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Chlorpromazine versus clotiapine for schizophrenia (Review)

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[Intervention Review]

Chlorpromazine versus clotiapine for schizophrenia

Shahrzad Mazhari[1], Saeed Esmailian[2], Armita Shah-Esmaeili[3], Ali S Goughari[2], Azam Bazrafshan[1], Morteza Zare[4]

[1]Neuroscience Research Center, Institute of Neuropharmacology, Kerman University of Medical Sciences, Kerman, Iran. [2]Department of Medicine, Kerman University of Medical Sciences, Kerman, Iran. [3]Research Center for Modeling in Health, Institute for Futures Studies in Health, Kerman University of Medical Sciences, Kerman, Iran. [4]Nutrition Research Center, School of Nutrition and Food Sciences, Shiraz University of Medical Sciences, Shiraz, Iran

Contact: Morteza Zare, Nutrition Research Center, School of Nutrition and Food Sciences, Shiraz University of Medical Sciences, Shiraz, Iran. zare_morteza34@yahoo.com.

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ABSTRACT

Background

Schizophrenia is a chronic, disabling and severe mental disorder, characterised by disturbance in perception, thought, language, affect and motor behaviour. Chlorpromazine and clotiapine are among antipsychotic drugs used for the treatment of people with schizophrenia.

Objectives

To determine the clinical effects, safety and cost-effectiveness of chlorpromazine compared with clotiapine for adults with schizophrenia.

Search methods

We searched Cochrane Schizophrenia's Trials Register (last update search 16/01/2016), which is based on regular searches of CINAHL, BIOSIS, AMED, Embase, PubMed, MEDLINE, PsycINFO and clinical trials registries. There are no language, date, document type, or publication status limitations for inclusion of records in the Register.

Selection criteria

All randomised clinical trials focusing on chlorpromazine versus clotiapine for schizophrenia. We included trials meeting our selection criteria and reporting useable data.

Data collection and analysis

We extracted data independently. For binary outcomes, we calculated risk ratio (RR) and its 95% confidence interval (CI), on an intention-to-treat basis. For continuous data, we estimated the mean difference (MD) between groups and its 95% CI. We employed a random-effects model for analyses. We assessed risk of bias for included studies and created a 'Summary of findings' table using GRADE.

Main results

We have included four studies, published between 1974 and 2003, randomising 276 people with schizophrenia to receive either chlorpromazine or clotiapine. The studies were poor at concealing allocation of treatment and blinding of outcome assessment. Our main outcomes of interest were clinically important change in global and mental state, specific change in negative symptoms, incidence of movement disorder (dyskinesia), leaving the study early for any reason, and costs. All reported data were short-term (under six months' follow-up).

The trials did not report data for the important outcomes of clinically important change in global or mental state, or cost of care. Improvement in mental state was reported using the Positive and Negative Syndrome Scale (PANSS). When chlorpromazine was compared

with clotiapine the average improvement scores for mental state using the PANSS total was higher in the clotiapine group (1 RCT, N = 31, MD 11.50 95% CI 9.42 to 13.58, very low-quality evidence). The average change scores on the PANSS negative sub-scale were similar between treatment groups (1 RCT, N = 21, MD -0.97 95% CI -2.76 to 0.82, very low-quality evidence). There was no clear difference in incidence of dyskinesia (1 RCT, N = 68, RR 3.00 95% CI 0.13 to 71.15, very low-quality evidence). Similar numbers of participants left the study early from each treatment group (3 RCTs, N = 158, RR 0.68 95% CI 0.24 to 1.88, very low-quality evidence).

Authors' conclusions

Clinically important changes in global and mental state were not reported. Only one trial reported the average change in overall mental state; results favour clotiapine but these limited data are very difficult to trust due to methodological limitations of the study. The comparative effectiveness of chlorpromazine compared to clotiapine on change in global state remains unanswered. Results in this review suggest chlorpromazine and clotiapine cause similar adverse effects, although again, the quality of evidence for this is poor, making firm conclusions difficult.

PLAIN LANGUAGE SUMMARY

Direct comparison of two antipsychotics (chlorpromazine versus clotiapine) for treating schizophrenia

Review question

The aim of this review was to find good quality evidence comparing the efficacy of chlorpromazine versus clotiapine for schizophrenia.

Background

Chlorpromazine is one of the first antipsychotics to successfully alleviate the symptoms of psychosis. It was introduced in the 1950s and is still one of the most commonly used antipsychotics. However, chlorpromazine can cause serious side effects, particularly unpleasant movement disorders, causing many people with schizophrenia to stop taking chlorpromazine. During the past 70 years newer medications have been developed and most clinicians now have a wide choice of drugs for managing schizophrenia, however, none cure, and all cause some sort of side effect. The choice of treatment is still challenging. Clotiapine is a newer antipsychotic drug, found to be effective for treating the symptoms of schizophrenia and also known to be effective for treating people with schizophrenia who are resistant to other medications, however, like chlorpromazine it can cause serious movement disorders.

Searching for evidence

Cochrane Schizophrenia's Information Specialist ran an electronic search in January 2016, searching their specialised register for trials that randomised people with schizophrenia to receive either chlorpromazine or clotiapine. The search identified six reports. We inspected these reports and found four trials, published between 1974 and 2003, randomising 276 participants that could be included in the review.

Main results

The four included trials were poorly conducted and did not report data for clinically important change in global or mental state, or cost of care. Improvement in overall mental state was reported and participants receiving clotiapine had better improvement scores than those receiving chlorpromazine. However the trials also reported data for improvement in the negative symptoms, no difference between the two treatments was found. Clotiapine did not cause more movement disorders than chlorpromazine, and similar numbers of participants left the trials early.

Conclusions

There is some very low-quality evidence that favours clotiapine over chlorpromazine for improving overall mental state. For other outcomes, including adverse effects, there is no evidence of a difference between these two antipsychotics. However these data are very difficult to draw conclusions from, only four small trials provided data and these were poorly conducted. We cannot draw conclusions on the comparative effectiveness of chlorpromazine versus clotiapine from such data.

Summary of findings for the main comparison. Chlorpromazine compared to Clotiapine for schizophrenia

Chlorpromazine compared with Clotiapine for schizophrenia

Patient or population: people with schizophrenia
Settings:
Intervention: chlorpromazine
Comparison: clotiapine

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Clotiapine for schizophrenia	Chlorpromazine				
Global state: clinically important change	Not reported in any study					
Mental state: 1a. General symptoms - average change (PANSS, short term)		The mean mental state: average improvement scores in the intervention groups was **11.50 higher** (9.42 to 13.58 higher)		31 (1 study)	⊕⊖⊖⊖ **very low** [1,2,5]	Pre-stated outcome of clinically important change in mental state not reported
Mental state: 2c. Specific - average change score for negative symptoms (PANSS - negative short term)		The mean mental state in the intervention groups was **0.97 lower** (2.76 lower to 0.82 higher)		21 (1 study)	⊕⊖⊖⊖ **very low** [1,2,3]	
Adverse effects: incidence of serious adverse effects. Movement disorders - dyskinesia -short-term	**Study population**		**RR 3.00** (0.13 to 71.15)	68 (1 study)	⊕⊖⊖⊖ **very low** [1,2,3]	
	179 per 1000	**243 per 1000** (168 to 354)				
	Moderate					
	49 per 1000	**67 per 1000** (46 to 97)				

Adverse effects: clinically significant extrapyramidal symptoms	Not reported in any study				
Leaving the study early: for any reason	**Study population**		**RR 0.68** (0.24 to 1.88)	158 (3 studies)	⊕⊝⊝⊝ **very low** [1,2,4]
	283 per 1000	**172 per 1000** (31 to 961)			
	Moderate				
	296 per 1000	**181 per 1000** (33 to 1000)			
Cost of care	Not reported in any study				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different.
Low quality: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low quality: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[1]Risk of bias: serious - downgraded by 1: study has an unclear risk of bias for random sequence generation, allocation concealment, or no wash-out period reported, or source of funding unclear.
[2]Imprecision: serious - downgraded by 1: there are very few participants, number of events small
[3]Publication bias: serious - downgraded by 1: the study results only published in a local Japanese journal.
[4]Inconsistency: serious - downgraded by 1: there was high heterogeneity in the pooled results.
[5]Indirectness: serious - downgraded by 1: not direct measure of prespecified outcome.

BACKGROUND

Description of the condition

Schizophrenia can be a chronic, disabling and severe mental disorder that is characterised by disturbance in perception, thought, language, affect and motor behaviour. Common symptoms include hallucinations, delusions, disorganised speech, social withdrawal, flat affect and cognitive impairments. Lifetime prevalence of schizophrenia is around 0.87% (Perala 2007).

