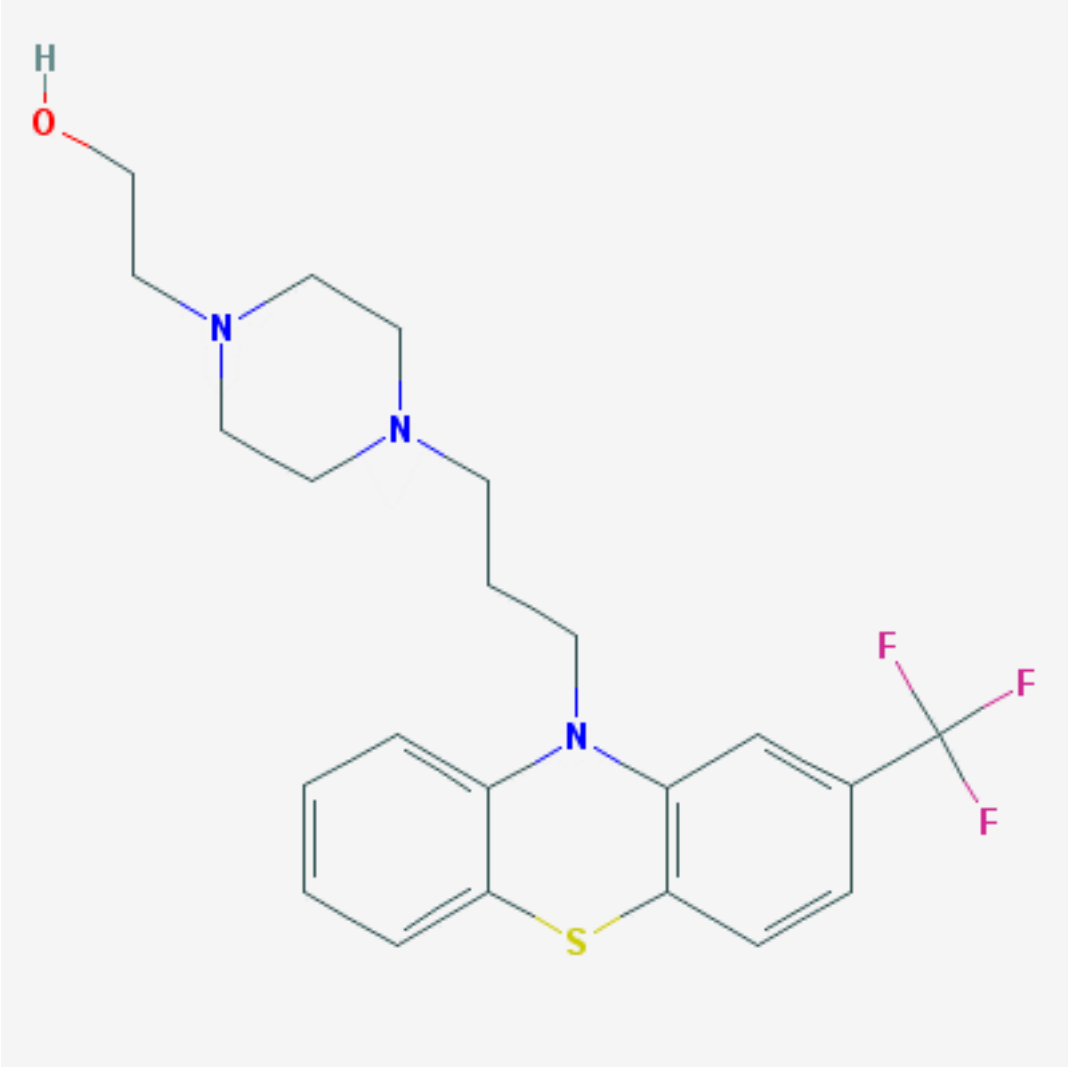
for people with schizophrenia, their relatives and other caregivers. 1.6% to 2.6% of total healthcare expenditure in western countries is related to schizophrenia, and in the USA, the economic burden of schizophrenia is more than $60 billion per year (Chong 2016). A number of risk factors have been associated with the development of schizophrenia, including living in an urban area (Krabbendam 2005; Pedersen 2001; Pedersen 2001a), immigration (Bourque 2011; Werbeloff 2012), obstetrical complications (Clarke 2006), late winter-early spring time of birth (perhaps reflecting exposure to influenza virus during neural development), and cannabis abuse (Auther 2012).

Description of the intervention

Schizophrenia is treatable. Treatment with medicines and psychosocial support is effective, one-third of those diagnosed with schizophrenia fully recover (Rattehalli 2010). Antipsychotics have been, and remain the main treatment option.

