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Chlorpromazine versus thiothixene for people with schizophrenia (Protocol)

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[Intervention Protocol]

Chlorpromazine versus thiothixene for people with schizophrenia

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ABSTRACT

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

To review the effects of chlorpromazine compared with thiothixene for people with schizophrenia.

BACKGROUND

Description of the condition

Schizophrenia is a chronic and disabling mental illness. Its symptoms include, but are not limited to, cognitive impairment, delusions (fixed beliefs that are not amenable to change in light of conflicting evidence) (Tandon 2013), and hallucinations (sensory perception that has the compelling sense of reality of a true perception) (Owen 2016). A previous systematic review found the incidence of schizophrenia diagnosis to be between 0.5% to 1% of the global population (McGrath 2004). Furthermore, its age of onset is usually between 15 and 30 years old (Sham 1994). The cause of schizophrenia remains unclear with a multitude of genetic and environmental factors being postulated to be the underlying genesis of the heterogeneous symptomology of this disorder. People with a genetic predisposition have a higher risk for schizophrenia (Goff 2016; Owen 2016). Half of all people with the illness have long-term disability and for about one in five people the symptoms will be chronic (Barbato 1998). Adding to this, depression is found in half of those with schizophrenia, one in three experience comorbid post-traumatic stress disorder, and one in four have comorbid obsessive-compulsive disorder (Buckley 2009). Life expectancy is 10 to 20 years below the norm (Chesney 2014). The World Health Organization (WHO) ranks schizophrenia as the ninth most burdensome illness globally (Deshpande 2016; WHO 2011). In England alone, the price of clinical healthcare and social community care is believed to be GBP 11.8 billion annually (Schizophrenia Commission 2012).

Description of the intervention

First-line treatment options for schizophrenia are use of antipsychotic medications, combined with psychological therapy and community support (Owen 2016). These medications, perhaps chlorpromazine in particular, have revolutionised the care of people with schizophrenia by effectively treating the core symptoms of this illness (Turner 2007). There are many antipsychotic drugs, old and new, available for the treatment of schizophrenia. With 80% of the world's population of people (therefore, 80% of those

with schizophrenia) living in low- to middle-income countries, inexpensive treatments are important to fully appraise; with, perhaps, the benefit of also helping wealthier care cultures not to forget valuable treatments (Adams 2005; WHO 2011).

Chlorpromazine was developed in 1951 by scientist Paul Charpentier, and was not created intentionally as an antipsychotic (Meyer 1997). Instead its primary purpose was to aid anaesthesia and prevent people from going into surgical shock (Hamon 1952). Researchers discovered that it was a multifunctional medication (so it has a commercial name of Largactil [large-act-ill]) (Bryan 2011), and that one of these functions was to affect psychotic symptoms. Chlorpromazine was the first antipsychotic medication available to people with schizophrenia who would have previously been treated with sedatives, such as bromides and barbiturates (Ban 2007; Turner 2007). Due to the success of chlorpromazine, many were able to be discharged and live lives largely outside of hospital (Bryan 2011). Chlorpromazine seemed able to stabilise symptoms of schizophrenia, especially delusions, hallucinations, and disorganisation in thought and behaviour (Meyer 1997). The success of chlorpromazine led the way for other antipsychotic medications to be manufactured (López-Muñoz 2005), and remains a medication of choice for many clinicians worldwide as it is listed on the WHO essential drugs list (WHO 2015).

Thiothixene is an antipsychotic from a different drug 'family' (thioxanthenes with anticholinergic properties as opposed to phenothiazine family of chlorpromazine), which was introduced to the market in 1967 under the trade name of Navane by the pharmaceutical company Pfizer (FDA 2016). Thiothixene is considered to be more potent than chlorpromazine (Leung 2015), and has been found to cause extrapyramidal symptoms (hand tremor, gait disturbances, muscle stiffness), anticholinergic effects (blurred vision, dry mouth), and neuroleptic malignant syndrome (Chew 2009; Karimi 2014). Although the use of thiothixene has significantly declined in recent decades, with newer antipsychotics such as risperidone being favoured by those who prescribe antipsychotics (NCBI 2016a), thiothixine continues to be manufactured and licensed in several countries (Table 1; Table 2).