Description of the intervention

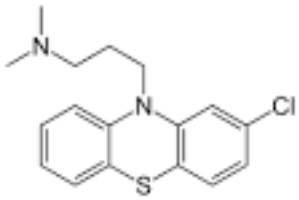
Chlorpromazine was synthesised in 1951 by Paul Charpentier, and was the first drug that significantly alleviated symptoms of psychosis (Ban 2007). Fifty years after its introduction, chlorpromazine is still one of the most commonly used antipsychotic drugs for management of people with schizophrenia (Adams 2005). Importantly, to evaluate a new drug for treatment of schizophrenia, studies often use chlorpromazine as a 'benchmark' drug (Adams 2014). However, chlorpromazine is associated with adverse effects ranging from inducing seizure, sudden death, neuroleptic malignant syndrome as well as sedation, decreased libido, blurred vision, and orthostatic hypotension (Pakpoor 2014).

Clotiapine has been manufactured since the late 1960s and is prescribed at least in Argentina, Belgium, Israel, Italy, South Africa, Spain, Switzerland and Taiwan for a range of conditions including schizophrenia, bipolar disorder (specifically mania) and other acute psychotic illnesses (Berk 2004). Clotiapine provides rapid treatment for the symptoms of schizophrenia, and its efficiency for people who are not responsive to other typical antipsychotics has been demonstrated (Geller 2005). Like chlorpromazine and other typical antipsychotics, clotiapine is linked to a number of adverse effects including extrapyramidal syndromes and a strong sedative effect (Geller 2005).

How the intervention might work

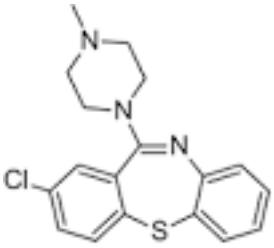
Chlorpromazine is a phenothiazine neuroleptic, 3-(2-chlorophenothiazin-10-yl)-N, N-dimethylpropan-1-amine (Figure 1). Like many antipsychotics, chlorpromazine acts as an antagonist (or blocking agent) for a number of postsynaptic receptors, resulting in the broad range of effects noted previously. Chlorpromazine's pharmacodynamics varies, but includes antagonist interactions with dopaminergic (especially the D2 subtype), and serotonergic 5-hydroxytryptamine (5-HT1 and 5-HT2) postsynaptic receptors (Amato 2015; Miyamoto 2012).

Figure 1. Chlorpromazine structure



Clotiapine is a dibenzothiazepine neuroleptic, named 2-chloro-11-(4-methyl-1-piperazinyl) dibenzo[b,f][1,4]thiazepine (Berk 2004) (Figure 2), and like chlorpromazine acts on multiple serotonergic and dopaminergic postsynaptic receptors. Clotiapine interacts with 5-HT serotonin receptors in a number of ways, including acting as a blocking agent for 5-HT3 and down-regulating 5-HT2 receptors (clotiapine has also been shown to possess a high affinity for 5HT-6 receptors) (Geller 2005). There is also evidence that clotiapine demonstrates limited blockage of dopaminergic D2 (Moore 1989) and D4 receptors (Zawilska 1994).

Figure 2. Clotiapine structure



Why it is important to do this review

Chlorpromazine is often considered a 'benchmark' antipsychotic and is used worldwide for treatment of people with schizophrenia, thus, it is important to compare its therapeutic and side effects with other medications. To our knowledge, there is no systematic review comparing the clinical outcomes and side effects of chlorpromazine to clotiapine.

The aim of this review is to compare chlorpromazine to clotiapine, which will then build up a series of Cochrane Reviews to give an overview of chlorpromazine's efficacy compared to other antipsychotics for the treatment of schizophrenia (Table 1).

OBJECTIVES

To determine the clinical effects, safety and cost-effectiveness of chlorpromazine compared with clotiapine for adults with schizophrenia.

METHODS

Criteria for considering studies for this review

Types of studies

We considered all relevant randomised controlled trials (RCTs). If a trial was described as 'double-blind' but implied randomisation, we included such trials in a sensitivity analysis (see Sensitivity analysis). We excluded quasi-randomised studies, such as those allocating by alternate days of the week. If people were given additional treatments within chlorpromazine, we planned to only include data if the adjunct treatment was evenly distributed between groups and it was only the chlorpromazine that was randomised.

Types of participants

We included adults, however defined, with schizophrenia or related disorders, including schizophreniform disorder, schizoaffective disorder and delusional disorder, again, by any means of diagnosis. If we found a trial where there was a range of diagnoses, we only included it if the majority of participants had schizophrenia.

We are interested in making sure that information is as relevant to the current care of people with schizophrenia as possible, and so proposed 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 whether the studies primarily focused on people with particular problems (for example, negative symptoms, treatment-resistant illnesses).

Types of interventions

1. Chlorpromazine

Any dose, any method of administration

2. Clotiapine

Any dose, any method of administration

Types of outcome measures

We divided outcomes into short-term (less than six months), medium-term (7 to 12 months), and long-term (over one year).

Primary outcomes

1. Global state

1.1 Clinically significant improvement in global state, as defined by each study

2. Mental state

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

3. Adverse events

3.1 Incidence of clinically important movement disorder, as defined by each study

Secondary outcomes

1. Global state

1.1 Average scores for global state
1.2 Relapse

2. Mental state

2.1 General symptoms - prevalence or average scores
2.2 Specific symptoms - prevalence or average scores
2.2.1 Positive symptoms (delusions, hallucinations, disordered thinking)
2.2.2 Negative symptoms (avolition, poor self care, blunted affect)
2.2.3 Mood - depression

3. Adverse effects

3.1 General - prevalence or average scores
3.2 Specific - prevalence or average scores
3.2.1 Deaths by suicide or natural causes
3.2.2 Movement disorders (extrapyramidal side effects, specifically tardive dyskinesia and neuroleptic malignant syndrome)
3.2.3 Sedation
3.2.4 Dry mouth
3.2.5 Others - categorised by system

4. Leaving the study

5. Behaviour

5.1 General behaviour - prevalence or average scores
5.2 Specific behaviour - prevalence or average scores
5.2.1 Social functioning
5.2.2 Employment status during trial (employed/unemployed)
5.2.3 Occurrence of violent incidents (to self, others, or property)

6. Service use

6.1 Days in hospital
6.2 Readmission due to relapse
6.3 Discharge from hospital (see Differences between protocol and review)

7. Quality of life

7.1 Important or average change in person's quality of life as defined by each study

8. Satisfaction with care

8.1 Important or average change in satisfaction of participant or care provider as defined by each study

9. Cost of care

'Summary of findings' table

We used the GRADE approach to interpret findings (Schünemann 2011) and used GRADEpro GDT to export data from our review 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 rated as important to patient care and decision-making. We selected the following main outcomes for inclusion in the 'Summary of findings' table.

1. Global State - clinically important change in global state as defined by each study
2. Mental State - general - clinically important change in mental state as defined by each study
3. Mental State - specific - average change in negative symptoms
4. Adverse effects - incidence of serious adverse events/effects
5. Adverse effects - clinically important extrapyramidal symptoms

6. Leaving the study early - for any reason
7. Cost of care

Search methods for identification of studies

Electronic searches

1. Cochrane Schizophrenia's trials register

The Information Specialist (IS) searched Cochrane Schizophrenia's Study-Based Register of Controlled Trials using the following search strategy.

(Chlorpromazine AND Clotiapine) in Intervention Field of STUDY

Cochrane Schizophrenia's register of trials 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 Group 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 inspected references of all included studies for further relevant studies.

2. Personal contact

For this review, we did not contact the first author of each included study for information regarding unpublished trials.

Data collection and analysis

Selection of studies

ASG and SE independently inspected citations from the searches and identified relevant abstracts. SM and ASE independently re-inspected a random 20% sample to ensure reliability. ASG and SE obtained and inspected the full reports of the abstracts meeting the review criteria. Again, SM and ASE re-inspected a random 20% of reports in order to ensure reliable selection. If it had not been possible to resolve disagreement by discussion, we would have attempted to contact the authors of the study for clarification, and if we could not resolve the disagreement we would not have included the trial, but placed it in the table 'Characteristics of studies awaiting classification' until a resolution was made. We included studies that met our inclusion criteria and reported useable data. We would have excluded studies that either did not meet our inclusion criteria or met our inclusion criteria but did not report useable data.

Data extraction and management

1. Extraction

Review authors AB and MZ extracted data from all included studies. In addition, to ensure reliability, SM and ASG independently extracted data from a random sample of these studies, comprising 10% of the total. We extracted data presented only in graphs and figures whenever possible, but only included the data if two reviewers independently had the same result. We attempted to contact study authors through an open-ended request in order to obtain missing information, or for clarification, whenever necessary. If studies had been multi-centred, where possible, we would have extracted data relevant to each component centre separately.