Antipsychotics are commonly divided into typical and atypical groups. They treat positive symptoms, with less efficacy on negative symptoms (Kane 1986), and they can lead to severe side effects such as akathisia, parkinsonism, and tardive dyskinesia (Gerlach 2002). Fluphenazine (Figure 1) is a typical antipsychotic drug from the phenothiazine group, and was approved by the US Food and Drug Administration (FDA) in 1959 (Drugs.com). Fluphenazine has two long-acting parenteral forms, a decanoate (Modecate) and an enanthate. The decanoate is more commonly prescribed (Marder 1990) and last longer in the body than enanthate (four to six weeks compared to one to three week respectively) (Maayan 2015). In addition, it is believed to produce slightly less adverse effects than the enanthate counterpart (Kurland 1970).

Figure 1. Fluphenazine structure (2-[4-[3-[2-(trifluoromethyl)phenothiazin-10-yl]propyl]piperazin-1-yl]ethanol) (PubChem)



Fluphenazine is characterised by variable pharmacokinetics, marked mostly with the oral forms. Fluphenazine undergoes extensive first-pass metabolism and is excreted in both urine and faeces, and it is highly protein-bound (greater than 90%) in plasma. Peak plasma levels occur within hours and half-life is approximately 15 hours (Dencker 1988; Dysken 1981). In addition, fluphenazine crosses the blood-brain barrier, crosses the placenta easily and cannot be removed by dialysis.

Fluphenazine decanoate is usually administered by deep intramuscular (IM) injection into the gluteal region. Most patients are successfully maintained within the dose range 12.5 mg to 100 mg given at a dose interval of two to five weeks (eMC 2014). However, the optimal amount of fluphenazine decanoate and the frequency of administration must be determined for each patient, since dosage requirements have been found to vary with clinical circumstances as well as with individual response to the drug. When administered as a maintenance therapy, a single injection is thought to be effective in controlling the symptoms of schizophrenia for up to four weeks (Drugs.com). However, the response to a single dose has been found to last as long as six weeks in a few patients on maintenance therapy (Medsafe 2013). Fluphenazine decanoate is not intended for use in children under 12 years of age (Bedford Laboratories 2008).

The side effects of fluphenazine range from orthostatic hypotension, to anticholinergic and extrapyramidal symptoms (tardive dyskinesia, pseudo-parkinsonism, dystonia, dyskinesia and akathisia). In addition, anti-psychotics -especially first generation- are responsible for a significant lowering in people's mood (Maayan 2015). Moreover, the use of fluphenazine has been associated with the potentially fatal neuroleptic malignant syndrome (Berman 2011).

How the intervention might work

An imbalance in the brains neurotransmitters dopamine and glutamate, and possibly others, plays a role in schizophrenia (NIMH). Fluphenazine blocks postsynaptic dopamine D1a receptors and D2 receptors in the limbic, cortical system and basal ganglia (PubChem Compound Database; Seeman 2002). This blockade is thought to be responsible for reducing positive symptoms such as hallucinations and delusions.

Fluphenazine (decanoate) has a half-life of 6.8 to 9.6 days following IM administration (Drugs.com). Intervals between fluphenazine decanoate doses may play a critical role in managing patients' symptoms and efficacy.

Depots mainly consist of an ester of the active drug held in an oily suspension. This is injected intramuscularly and is slowly released. With depot treatment, a better correlation between administered dose and drug concentration in plasma is achieved, which gives clinicians more control over the amount of drug delivered. In addition, depot treatment provides stable plasma concentration over long periods (Drugs.com). However, this may represent a disadvantage as this may lead to lack of flexibility of administration (on adverse events, the drug cannot be quickly withdrawn). Moreover, it becomes a long-term strategy to adjust to the optimal dose.

The main suggested advantage of depot antipsychotic medication is that it eradicates covert non-compliance. It is suggested to play major impact on compliance, which consequently affects and reduces the risk of relapse and hospitalisation. Patients may be monitored in the community on a regular basis by community psychiatric nurses who administrate regular injections (Barnes 1994).

Why it is important to do this review

Given the need for long-acting drugs for the management of schizophrenia, many drugs have gained great Interest. Fluphenazine decanoate is still one of the drugs used widely (Marcus 2015). As a long-acting drug, it may be prescribed at different times in the course of schizophrenia (Uchida 2014). While it is most commonly prescribed every four weeks, it is sometimes prescribed every two to three weeks, and every five to six weeks (Baron 1989; Uchida 2014). It is important to identify the best timing of administration of fluphenazine decanoate as it contributes to the efficacy in relieving symptoms, reducing side effects, improving treatment adherence and limiting relapse and disability (Levinson 1992; Marcus 2015).This review aims to detect the best timing of application to treat schizophrenia and improve the quality of patients' lives by relieving symptoms, reducing relapse and increasing compliance.