How the intervention might work

The antipsychotic effects of chlorpromazine and thiothixene seem to be due to their action as an antagonist (blocking agent) at the dopamine receptors (D2) of the mesolimbic pathway, reducing the absorption of excess dopamine (Bryan 2011; Howes 2009; Weaver 2015).

Chlorpromazine (2-chloro-10-(3-dimethylaminopropyl)phenothiazine) (Figure 1; Figure 2) is an antipsychotic drug of the phenothiazine series, and acts as an antagonist at D1 and D2 receptors (Seeman 1987). Chlorpromazine also produces effects in the central nervous system (principally at subcortical levels), has powerful antiadrenergic properties, and to a lesser extent antihistaminic, anticholinergic, and antiserotonin properties (NCBI 2016b). Due to its minor effect as a presynaptic inhibitor of dopamine reuptake, chlorpromazine may act to reduce depression and parkinsonism (Wishart 2006).

Figure 1. Chlorpromazine: (2-chloro-10-(3-dimethylaminopropyl)phenothiazine)

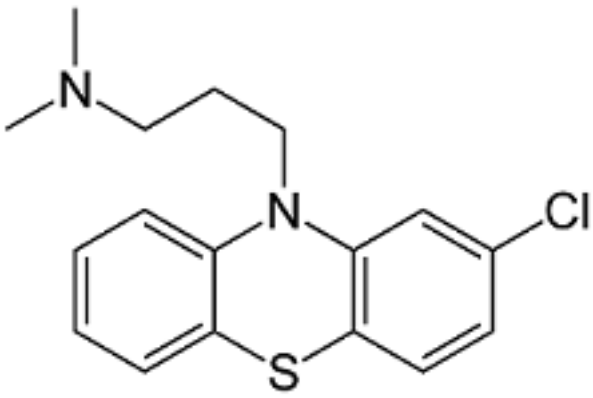
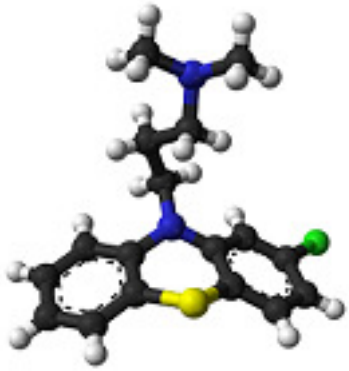
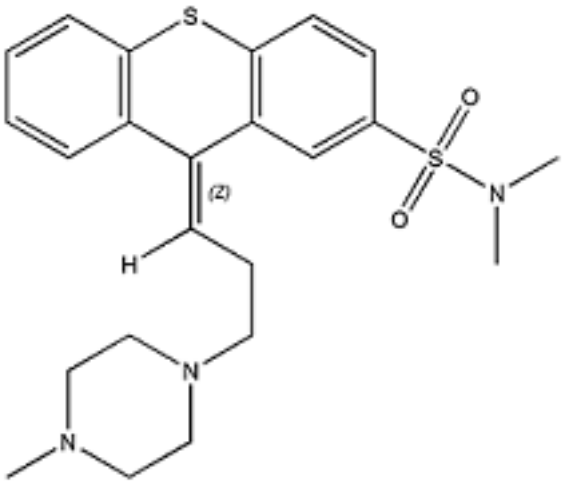


Figure 2. Chlorpromazine: (2-chloro-10-(3-dimethylaminopropyl)phenothiazine)



Thiothixene ((9E)-N,N-dimethyl-9-[3-(4-methylpiperazin-1-yl)propylidene]thioxanthene-2-sulfonamide) (Figure 3) acts as an antagonist by targeting the D1, D2, D3, and D4 dopamine receptors, 5-HT1 and 5-HT2 serotonin receptors, H1 histaminergic receptors, alpha-adrenergic receptors, and the cholinergic M1/M2-receptors (Wishart 2006). Dopamine turnover is increased in response to thiothixene's action as an antagonist at the somatodendritic autoreceptor (NCBI 2016a). Additionally, thiothixene is an antiemetic; its effect of decreasing dopamine receptor activity in turn reduces activity of the vomiting centre in the brain (NCBI 2016a).