2. Management

2.1 Forms

We extracted data onto standard, simple forms provided by Cochrane Schizophrenia.

2.2 Scale-derived data

We included continuous data from rating scales only if:

- the psychometric properties of the measuring instrument had been described in a peer-reviewed journal (Marshall 2000);
- the measuring instrument had not been written or modified by one of the trialists for that particular trial;
- the instrument was a global assessment of an area of functioning and not sub-scores which were not, in themselves, validated or shown to be reliable. However there would be exceptions: we would include sub-scores from mental state scales measuring positive and negative symptoms of schizophrenia.

Ideally the measuring instrument should either be i. a self-report, or ii. completed by an independent rater or relative (not the therapist). We realise that this is not often reported clearly; in 'Description of studies' in the Results section we have noted 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 intended to primarily use endpoint data, and only use change data if the former were not available. We would have, where necessary, combined endpoint and change data in the analysis as we planned to use mean differences (MDs) rather than standardised mean differences (SMDs) throughout (Deeks 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 applied the following standards:

For change data

- We entered change data, as when continuous data are presented on a scale that included a possibility of negative values (such as change data), it was difficult to tell whether data were skewed or not. We presented and entered change data into statistical analyses.

For endpoint data from studies with fewer than 200 participants:

- When a scale started from the finite number 0, we subtracted the lowest possible value from the mean, and divided this by the standard deviation (SD). If this value was lower than 1, it strongly suggested a skew, and we would exclude such data. If this ratio was higher than 1 but below 2, there was a suggestion of skew. We would enter such data and test whether its inclusion or exclusion changed the results substantially. Finally, if the ratio

was larger than 2, we would include such data because skew was less likely (Altman 1996; Higgins 2011a).

- If a scale started from a positive value (such as the Positive and Negative Syndrome Scale (PANSS), which could have values from 30 to 210) (Kay 1986), we modified the calculation described above to take into account the scale starting point. In such cases skew is present if 2 SD > (S - S min), where S was the mean score and S min was the minimum score.

(Please note, irrespective of the above rules, we would enter endpoint data from studies of at least 200 participants in the analysis because skewed data pose less of a problem in large studies).

2.5 Common measure

To facilitate comparison between trials, we intended to convert variables that could 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 made 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 PANSS) (Kay 1986), this can be considered as a clinically significant response (Leucht 2005). If data based on these thresholds were not available, we used the primary cut-off presented by the original study authors.

2.7 Direction of graphs

Where possible, we entered data in such a way that the area to the left of the line of no effect indicated a favourable outcome for clotiapine. Where keeping to this made it impossible to avoid outcome titles with clumsy double-negatives (e.g. 'Not un-improved') we reported data where the left of the line indicated an unfavourable outcome and noted this in the relevant graphs.

Assessment of risk of bias in included studies

Again review authors MZ and AB worked independently to assess risk of bias by using criteria described in the *Cochrane Handbook for Systemic Reviews of Interventions* (Higgins 2011b) to assess trial quality. This set of criteria is based on evidence of associations between an 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 disagreed, we made the final rating by consensus, with the involvement of another member of the review group (SM). Where inadequate details of randomisation and other characteristics of trials were provided, we contacted authors of the studies in order to obtain, if possible, further information. We reported non-concurrence in quality assessment, but if disputes arose as to which category a trial was to be allocated, again, we attempted to resolve by discussion.

Measures of treatment effect

1. Binary data

For binary outcomes we calculated 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 (ORs) and that ORs tend to be interpreted as RR by clinicians (Deeks 2000). The number needed to treat for an additional beneficial outcome/harmful outcome (NNTB/NNTH) statistic with its CIs is intuitively attractive to clinicians, but is problematic both in its accurate calculation in meta-analyses and interpretation (Hutton 2009). For binary data presented in the 'Summary of findings' table, where possible, we calculated illustrative comparative risks.

2. Continuous data

For continuous outcomes we estimated the MD between groups. We preferred not to calculate effect size measures (SMD). However, if scales of very considerable similarity were used, we would presume that there was a small difference in measurement, and we would have calculated effect size and transformed 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 intra-class correlation in clustered studies, leading to a 'unit of analysis' error (Divine 1992), whereby P values are spuriously low, CIs unduly narrow, and statistical significance overestimated. This causes type I errors (Bland 1997; Gulliford 1999).

If clustering had not been accounted for in primary studies, we would have presented data in a table, with a (*) symbol to indicate the presence of a probable unit of analysis error. Where clustering was incorporated into the analysis of primary studies, we would have presented these data as if from a non-cluster randomised study, but adjusted 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 was not reported we would assume it to be 0.1 (Ukoumunne 1999).

If cluster studies have been appropriately analysed taking into account ICC and relevant data documented in the report, synthesis with other studies would 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 only used data from the first phase of cross-over studies.

3. Studies with multiple treatment groups

Where a study involved more than two treatment arms, if relevant, we presented additional treatment arms in comparisons. If data were binary we simply added and combined within the two-by-two table. If data were continuous we would have combined data following the formula in section 7.7.3.8 (Combining groups) of the *Cochrane Handbook for Systemic Reviews of Interventions* (Higgins 2011a). Where the additional treatment arms were not relevant, we did 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 chose that, for any particular outcome, should more than 50% of data be unaccounted for, we would not reproduce these data or use them within analyses. If, however, more than 50% of those in one arm of a study were lost, but the total loss was less than 50%, we would address this within the 'Summary of findings' table by downgrading quality. We also downgraded quality within the 'Summary of findings' table, should total loss be 25% to 50%.

2. Binary

Where attrition for a binary outcome was between 0% and 50% and where these data were not clearly described, we presented data on a 'once-randomised-always-analyse' basis (an intention-to-treat analysis (ITT)). Where studies did not use an ITT analysis, we presented completer-only data.

3. Continuous

3.1 Attrition

Where attrition for a continuous outcome was between 0% and 50%, and data only from people who completed the study to that point were reported, we used and presented these data.

3.2 Standard deviations

If SDs were not reported, we first tried to obtain the missing values from the study authors. If not available, where there were 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 could calculate them according to the rules described in the *Cochrane Handbook for Systemic Reviews of Interventions* (Higgins 2011a). When only the SE was reported, we calculated SDs by the formula SD = SE * square root (n). Chapters 7.7.3 (Higgins 2011a) and 16.1.3 (Higgins 2011c) of the *Cochrane Handbook for Systemic Reviews of Interventions* present detailed formulas for estimating SDs from P values, t or F values, CIs, ranges, or other statistics. If these formulae did not apply, we would calculate the SDs according to a validated imputation method based on the SDs of the other included studies (Furukawa 2006). Although some of these imputation strategies can introduce error, the alternative would be to exclude a given study's outcome, and thus to lose information. We nevertheless examined the validity of the imputations in a sensitivity analysis, excluding 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 leave trials early or are 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 recent 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 in the reasons for leaving the studies early between groups is often the core problem in randomised schizophrenia trials. We did not, therefore exclude studies based on the statistical approach used but preferred more sophisticated approaches. For example, We preferred MMRM or multiple-imputation to LOCF, and only presented completer analyses if some kind of ITT data were not available at all. Moreover, we addressed this issue in the 'Incomplete outcome data' domain of the 'Risk of bias' tool.

Assessment of heterogeneity

1. Clinical heterogeneity

We considered all included studies initially, without seeing comparison data, to judge clinical heterogeneity. We simply inspected all studies for clearly outlying people or situations that we had not predicted would arise, and would have fully discussed outliers.

2. Methodological heterogeneity

We considered all included studies initially, without seeing comparison data, to judge methodological heterogeneity. We simply inspected all studies for clearly outlying methods which we had not predicted would arise and would have discussed such methodological outliers if they arose.

3. Statistical heterogeneity

3.1 Visual inspection

We visually inspected graphs to investigate the possibility of statistical heterogeneity.

3.2 Employing the I^2 statistic

We investigated heterogeneity between studies 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 CI for I^2). We would have interpreted an I^2 estimate greater than or equal to around 50%, accompanied by a statistically significant Chi^2 test as statistical evidence of substantial levels of heterogeneity (Deeks 2011). If we had found substantial levels of heterogeneity in the primary outcome, we would have explored 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 the *Cochrane Handbook for Systemic Reviews of Interventions* (Sterne 2011). We tried to locate protocols of included randomised trials. If the protocol was available, we compared outcomes in the protocol with those in the published report. If the protocol was not available, we compared outcomes listed in the methods section of the trial report 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 described in the *Cochrane Handbook for Systemic Reviews of Interventions* (Sterne 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 would not use funnel plots for outcomes where there were 10 or fewer studies, or where all studies were of similar size. In future versions if 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 chose a random-effects model for all analyses.