OBJECTIVES

To investigate the benefits and harm of administering fluphenazine decanoate at different time intervals for people with schizophrenia.

METHODS

Criteria for considering studies for this review

Types of studies

We will include all relevant randomised controlled trials that investigate fluphenazine decanoate timing of administration for people with schizophrenia. We will include trials that are described as 'double-blind' in which randomisation is implied in a sensitivity analysis (see Sensitivity analysis). If their inclusion does not result in a substantive difference, they will be retained in the analysis. If their inclusion does result in important clinically significant, but not necessarily statistically significant differences, we would not add the data from these lower-quality studies. 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 fluphenazine, we will only include data if the adjunct treatment is evenly distributed between groups and it is only the timing of fluphenazine administration that is randomised.

Types of participants

Adolescents (aged 11 to 17 years) and adults (aged 18 years and over) with schizophrenia or related disorders, including schizophreniform disorder, schizoaffective disorder and delusional disorder, by any means of diagnosis.

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 focused on people with particular problems (for example, negative symptoms, treatment-resistant illnesses).

Types of interventions

1. Fluphenazine decanoate at any dose: administered every four weeks.

2. Fluphenazine decanoate at any dose: administered in more than four-week intervals.
3. Fluphenazine decanoate at any dose: administered in less than four-week intervals.

Types of outcome measures

If possible, we will divide all outcomes into immediate (zero to five weeks) short term (six weeks to five months), medium term (six months to one year) and long term (over 12 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 changes in global state, as defined by each study
1.2 Clinically important change in compliance with treatment
1.3 Relapse

2. Mental state

2.1 General

2.1.1 Clinically important change in overall mental state, as defined by each study

3. Quality of life

3.1 Clinically important changes in quality of life/satisfaction, as defined by each study

4. Adverse effects/events

4.1 Clinically important specific adverse effects - movement disorder, as defined by each of the studies

Secondary outcomes

1. Global state

1.1 Any change in global state, as defined by each of the studies
1.2 Average endpoint/change score on global state scale

2. Mental state

2.1 General

2.1.2 Any change in overall mental state, as defined by each study
2.1.3 Average endpoint/change scores on general mental state scale

2.2 Specific

2.2.1 Clinically important change in positive symptoms (e.g. delusions, hallucinations), as defined by each study
2.2.2 Any change in positive symptoms, as defined by each study
2.2.3 Average endpoint/change scores on positive symptom scale
2.2.4 Clinically important change in negative symptoms (e.g. affective flattening, alogia, or avolition), as defined by each study
2.2.5 Average endpoint/change scores on negative symptom scale

3. Quality of life

3.1 Any change in quality of life, as defined by each of the studies
3.2 Average endpoint/change score on quality of life scale

4. Adverse effects/event

4.1 At least one adverse effect/event
4.2 Clinically important specific adverse effects, as defined by each of the studies (e.g. anticholinergic, antihistamine, endocrinological, cardiovascular, genitourinary, gastrointestinal, neurological, respiratory, abnormal laboratory tests and any other specific adverse effects)
4.3 Average endpoint/change score on general adverse effect scale
4.4 Death - suicide or other causes

5. Service use

5.1 Hospital admissions
5.2 Duration of stay in hospital
5.3 Change in hospital status

6. Satisfaction with care for either recipients of care or caregivers

6.1 Clinically important change in satisfaction, as defined by each study
6.2 Any change in satisfaction, as defined by each study
6.3 Average endpoint/change scores on satisfaction scale

7. Leaving the study early

7.1 For any reason
7.2 Due to relapse
7.3 Due to adverse effects

8. Cognitive functioning

8.1 Clinically important change in cognitive functioning, as defined by each study
8.2 Any change in cognitive functioning, as defined by each study
8.3 Average endpoint/change score on cognitive functioning scale

9. Behaviour

9.1 Clinically important change in general behaviour, as defined by each study
9.2 Any change in general behaviour, as defined by each study
9.3 Average endpoint/change scores on general behaviour scale
9.4 Incidence aggression/violence.

10. Social functioning

10.1 Clinically important change in social functioning, as defined by each study
10.2 Any change in social functioning, as defined by each study
10.3 Average endpoint/change scores on social functioning scale

11. Economic costs

11.1 Costs due to treatment, as defined by each study
11.2 Savings due to treatment, as defined by each study

'Summary of findings' table

We will use the GRADE approach to interpret findings (Schunemann 2011); and will use GRADE profiler 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 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.