Figure 3. Thiothixine: (9E)-N,N-dimethyl-9-[3-(4-methylpiperazin-1-yl)propylidene]thioxanthene-2-sulfonamide)



Why it is important to do this review

Chlorpromazine and thiothixine are two antipsychotic medications used to treat people with schizophrenia. It is important to know if one drug offers an advantage over another in order to provide the optimal care for patients. As far as we understand these medications enjoy markedly different market exposure and should the less-widely distributed thiothixene have advantage over chlorpromazine, this would be important to know. We know of no up-to-date systematic reviews that directly compare these two antipsychotic drugs. This Cochrane Review is one of a series of reviews in order to evaluate chlorpromazine in comparison with other antipsychotics so that a full overview of chlorpromazine's clinical efficacy can be completed (Table 3).

OBJECTIVES

To review the effects of chlorpromazine compared with thiothixene for people with schizophrenia.

METHODS

Criteria for considering studies for this review

Types of studies

We will include all relevant randomised controlled trials (RCTs). We will include trials that are described as 'double blind', in which randomisation is implied, in a sensitity analysis ('Sensitivity analysis' section). We will exclude quasi-randomised studies, such as those that allocate intervention by alternate days of the week.

Types of participants

We will include studies where at least 80% of their participants are aged 18 to 65 years old (representing the adult population in the mental healthcare services) and have a primary diagnosis of schizophrenia by any means of diagnosis (for inclusion no fewer than 60% of the participants in the trial must have schizophrenia). We will not include trials that include people with dual diagnosis. We wish to ensure that we identify information that is as relevant as possible to the current care of people with schizophrenia. Therefore, we will aim, if possible, 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 (e.g. negative symptoms, treatment-resistant illnesses).

Types of interventions

1. Chlorpromazine: any dose, in any form (standard dose ranges are 75 mg to 300 mg)

Brand names: Anadep, Cain, Chloractil, Chlorazin, Chlorectil Plus, Chlorprol, Chlorpromados, Chlorpromanyl, Chlorpromezets, Chlor-PZ, Clozine Forte, Clozine Plus, Cromedazine, Elmarine, Emetil, Emetil-DS, Emetil Plus, Esmind, Fenactil, Hibanil, Hibernal, Klorazine, klorproman, Klorpromex, Lacalm Forte, Largactil, Megaphen, Megatil, Neurazine, Onazine, Plegomazine, Procalm, Promachel, Promachlor, Promacid, Promapar, Promexin, Promexy-HF, Prophaphenin, Prozil, Psychozine, Psylaktil, Reliclam Forte, Reliclam-SF, Relitil, Scrazone, Ser, Serectil, Sonazine, Sun Prazin, Thoradex, Thorazine, Tranzine, Trinicalm forte, and Zinetil.

2. Thiothixine: any dose, in any form (standard dose ranges are 20 mg to 60 mg)

Brand names: Navane, Orbinamon, Navaron, and Tiotixene (inn/usan).

Types of outcome measures

We will, where possible, categorise outcomes as either short- (zero to eight weeks), medium- (two to six months), or long-term (six months to two years).
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, as defined by individual trials

2. Mental state

2.1 General: clinically important overall change, as defined by individual trials

3. Adverse effects

3.1 Specific: movement disorders (such as extrapyramidal side effects, specifically tardive dyskinesia, and neuroleptic malignant syndrome) - clinically important overall change, as defined by individual trials

Secondary outcomes

1. Global state

1.1 Relapse, as defined by each study
1.2 Any change in global state
1.3 Average endpoint or change score global state scale

2. Mental state

2.1 General

2.1.1 Any change in overall mental state, as defined by each of the studies
2.1.2 Average endpoint or change score on overall mental state scale