Subgroup analysis and investigation of heterogeneity

1. Subgroup analyses

1.1 Primary outcomes

We did not anticipate any subgroup analyses.

1.2 Clinical state, stage or problem

We proposed to undertake this review and provide an overview of the effects of chlorpromazine compared with clotiapine for people with schizophrenia in general. In addition, however, if relevant data had been available we would have reported data on subgroups of people in the same clinical state, stage and with similar problems.

2. Investigation of heterogeneity

If inconsistency had been high, we would have reported this. First, we would have investigated whether data had been entered correctly. Second, if data were correct, we would have visually inspected the graph, and successively removed studies outside of the company of the rest to see if homogeneity was 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, we would have presented such data. If not, we would not pool data, but would have discussed the issues. We knew of no supporting research for this 10% cut-off, but were investigating use of prediction intervals as an alternative to this unsatisfactory state.

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

Sensitivity analysis

1. Implication of randomisation

We would have included trials in a sensitivity analysis if they had been described in some way as to imply randomisation. For the primary outcomes, if there had been no substantive difference when we added the implied randomised studies to those with better descriptions of randomisation, then we would have employed all data from these studies. If there was a substantive difference then we would have presented these data as 'other data'.

2. Assumptions for lost binary data

Where assumptions had to be made regarding people lost to follow-up (see Dealing with missing data) we compared the findings of the primary outcomes when we used our assumptions and when we used data only from people who completed the study to that point. If there had been a substantial difference, we would have reported results and discussed them, but continued to employ our assumptions.

If assumptions were needed regarding missing SDs (see Dealing with missing data), we would have compared the findings of the primary outcomes when we used our assumptions and when we used data only from people who completed the study to that point. We would have undertaken a sensitivity analysis, testing how prone results were to change when we only compared completer-only data to the imputed data using the above assumptions. If there had been a substantial difference, we would have reported results and discussed them, but continued to employ our assumptions.

3. Risk of bias

We would have analysed the effects of excluding trials that were judged to be 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. If the exclusion of trials at high risk of bias did not substantially alter the direction of effect or the precision of the effect estimates, then we would have included data from these trials in the analysis.

4. Imputed values

We would have undertaken a sensitivity analysis to assess the effects of including data from trials if we had used imputed values for ICC in calculating the design effect in cluster-randomised trials.

If we noted substantial differences in the direction or precision of effect estimates in any of the sensitivity analyses listed above, we would not pool data from the excluded trials with the other trials contributing to the outcome, but would present them separately.

5. Fixed-effect and random-effects

We synthesised all data using a random-effects model. However, we also synthesised data for the primary outcome using a fixed-

effect model to evaluate whether this altered the significance of the results.

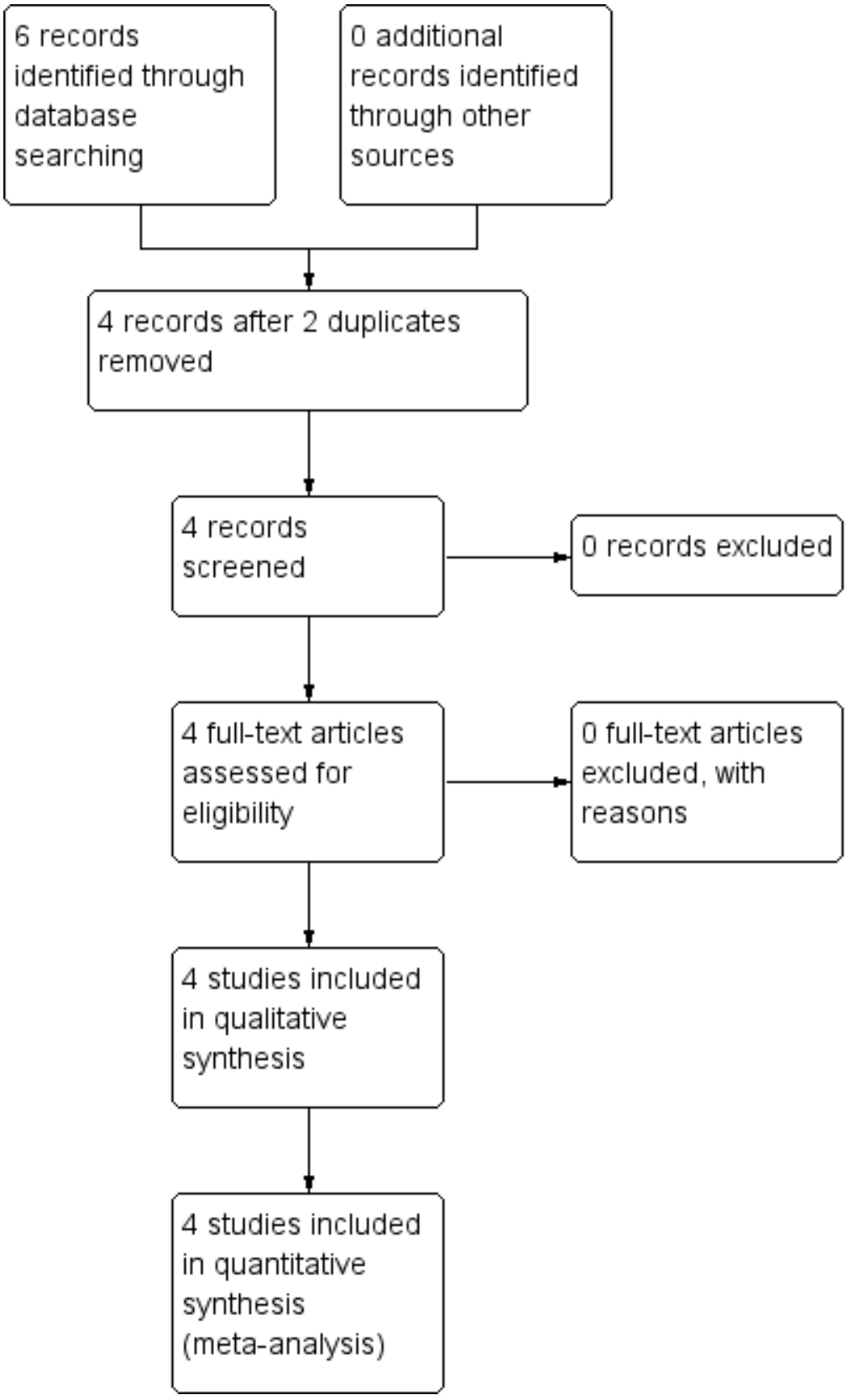
RESULTS

Description of studies

Results of the search

The PRISMA table shows results of our search Figure 3 (Moher 2009).

Figure 3. Study flow diagram of trial selection from 2016 electronic search



In the original search we found six reports that were potentially relevant. After removing two duplicates, we inspected full texts of the remaining four reports.

Included studies

All four full-text articles referred to individual studies and we were able to include all four studies.

1. Methods

One study was a cross-over trial (Schliefer 2003) and the three remaining studies were parallel trials (Jacobsson 1974; Kaneko 1969; Van Wyk 1971). All included studies were randomised - one, Kaneko 1969, implied randomisation.

2. Length of trials

Trial duration ranged from four weeks (Jacobsson 1974) to 12 weeks (Schliefer 2003, Van Wyk 1971).

3. Participants

Three studies reported that they included people with schizophrenia, one (Jacobsson 1974) included participants with acute psychotic syndromes including "schizophrenic type" illnesses. Only Kaneko 1969 reported the diagnostic criteria ("cases with catatonic excitation, marked irritability, violence and manneristic act; hallucination; delusion; deficiency of initiative and apathy") and described the symptoms required for participants to be included in the study. In total, we included 276 participants in this review.

4. Setting

All included studies were conducted in hospitals.

5. Study size

The average number of participants was 69, ranging from 49 (Jacobsson 1974) to 101 (Van Wyk 1971).

6. Intervention

6.1 Chlorpromazine

All the included studies compared chlorpromazine with clotiapine. The doses of chlorpromazine in the included studies ranged from 40 mg/day to 600 mg/day. The mean dose of chlorpromazine provided by Jacobsson 1974 was 404.5 mg/day ().

6.2 Clotiapine

The doses of clotiapine in the included studies ranged from 40 mg/day (Kaneko 1969) to 240 mg/day (Jacobsson 1974; Kaneko 1969). The mean dose was 125.2 mg/day in Jacobsson 1974. The other studies provided no further details for the prescribed dose of the medication.

6.3 Other treatments

Van Wyk 1971 also included one more treatment arm, thioridazine, in addition to chlorpromazine and clotiapine. We did not include data from this group.

7. Outcomes

Binary and continuous data were available. Outcomes reported by the studies included mental state, leaving the study early and adverse events. None of the included studies reported global state, quality of life, cost of care or behaviour.