- Global state: Clinically important change in global state, as defined by each study - long-term
- Global state: Clinically important change in compliance with treatment
- Global state: Relapse
- Mental state: Clinically important change in overall mental state, as defined by each of the studies - long term
- Quality of life: Clinically important change in quality of life/satisfaction, as defined by each of the studies - long term
- Adverse effects/events: Clinically important specific adverse effects - movement disorder, as defined by each of the studies - medium term
- Satisfaction with care: Clinically important change in satisfaction, as defined by each of the studies

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

Search methods for identification of studies

Electronic searches

Cochrane Schizophrenia Group's Study-Based Register of Trials

The Information Specialist of the Cochrane Schizophrenia Group will search the register using the following search strategy:
"Timing - Fluphenazine Decanoate" in Intervention Field of STUDY
In such study-based register, searching the major concept retrieves all the synonyms and relevant studies because all the studies have already been organised based on their interventions and linked to the relevant topics (Shokraneh 2017).
This register is compiled by systematic searches of major resources (AMED, BIOSIS, CINAHL, ClinicalTrials.Gov, Embase, MEDLINE, PsycINFO, PubMed, WHO ICTRP) and their monthly updates, ProQuest Dissertations and Theses A&I and its quarterly update, Chinese databases (CBM, CNKI, and Wanfang) and their annual updates, hand-searches, grey literature, and conference proceedings (see Group's Module). There is no language, date, document type, or publication status limitations for inclusion of records into the register.

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. We will note the outcome of this contact in the 'Included studies' or 'Studies awaiting classification' tables.

Data collection and analysis

Selection of studies

All review authors will independently inspect all citations from the searches and identify relevant abstracts. Where disputes arise, we will retrieve the full-text report for further assessment. We will obtain full reports of conference proceedings which meet the review criteria and all review authors will independently inspect these before adding relevant trials to the review. Where it is not possible to resolve the disagreement, we will add these trials to the list of those awaiting and we will attempt to contact the authors of the study for clarification. We will include trials meeting our selection criteria and reporting useable data.

Data extraction and management

1. Extraction

All review authors will independently extract data from all included studies, again, we will discuss any disagreement, document our decisions and, if necessary, we will attempt to contact authors of studies for clarification, and we will document the final decisions. We will attempt to extract data presented only in graphs and figures whenever possible, but will only include data for which the review authors have independently extracted the same results. We will attempt to contact authors through an open-ended request in order to obtain missing information or for clarification whenever necessary. For multicentric studies, if possible, we will extract data relevant to each component centre separately.

2. Management

2.1 Forms

We will extract data onto pre-standardised data extraction 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);
b) the measuring instrument has not been written or modified by one of the trialists for that particular trial; and
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, we will include sub-scores from mental state scales measuring positive and negative symptoms of schizophrenia.

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. Where relevant, 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 such data 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.
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 intend, where possible, 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 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 fluphenazine decanoate. 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 make a note of this in the relevant graphs.

Assessment of risk of bias in included studies

All review authors will work independently to assess risk of bias by using 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 potential overestimation of effect and the level of risk of bias of the article that may be due to aspects of sequence generation, allocation concealment, blinding, incomplete outcome data and selective reporting, or the way in which these 'domains' are reported.
If the raters disagree, we will make the final rating by consensus. Where inadequate details of randomisation and other characteristics of trials are provided, we will attempt to contact authors of the studies in order to obtain 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.

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. 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 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 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 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 30% of data be unaccounted for we will not reproduce these data or use them within analyses. If, however, more than 30% of those in one arm of a study are lost, but the total loss is less than 30%, 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 30% in total.

2. Binary

In the case where attrition for a binary outcome is between 0% and 30% 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 30%, 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* (Higgins 2011). When only the SE is reported, SDs are calculated by the formula SD = SE * $\sqrt{}$(n). The *Cochrane Handbook for Systematic Reviews of Interventions* presents detailed formulae for estimating SDs from P, t or F values, CIs, ranges or other statistics (Higgins 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 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 I^2 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 confidence interval for I^2). We will interpret an I^2 estimate greater than or equal to 50% and accompanied by a statistically significant Chi^2 statistic as evidence of substantial heterogeneity (Chapter 9. *Cochrane Handbook for Systematic Reviews of Interventions*) (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 to use random-effects for all analyses.

Subgroup analysis and investigation of heterogeneity

1. Subgroup analyses

We do not anticipate any subgroup analyses

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

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* *Indicates the major publication for the study*

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Fatima Abbas: initiated and wrote protocol.

Tawfik Rajab and Nawras Alhalabi developed the background.

Omar Alsamarrai and Oubadah Mheish and Sarah Zaher Addeen and Aisha Aljojo drafted and reviewed methods of the protocol.

Adib Essali revised the methodology, writing and content of the protocol before submission.

DECLARATIONS OF INTEREST

Fatima Abbas: none known.

Tawfik Rajab: none known.

Omar Alsamarrai: none known.

Nawras Alhalabi: none known.

Sarah Zaher Addeen: none known.

Oubadah Mheish: none known.

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