2.2 Specific (e.g. positive, negative, affective, cognitive symptoms of schizophrenia)

2.2.1 Clinically important change in specific symptoms, as defined by each of the studies
2.2.2 Any change in specific symptoms, as defined by each of the studies
2.2.3 Average endpoint or change score specific symptom scale

3. Adverse effects

3.1 General adverse effects

3.1.1 At least one adverse effect
3.1.2 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 Cardiovascular
3.2.3 Central nervous system
3.2.4 Gastrointestinal
3.2.5 Endocrine (e.g. amenorrhoea, galactorrhoea, hyperlipidaemia, hyperglycaemia, hyperinsulinaemia)
3.2.6 Haematology (e.g. haemogram, leukopenia, agranulocytosis/neutropenia)
3.2.7 Hepatic (e.g. abnormal transaminase, abnormal liver function)
3.2.8 Metabolic
3.2.9 Movement disorders (other than primary outcome effects)
3.2.10 Various other
3.2.11 Death - suicide and natural causes

4. Service use

4.1 Hospital admission/re-admission
4.2 Duration of hospital stay

5. Leaving the study early

5.1 Any reason
5.2 Specific reasons

6. Behaviour

6.1 General behaviour

6.1.1 Clinically important change overall behaviour, as defined by individual trials
6.1.2 Average endpoint/change scores general behaviour scale

6.2 Specific behaviours

6.2.1 Aggressive or violent behaviour

7. Functioning

7.1 Clinically important change in specific aspects of functioning, such as life skills or social functioning, as defined by each of the studies
7.2 Any change in specific aspects of functioning, such as life skills or social functioning, as defined by each of the studies
7.3 Average endpoint or change score nonspecific aspects of functioning scale, such as life skills or social functioning, as defined by each of the studies
7.4 Any change in employment status (employed/unemployed) during trial, as defined by each study.

8. Satisfaction with care (recipients of care or carers) (including subjective well-being and family burden)

8.1 Recipient

8.1.1 Clinically important change in satisfaction, as defined by each of the studies
8.1.2 Recipient of care satisfied/not satisfied with treatment
8.1.3 Recipient of care average endpoint or change score on satisfaction scale

8.2 Carers (including health professionals)

8.2.1 Clinically important change in satisfaction, as defined by each of the studies
8.2.2 Carer satisfied/not satisfied with treatment (general impression of carer/other)
8.2.3 Carer average endpoint or change score on satisfaction scale

9. Economic outcomes

9.1 Costs due to treatment, as defined by each study
9.2 Total direct and indirect costs
9.3 Average change in total cost of medical and mental health care

'Summary of findings' table

We will use the GRADE approach to interpret findings Schünemann 2011 and use GRADEpro to export data from our review to create a 'Summary of findings' table. These tables provide outcome-specific information concerning the overall quality of evidence from each study in the comparison, the magnitude of effect of the interventions, and the sum of available data on all outcomes we consider important to patient-care and decision making. We have selected the following main outcomes for inclusion in the 'Summary of findings' table.

1. Global state: clinically important overall change
2. Mental state: general symptoms - clinically important overall change
3. Adverse effects: specific - movement disorders (extrapyramidal side effects, specifically tardive dyskinesia and neuroleptic malignant syndrome) - clinically important overall change
4. Behaviour: specific - aggressive or violent behaviour
5. Leaving the study early: any reason
6. Satisfaction with care: recipients of care or carers - clinically important change - as defined by each of the studies
7. Cost of care: total direct and indirect costs

If data are unavailable for these prespecified outcomes but are available for ones that are similar, we will present the closest outcome to the prespecified one in the table but take this into account when grading the finding.

Search methods for identification of studies

Electronic searches

The Information Specialist will search the Cochrane Schizophrenia Group's trials register using the following search strategy: (*chlorpromazine* AND *thiothixene*) in Intervention Field of STUDY.