7.1 Outcome scales

The following scales provided continuous data for the analyses.

7.1.2 Mental state

i. Positive and Negative Syndrome Scale (PANSS) (Kay 1987)

A brief rating scale used to assess the severity of positive and negative symptoms of schizophrenia, this scale has been reported as an operationalised, drug-sensitive instrument, providing balanced representation of positive and negative symptoms as well as measuring their relationship to one another. Using PANSS, the patient is rated from 1 to 7 on 30 different symptoms based on interview in addition to reports of family members or clinical staff. PANSS scores can range from 30 to 210, high scores indicating more severity of positive, negative or global psychopathology.

ii. Martens' Symptom Scale (S-Scale) (Helgason 1983)

This scale is designed for measuring possible improvements in people with schizophrenia. This scale comprises 23 items, measuring severity of signs or symptoms. Two items are bipolar with 9 possible scores, the others are unipolar with 5 possible scores (ranging from absence to high severity of a sign or a symptom).

Excluded studies

We did not exclude any studies. This was partly because the search was very specific.

Awaiting assessment

No studies are awaiting assessment.

Ongoing studies

We did not identify any ongoing studies.

Risk of bias in included studies

Please also see Figure 4 and Figure 5.

Figure 4. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies

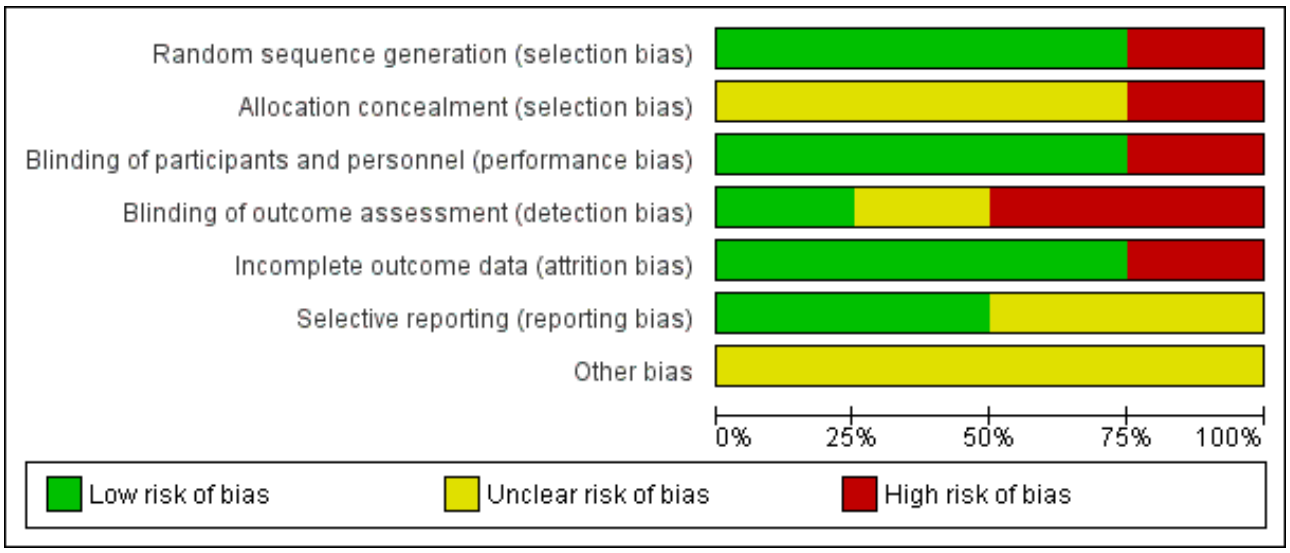
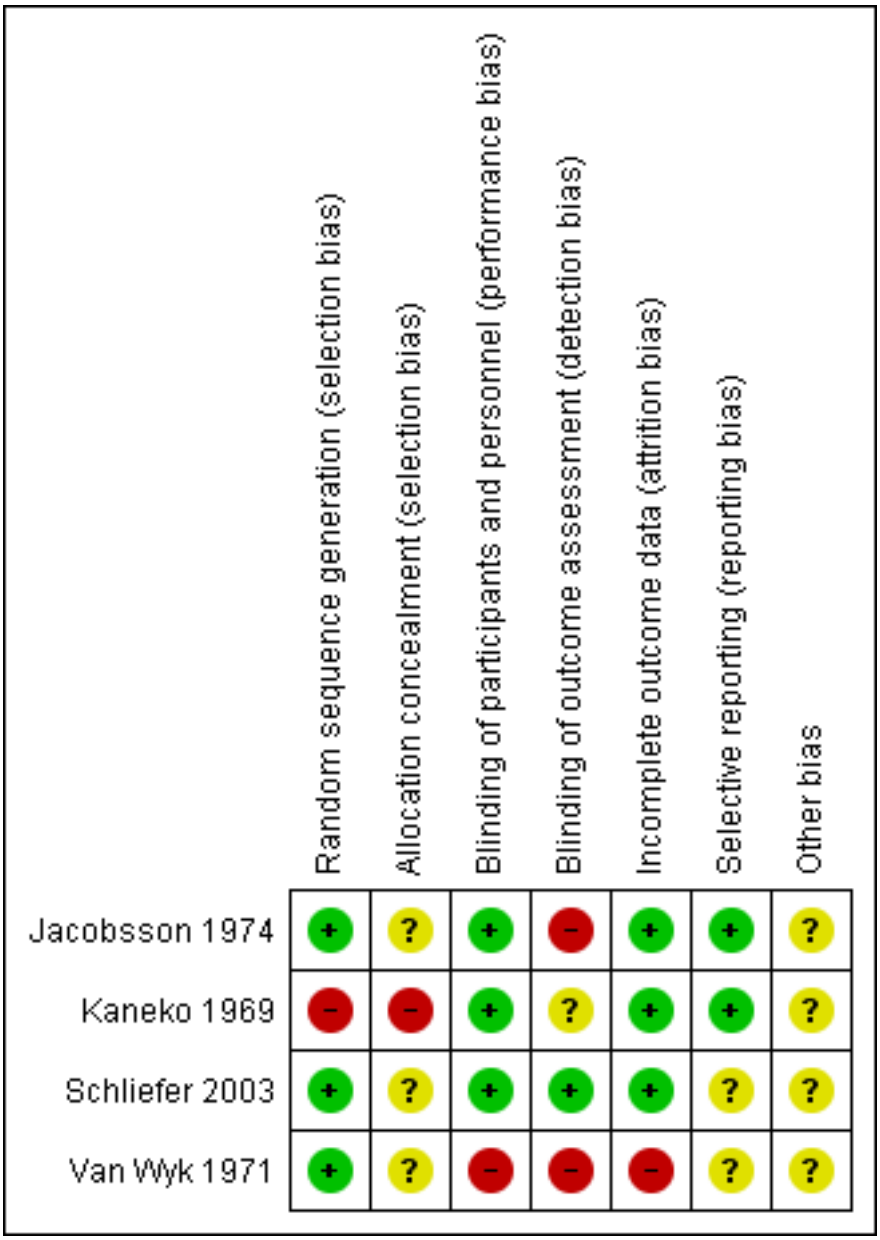


Figure 5. Risk of bias summary: review authors' judgements about each risk of bias item for each included study



Allocation

Three studies (Jacobsson 1974, Schliefer 2003, Van Wyk 1971) were randomised, however only Jacobsson 1974 reported the method used for generating random allocation. In Jacobsson 1974 participants were randomised by pre-established randomised codes. None of these three studies described how allocation was concealed. Kaneko 1969 did not provide clear information for either randomisation or allocation concealment. Randomisation was implied and we rated this study high risk for selection bias.

Blinding

Jacobsson 1974, Kaneko 1969 and Schliefer 2003 were double-blind and had low risks of bias for performance bias. Identical capsules and tablets were reported as the most common procedure for blinding both participants and personnel. Van Wyk 1971 had high risk of performance bias as it reported that due to administrative and staff shortage, they couldn't introduce any blind procedures into the trial. Detection bias (blinding of outcome assessment) varied. Schliefer 2003 was low risk, reporting that trained observers were blind to the participants' treatment status. Jacobsson 1974 was high risk, mentioning that a separate envelope for each participant was provided, in case it should be necessary to know what drug an individual participant was receiving, and Kaneko 1969 was at unclear risk of bias, with no clear information regarding blinding of outcome assessment.

Incomplete outcome data

Three included studies (Jacobsson 1974; Kaneko 1969; Schliefer 2003) had low risk of bias for incomplete outcome data. Only Van Wyk 1971 did not provide information about missing data and participants who left the study early.

Selective reporting

Two studies (Jacobsson 1974; Kaneko 1969) reported data for all outcomes. Schliefer 2003 and Van Wyk 1971 did not provide pre-specified outcomes so it is unclear if they reported all outcomes.

Other potential sources of bias

Schliefer 2003 was financially supported by a research grant from Stanley Medical Research Institute and had no wash-out period for the study. Jacobsson 1974 and Van Wyk 1971 declared who supplied their drugs but did not report the source of funding. Kaneko 1969 was also unclear about their funding source.

Effects of interventions

See: **Summary of findings for the main comparison** Chlorpromazine compared to Clotiapine for schizophrenia

Studies relevant to this review fell into a single comparison. We were able to extract numerical data from four randomised studies.

1. Comparison 1: chlorpromazine versus clotiapine

1.1 Mental state: 1a. General symptoms - average change score (PANSS total, high = good)

For this outcome we found a single study, with a total of 31 people. We found evidence of a clear difference, favouring clotiapine, between chlorpromazine and clotiapine (MD 11.50, 95% CI 9.42 to 13.58, Analysis 1.1).

1.2 Mental state: 1b. General symptoms - average change score (S-scale, high = poor)

There was a clear difference, favouring chlorpromazine between chlorpromazine and clotiapine (1 RCT, N = 38, MD 1.45, 95% CI 0.38 to 2.52, Analysis 1.2).

1.3 Mental state: 2a. Specific - positive symptoms - frequency

A single study (Kaneko 1969) reported incidence of positive and negative symptoms (Analysis 1.3).

We found no evidence of a clear difference between chlorpromazine and clotiapine for several specific symptoms (Analysis 1.3).

1.3.1 Delusions: 1 RCT, N = 12, RR 1.33, 95% CI 0.50 to 3.55

1.3.2 Hallucinations: 1 RCT, N = 25, RR 0.46, 95% CI 0.15 to 1.40

1.3.3 Severe excitation: 1 RCT, N = 5, RR 0.75, 95% CI 0.15 to 3.72

1.4 Mental state: 2a. Specific - positive symptoms - average change score (PANSS-positive, high = good)

Kaneko 1969 also provided mental state data, reporting the average change scores on the PANSS for both positive and negative symptoms.

For delusions we found evidence of a clear effect, favouring clotiapine (1 RCT, N = 11, MD 7.36, 95% CI 3.54 to 11.18) but no effect for the outcome of 'hallucinations' (1 RCT, N = 16, MD -3.00, 95% CI -6.75 to 0.75, Analysis 1.4).

1.5 Mental state: 2c. Specific - negative symptoms - average change scores (PANSS-negative, high = good)

For the outcome of 'deficiency of initiative and apathy' we found no evidence of a clear difference between chlorpromazine and clotiapine (MD -0.97, 95% CI -2.76 to 0.82, Analysis 1.5).

1.6 Mental state: 2d. Specific - various symptoms - average change score (S-Scale, high = poor)

Jacobsson 1974 (N = 49) measured mental state using Martens' Symptom Scale (S-Scale). Findings were varied. For the outcome of 'delusions' we did not find evidence that chlorpromazine was clearly different in its effects compared with clotiapine (1 RCT, N = 38, MD -0.06, 95% CI -0.3 to 0.18). For 'hallucinations', however, we did find evidence of an effect, favouring clotiapine (1 RCT, N = 38, MD -0.24, 95% CI -0.46 to -0.02, Analysis 1.6). We also found evidence that chlorpromazine was better in its effects compared with clotiapine for 'influence of thought' (1 RCT, N = 38, MD 0.28, 95% CI 0.17 to 0.39) but no evidence of a clear difference between chlorpromazine and clotiapine for 'splitting' (1 RCT, N = 38, MD 0.01, 95% CI - 0.09 to 0.11, Analysis 1.6).

1.7 Adverse effects 1. Central nervous system - short term

Kaneko 1969 (N = 68) reported on several general central nervous system effects. The study did not find evidence of a clear difference between chlorpromazine and clotiapine for drowsiness (RR 1.89, 95% CI 0.98 to 3.63), somnipathy (RR 1.38, 95% CI 0.63 to 2.99), unsteadiness (RR 1.71, 95% CI 0.77 to 3.82) nor weakness (RR 0.75, 95% CI 0.42 to 1.34, Analysis 1.7).

1.8 Adverse effects: 2. Movement disorders - short term

There was not a clear difference between chlorpromazine and clotiapine for the outcome of akathisia (1 RCT, N = 68, RR 3.00, 95% CI 0.65 to 13.83), dyskinesia (1 RCT, N = 68, RR 3.00, 95% CI 0.13 to 71.15) nor Parkinsonism (2 RCTs, N = 106, RR 1.17, 95% CI 0.87 to 1.57, Analysis 1.8).

1.9 Adverse effects: 3. Various other - short term

Kaneko 1969 (N = 68) reported 'weight gain (of not less than 3 kg at the end of study)' and did not find a clear difference between chlorpromazine and clotiapine (RR 1.12, 95% CI 0.71 to 1.75). The same study also reported 'thirst' and, again, found no clear difference between the drugs (RR 1.29, 95% CI 0.54 to 3.06, Analysis 1.9).

1.10 Leaving the study early - short term

Around 17% left the studies but there was no clear difference between chlorpromazine and clotiapine (3 RCTs, N = 158, RR leaving for any reason 0.68, 95% CI 0.24 to 1.88), this outcome had moderate levels of heterogeneity (I^2 = 47%). Attrition fell to about 14% when the reason of 'due to deterioration or adverse effects' was reported (2 RCTs, N = 117, RR 1.23, 95% CI 0.51 to 2.99) but there was still no difference between groups (Analysis 1.10).

1.11 Service use: discharge from hospital - short term (12 weeks)

Only Van Wyk 1971 (N = 70), reported data on numbers of participants discharged from hospital by 12 weeks. There is evidence of an effect favouring clotiapine for this outcome (RR 1.49, 95% CI 1.07 to 2.08, Analysis 1.11).

We also performed analysis of subclasses of mental state by positive symptoms and the results are reported in Table 2.

DISCUSSION

Summary of main results

The summary below refers to the outcomes selected for Summary of findings for the main comparison, and highlights the important findings of this review for evidence-based decision making.

1. Global state

We could not extract any usable data from the trials comparing chlorpromazine with clotiapine, therefore it is not possible to draw any conclusions about whether clotiapine is more or less effective in improving the global state of people with schizophrenia. This is a real omission of even the few trials we have identified.

2. Mental state: general

Only one trial specifically reported mental state as measured by the PANSS total scores. Results favoured efficacy of chlorpromazine compared with clotiapine but these are short-term, very low-quality data, from one tiny trial, reporting a proxy outcome (continuous measure rather than binary), the interpretation of which is problematic in clinical life. A meta-analysis of three randomised trials that evaluated the global improvements in people with acute psychotic disorders - rather than more narrowly defined and stable schizophrenia - indicated no distinct superiority of clotiapine compared with other standard treatments like chlorpromazine (Berk 2004). At best, this current review suggests no dramatic difference between the two compounds.

3. Mental state: specific

Our findings fail to indicate a clear difference between the efficacy of chlorpromazine versus clotiapine for improving negative symptoms, and both drugs were not effective in improving negative symptoms. This is an important outcome and there is little convincing evidence from any comparison of any treatment for people with schizophrenia that negative symptoms are responsive to drugs. The call for larger, longer, better trials in this area is not specific to the comparison which was the focus of this review.

4. Adverse effects: incidence of movement disorders, and clinically significant extrapyramidal symptoms

For the limited data we had to work with, chlorpromazine and clotiapine seem to produce a similar profile of movement disorders in people with schizophrenia. However, another review suggested that clotiapine may induce fewer movement disorders (Parkinsonism symptoms) (Berk 2004). This is important and merits further investigation of safety and tolerability profiles.

5. Leaving the study early

These studies were short. Around 17% of both groups left early (any reason) and 14% when it came to the specific reason of deterioration or adverse effects. These figures compare favourably to many of the more modern trials where attrition rate is far greater - even over a matter of a few weeks. There seems to be no implication in the studies that attrition was for different reasons in each group. More detailed information would have been helpful and it might have been possible to extract outcome data, even on those who left. Nevertheless, we found no evidence that one or other drug was more unacceptable to either trial participants, or researchers.

7. Service use

At the end of 12 weeks in one study around 80% of people receiving clotiapine were able to be discharged from hospital compared with around 50% receiving chlorpromazine. This was statistically significant. If reproduced this is a most important result. If clotiapine is genuinely faster at getting people better this is very important with enormous implications. This result needs to be reinvestigated.