The Cochrane Schizophrenia Group's Trials Register is compiled by systematic searches of major resources (including AMED, BIOSIS, CINAHL, Embase, MEDLINE, PsycINFO, PubMed, and registries of clinical trials) and their monthly updates, handsearches, grey literature, and conference proceedings (see the Group's Module for further information). There are 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 the references of all identified studies for further studies.

2. Pharmaceutical companies

We will contact pharmaceutical companies for any unpublished and published trials.

Data collection and analysis

Selection of studies

Three review authors (PS, BD, and JW) will independently screen citations from the searches and identify relevant abstracts. One review author (DC) will independently re-inspect a random 20% sample of these abstracts to ensure reliability. Where disputes arise, we will acquire the full-text article for more detailed scrutiny. Three review authors (PS, BD, and JW) will then obtain and inspect the full reports of the abstracts or reports that meet the review criteria. One review authors, DC, will re-inspect a random 20% of these full reports in order to ensure reliable selection. We will resolve any disagreement by discussion. We will include studies that meet our inclusion criteria and report useable data. We will list all studies excluded after full-text assessment and their reason(s) for exclusion in a 'Characteristics of excluded studies' table. We will illustrate the study selection process in a PRISMA flow diagram.

Data extraction and management

1. Extraction

Two review authors (PS and BD) will extract data from all included studies. In addition, to ensure reliability, review author DC will independently extract data from a random sample of these studies, which will comprise 10% of the total. Again, we will discuss and document any disagreement and, if necessary CEA (see Acknowledgements) will help clarify issues and we will document these final decisions. We will attempt to extract data presented only in graphs and figures whenever possible. 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 standardized, 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 trial authors for that particular trial.
c) the instrument should be a global assessment of an area of functioning and not subscores which are not, in themselves, validated or shown to be reliable.
However there are exceptions, we will include subscores 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 the 'Description of studies' section of the review 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) that can be difficult to obtain in unstable and difficult-to-measure conditions, such as schizophrenia. We have decided primarily to use endpoint data, and only use change data if the former are not available. If necessary, we will combine endpoint and change data in the analysis, as we prefer to use mean difference (MD) values rather than standardised mean difference (SMD) values 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 nite 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 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 1987)), 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 such 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 1987), this could be considered as a clinically significant response (Leucht 2005). If data based on these thresholds are not available, we will use the primary cut-off presented by the original study 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 and the area to the right of the line of no effect indicates a favourable outcome for thiothixene. 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 and note this in the relevant graphs.

Assessment of risk of bias in included studies

Two review authors (PS and BD) 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.

We will note the level of risk of bias in both the text of the review, 'Risk of bias' figures, and the 'Summary of findings' table(s).

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 (ORs) (Boissel 1999); and that ORs tend to be interpreted as RRs by clinicians (Deeks 2002). 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, study authors often fail to account for intraclass correlation in clustered studies, leading to a unit-of-analysis error whereby P values are spuriously low, CIs unduly narrow, and statistical significance overestimated (Divine 1992). This causes type I errors (Bland 1997; Gulliford 1999).

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

Where clustering is not accounted for in primary studies, we will present data in a table, with a (*) symbol to indicate the presence of a probable unit of analysis error. We will seek to contact first authors of studies to obtain intraclass correlation coefficients (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 washout phase. For the same reason cross-over trials are not appropriate if the condition of interest is unstable (Elbourne 2002). As both carry-over and unstable conditions are very likely in severe mental illness, we will only use data from the first phase of cross-over studies.

3. Studies with multiple treatment groups

Where a study involves more than two treatment arms, if relevant, we will present the additional treatment arms in comparisons. If data are binary we will simply add these and combine within the 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 irrelevant, we will not reproduce these data.

Dealing with missing data

1. Overall loss of credibility

Loss to follow-up is a reality of RCTs (Xia 2009), when loss to follow-up becomes considerable this limits the quality of the study. If trials have missing data for more than 50% of participants in the arms of interest in the trial (those treated with chlorpromazine or thiothixene), we will report this. We will penalise studies that have a loss to follow-up rate of above 25% accordingly by altering their ratings of quality in the 'Summary of findings' table.