6. Cost of care

Again, we could not extract any usable data from the trials comparing chlorpromazine with clotiapine, therefore it is not possible to draw any conclusions about whether chlorpromazine is more or less effective than clotiapine in terms of cost. However, as there is little difference in the cost of the drugs, all else being equal, then service use is a good proxy for cost. Should the finding for service use be true and clotiapine really does get people better, faster, then savings by use of clotiapine would be huge.

Overall completeness and applicability of evidence

1. Completeness

There are some relevant limitations for the conclusions of this meta-analysis, which should be pointed out. Of the four included studies, almost all of them provided some data on the primary outcomes mental state and adverse effects. However, no study reported usable data for the primary outcome 'global state'. Therefore, the evidence on this primary outcome is not complete. In addition, only three studies reported on secondary outcomes. The evidence on prespecified adverse effects is particularly incomplete, as none of the included trials specifically reported important side effects such as death, suicide or cardiac effects. There were also no usable data on behaviour, quality of life, service use, satisfaction with care or cost of care. The total number of participants in the included studies is extremely limited, which can lead to inconclusive results (Davey Smith 1998), regardless of whether the estimations were significant. Therefore, new large trials with better outcome reporting are needed for clear interpretation and precise decisions about the differences between the efficacy of chlorpromazine and clotiapine. These outcomes do not need to depend on sophisticated rating but could be clear, binary and pragmatic.

2. Applicability

2.1 Diagnosis

All of the included studies except Schliefer 2003 were conducted over 40 years ago, which could have led to serious limitations for applicability of this review. Almost all the included studies in this review provided less rigorous criteria for diagnosis of schizophrenia than would, perhaps, be seen in more modern trials. It is likely that some included participants in those studies would reflect other diagnosis than schizophrenia. However, this is rather like normal clinical practice where diagnosis is not an exact science.

2.2 Setting

All included studies were conducted in hospitals and inpatient settings. However, today much schizophrenia is diagnosed and

treated in the early stages in the community, which could reduce the applicability of this review for current practice.

Quality of the evidence

The data reported are limited and poor quality; we rated available evidence as very low based on GRADE (Schünemann 2011). Three studies stated that they were randomised and provided information about how this was achieved. One study said it was randomised but provided no information about the randomisation method. Three studies had serious risk of bias for allocation concealment. One study was not blinded. Two studies reported that the assessor was not blinded to which drug the participants were receiving. We also detected inconsistency, imprecision and serious publication bias detected for two studies. None of the included studies reported usable data for most important outcomes as they provided no standard deviation or standard error of mean for estimations.

Potential biases in the review process

The search was based on Cochrane Schizophrenia's Trials Register. There may be some unpublished trials that we are not aware of. At the time this review's trials were published there was pharmaceutical industry interest in the findings and this could have led to publication or reporting bias.

Agreements and disagreements with other studies or reviews

We are not aware of any other systematic reviews on the efficacy of chlorpromazine versus clotiapine for schizophrenia - but would be really interested in finding any.

AUTHORS' CONCLUSIONS

Implications for practice

1. For people with schizophrenia

Where clotiapine is available it is unclear of its advantages over chlorpromazine. It may be better at improving mental state compared to chlorpromazine but data are really so limited and of such poor quality that it is impossible to be certain of this. Schizophrenia is such a potentially difficult and damaging illness that it is important to not dismiss older treatments and clotiapine may have its place in treatment of some people who it would 'suit'. People with schizophrenia and their families should expect better data than are available from the few existing trials.

2. For clinicians

This review suggests effects of clotiapine and these effects may be important. We really do not have good data on any outcomes but almost none on global state, and service use. Where clotiapine is used, and there is a dilemma about whether to use it, clinicians could help increase data on the effects of this antipsychotic drug by organising its evaluation in real world settings.

3. For policy makers

Where clotiapine is an available option for use for people with schizophrenia, this review gives no evidence to discourage its inclusion within policy except that the data, when compared with one benchmark antipsychotic - chlorpromazine - is surprisingly and disappointingly thin.

Implications for research

1. General

Better reporting of trials would have resulted in this review being more informative. We recognise that we are largely using standards of today to judge trials of the past but we anticipate that adherence to the CONSORT statement (Moher 2001) would improve the quality of reporting data for future research.

2. Specific

Where clotiapine is available trials could be undertaken and, as this review shows, such studies are justified if the drug is in use. Long-term effects are important. We realise that design of such a study takes time and methodical planning but we have given this some thought and outline a draft design (Table 3).

ACKNOWLEDGEMENTS

Cochrane Schizophrenia 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 terms were developed by Cochrane Schizophrenia's Information Specialist and the contact author of this review.

We would like to thank Professor Clive Adams (Co-ordinating Editor of Cochrane Schizophrenia, Faculty of Medicine and Health Sciences, University of Nottingham) for providing advice, guidance and support throughout the undertaking of this review. We would also like to thank Claire Irving for providing additional support.

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Parts of this review were generated using RevMan HAL v 4.0. You can find more information about RevMan here.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Jacobsson 1974

Methods	Allocation: randomised by pre-established randomised code
	Blindness: double-blind - tablets of the same appearance and taste
	Duration: 4 weeks
	Design: parallel
	Setting: hospital

Jacobsson 1974 *(Continued)*

	Country: Sweden
Participants	Diagnoisis: "acute psychotic syndromes of a schizophrenic type" N = 49 Age: 18-60 years Sex: 23 M, 26 F History: suffering from acute psychotic syndromes of a schizophrenic type, either during their first episode or on a re-occurrence of an acute stage Excluded: gross neurological or somatic disorders unrelated to the principal condition, alcoholism or drug addiction, and spontaneous remission
Interventions	1. Clotiapine: range: 40-220 mg/d, maximum dose: 240 mg/d, mean dose: 125.2 mg/d. N = 23 2. Chlorpromazine: range: 200-600 mg/d, maximum dose: 600 mg/d, mean dose: 404.5 mg/d. N = 26
Outcomes	Mental state: general, specific symptoms (Martens' Symptom Scale (S-Scale)) Adverse effects: incidence of Parkinsonism Leaving the study early Unable to use - Mental state: general - average endpoint score (scale not named - unsure if peer reviewed) Behaviour: Wing rating scale (no SD reported) Adverse effects: haematology, hepatic, ophthalmic (no SD reported), constipation, tiredness - average change score (scale not named - unsure if peer reviewed)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised: quote: "according to a pre-established randomized code."
Allocation concealment (selection bias)	Unclear risk	No details provided for allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "clotiapine or 100 mg chlorpromazine were administered using the double-blind technique"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "A separate envelope for each code-number was also prepared in case it should be necessary to know what drug an individual patient was receiving"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data were addressed in the study.
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes were reported in the study.

Jacobsson 1974 *(Continued)*

Other bias	Unclear risk	Drugs were supplied by AstraZeneca, Mölndal. Source of funding not reported

Kaneko 1969

Methods	Allocation: implied randomisation Blindness: double-blind - tablets of the same external form Duration: 10 weeks (2 weeks placebo before the study started- 8 weeks for intervention) Design: parallel Setting: hospital Country: Japan
Participants	Diagnosis: schizophrenia N = 68 Age: 18-60 years Sex: 52 M, 16 F History: including symptoms of severe excited state, stuporous state, hallucination, delusion or apathy. Symptoms were evaluated by a simplified scale for evaluation of psychogenic symptoms (for schizophrenia and for use by doctors) as 12 items, and the intensity of each item was assessed in five grades. Excluded: marked exacerbation or serious side effects, complete remission
Interventions	1. Clotiapine: maximum dose: 240 mg/d. N = 34 2. Chlorpromazine: maximum dose: 600 mg/d. N = 34
Outcomes	Mental state: average change score (PANSS positive and negative sub-scale) Adverse effects: movement disorders, central nervous system, weight gain, thirst Leaving the study early Unable to use Mental state: improvement using Keio-Gijuku University type, simplified scale, (no mean or SD)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	No information was provided for randomisation
Allocation concealment (selection bias)	High risk	No information was provided for allocation concealment
Blinding of participants and personnel (performance bias)	Low risk	Quote: "Employed as the experimental method in the present study. was the double-blind, controlled technique "

Kaneko 1969 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data and attrition were addressed in the study.
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes were reported in the study.
Other bias	Unclear risk	Source of funding not reported

Schliefer 2003

Methods	Allocation: randomised Blindness: double-blind - identical capsules Duration: 12 weeks Design: cross-over Setting: both inpatient and outpatients Country: Israel
Participants	Diagnosis: severe chronic schizophrenia N = 58 Age: 18-65 years Sex: 44 M, 14 F History: severe chronic active psychotic hospitalised patients with a history of non-response to at least 3 antipsychotics Excluded: currently in an exacerbation, unstable or serious physical illnesses, suicidality, drug abuse or unstable family situations
Interventions	1. Clotiapine: maximum dose: 240 mg/d. N = 19 2. Chlorpromazine: maximum dose: 600 mg/d. N = 12 33 participants received additional trihexyphenidyl for EPS throughout the study and 27 received benzodiazepines for helping to sleep
Outcomes	Mental state: improvement (average change score PANSS) Leaving the study early Unable to use Mental state: improvement (CGI, NOSIE): no usable data reported for first phase of cross-over
Notes	*Only data from first phase of cross-over used

Schliefer 2003 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "patients were randomized"
Allocation concealment (selection bias)	Unclear risk	No information was provided for allocation concealment.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The design was double-blind crossover"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "by trained observers blind to the patient's treatment status"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data and attrition were addressed in the study.
Selective reporting (reporting bias)	Unclear risk	No information was provided for pre-specified outcomes.
Other bias	Unclear risk	There was no wash-out period in the study. This study was supported by a clinical trial grant from the Stanley Medical Research Institute.