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 (ITT)). 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 testing 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

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 SDs

If SDs are not reported, 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). 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 (Deeks 2011).

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 'Incomplete outcome data' item 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 CI for I^2 statistic value). We will interpret an I^2 statistic value estimate of greater than or equal to 50% and accompanied by a statistically significant Chi^2 statistic as evidence of substantial heterogeneity (Section 9.5.2 of the *Cochrane Handbook for Systematic Reviews of Interventions*) (Deeks 2011). When we identify substantial levels of heterogeneity in the primary outcome, we will explore the 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 Systemic 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 unavailable, 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 will use a fixed-effect model for all analyses.

Subgroup analysis and investigation of heterogeneity

1. Subgroup analyses

1.1 Primary outcomes

We anticipate no subgroup analysis.

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 Cochrane 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 the 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 we have to make assumptions 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 we have to make assumptions regarding missing SD values (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-effect and random-effects

We will synthesise data using a fixed-effect model. However, we will also synthesise data for the primary outcome using a random-effects 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. Thiothixene prescription products

Approved prescription products			
Name	**Dose available**	**Company**	**Country**
Navane Capsule	5mg	ERFA 2012	Canada
Approved generic prescription products			
Name	**Dose available**	**Company**	**Country**
Thiothixene capsule	1 mg/2 mg/5 mg/10 mg	Sandoz Inc. (Drugbank 2017)	USA
Thiothixene capsule	1 mg/2 mg/5 mg/10 mg	Mylan Pharmaceuticals Inc. (Drugbank 2017)	USA
Thiothixene capsule	1 mg/2 mg/5 mg/10 mg	REMEDYREPACK Inc. (Drugbank 2017)	USA
Thiothixene capsule	5 mg	Carilion Materials Management (Drugbank 2017)	USA
Thiothixene capsule	5 mg	Rebel Distributors Corp (Drugbank 2017)	USA
Thiothixene capsule	10 mg	Florida DOH Central Pharmacy (Drugbank 2017)	USA

Table 2. Thiothixene prescription details by country

Prescription details by country			
Country of prescriber	**Total number of prescribers**	**Total number of patients**	**Total number of prescriptions**
USA[1]	16,149	19,085	156,000

[1]USA Medicaid claims 2013 (ProPublica)

Table 3. Cochrane Reviews of chlorpromazine

Title	Reference	Publication s tage
Acetophenazine versus chlorpromazine for schizophrenia	Bazrafshan 2015	Protocol
Aripiprazole versus chlorpromazine for people with schizophrenia and schizophrenia-like psychoses	Bhattacharjee 2016	Protocol
Chlorpromazine versus clotiapine for schizophrenia	Mazhari 2017	Full review
Haloperidol versus chlorpromazine for schizophrenia	Leucht 2008	Full review
Chlorpromazine versus metiapine for schizophrenia	Zare 2017	Full review
Chlorpromazine versus penfluridol for schizophrenia	Khalili 2015	Protocol
Chlorpromazine versus piperacetazine for schizophrenia	Eslami Shahrbabaki 2015	Protocol
Chlorpromazine versus placebo for schizophrenia	Adams 2014	Full review
Chlorpromazine versus reserpine for schizophrenia	Nur 2016	Full review
Chlorpromazine versus pimozide		Registered title
Cessation of medication for people with schizophrenia already stable on chlorpromazine	Almerie 2007	Full review

Table 3. Cochrane Reviews of chlorpromazine (*Continued*)

Chlorpromazine versus atypical antipsychotic drugs for schizophrenia	Saha 2016	Full review
Chlorpromazine dose for people with schizophrenia	Dudley 2017	Full review
Chlorpromazine for psychosis induced aggression or agitation	Ahmed 2010	Full review

CONTRIBUTIONS OF AUTHORS

DC wrote and developed the protocol.

JW wrote and developed the protocol.

PS was involved in the initial drafting of the protocol.

BD was involved in the initial drafting of the protocol.

LW was involved in the initial drafting of the protocol.

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DC: none known.

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