Van Wyk 1971

Methods	Allocation: randomised Blindness: not blind Duration: 12 weeks Design: parallel Setting: hospital Country: South Africa
Participants	Diagnosis: schizophrenia and "toxic psychoses" N = 101 Age: adults (no further information provided) Sex: male History: acute psychoses, no epilepsy or depressive psychoses
Interventions	1. Clotiapine: 40 mg/d orally. N = 36 2. Chlorpromazine: 200 mg/d orally. N = 34 3. Thioridazine: 200 mg/d orally. N = 31

Van Wyk 1971 *(Continued)*

Outcomes	Service use: number discharged by 12 weeks Unable to use Mental state: general - average endpoint score (scale not named - unsure if peer reviewed) Adverse effects: adverse effects mentioned in text, but no data reported to support statements
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Allocation to either of the 3 drug groups was at random"
Allocation concealment (selection bias)	Unclear risk	No information provided for allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Because of the administrative and staff shortage problems we could not introduce· any 'blind' procedures into the trial"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "Because of the administrative and staff shortage problems we could not introduce· any 'blind' procedures into the trial"
Incomplete outcome data (attrition bias) All outcomes	High risk	No information was provided for attrition and missing data
Selective reporting (reporting bias)	Unclear risk	No information was provided for pre-specified outcomes
Other bias	Unclear risk	Clotiapine was supplied by a researcher from Switzerland. No source of funding reported

EPS: extrapyramidal symptoms
F: female
M: male
N: number
SD: standard deviation
Scales
PANSS: Positive and negative syndrome scale
S-Scale: Marten's Symptom scale
CGI: Clinical Global Impression
NOSIE: Nurses' Observational Scale for Inpatient Evaluation

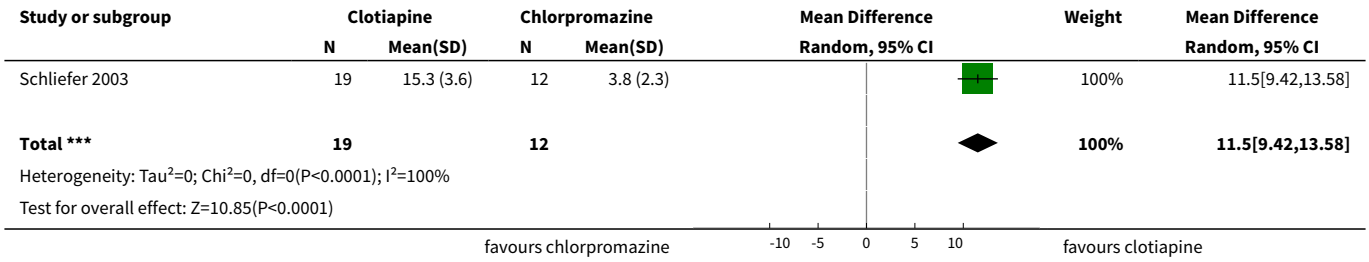
DATA AND ANALYSES

Comparison 1. Chlorpromazine versus Clotiapine

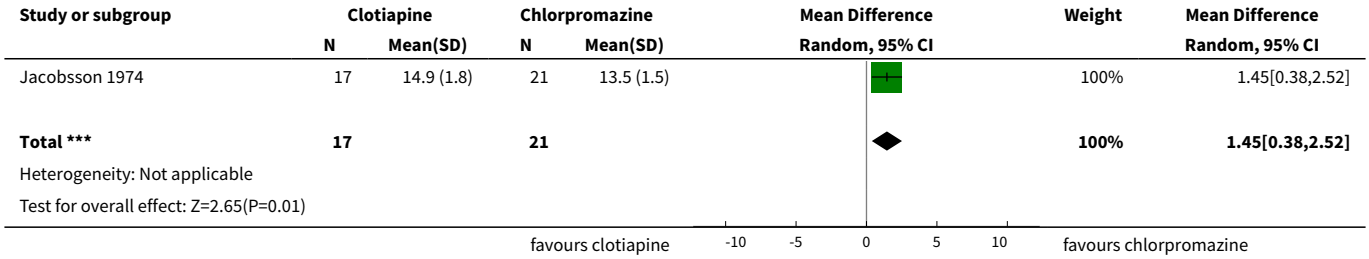
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mental state: 1a. General - average change scores (PANSS total, high = good)	1	31	Mean Difference (IV, Random, 95% CI)	11.50 [9.42, 13.58]
2 Mental state: 1b. General - average change scores (S-scale, high = poor)	1	38	Mean Difference (IV, Random, 95% CI)	1.45 [0.38, 2.52]
3 Mental state: 2a. Specific - positive symptoms - frequency	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Delusion	1	12	Risk Ratio (M-H, Random, 95% CI)	1.33 [0.50, 3.55]
3.2 Hallucination	1	25	Risk Ratio (M-H, Random, 95% CI)	0.46 [0.15, 1.40]
3.3 Severe excitation	1	5	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.15, 3.72]
4 Mental state: 2b Specific - positive symptoms - average change scores (PANSS positive subscale, high = good)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
4.1 Delusion	1	11	Mean Difference (IV, Random, 95% CI)	7.36 [3.54, 11.18]
4.2 Hallucination	1	16	Mean Difference (IV, Random, 95% CI)	-3.0 [-6.75, 0.75]
5 Mental state: 2c. Specific - negative symptoms - average change scores (PANSS negative subscale, high = good)	1	21	Mean Difference (IV, Random, 95% CI)	-0.97 [-2.76, 0.82]
5.1 Deficiency of initiative and apathy	1	21	Mean Difference (IV, Random, 95% CI)	-0.97 [-2.76, 0.82]
6 Mental state: 2d. Specific - various symptoms - average change score - (S-Scale, high = poor)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
6.1 Delusion	1	38	Mean Difference (IV, Random, 95% CI)	-0.06 [-0.30, 0.18]
6.2 Hallucination	1	38	Mean Difference (IV, Random, 95% CI)	-0.24 [-0.46, -0.02]
6.3 Influence of thought	1	38	Mean Difference (IV, Random, 95% CI)	0.28 [0.17, 0.39]
6.4 Splitting	1	38	Mean Difference (IV, Random, 95% CI)	0.01 [-0.09, 0.11]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7 Adverse effects: 1. Central nervous system - short term	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
7.1 Drowsiness	1	68	Risk Ratio (M-H, Random, 95% CI)	1.89 [0.98, 3.63]
7.2 Somnipathy	1	68	Risk Ratio (M-H, Random, 95% CI)	1.38 [0.63, 2.99]
7.3 Unsteadiness	1	68	Risk Ratio (M-H, Random, 95% CI)	1.71 [0.77, 3.82]
7.4 Weakness	1	68	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.42, 1.34]
8 Adverse effects: 2. Movement disorders - short term	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
8.1 Akathisia	1	68	Risk Ratio (M-H, Random, 95% CI)	3.0 [0.65, 13.83]
8.2 Dyskinesia	1	68	Risk Ratio (M-H, Random, 95% CI)	3.0 [0.13, 71.15]
8.3 Parkinsonism	2	106	Risk Ratio (M-H, Random, 95% CI)	1.17 [0.87, 1.57]
9 Adverse effects: 3. Various other - short term	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
9.1 Weight gain (not less than 3 kg at the end of study)	1	68	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.71, 1.75]
9.2 Thirst	1	68	Risk Ratio (M-H, Random, 95% CI)	1.29 [0.54, 3.06]
10 Leaving the study early - short term	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
10.1 for any reason	3	158	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.24, 1.88]
10.2 due to deterioration or adverse effects	2	117	Risk Ratio (M-H, Random, 95% CI)	1.23 [0.51, 2.99]
11 Service use: discharge from hospital - short term (12 weeks)	1	70	Risk Ratio (M-H, Random, 95% CI)	1.49 [1.07, 2.08]

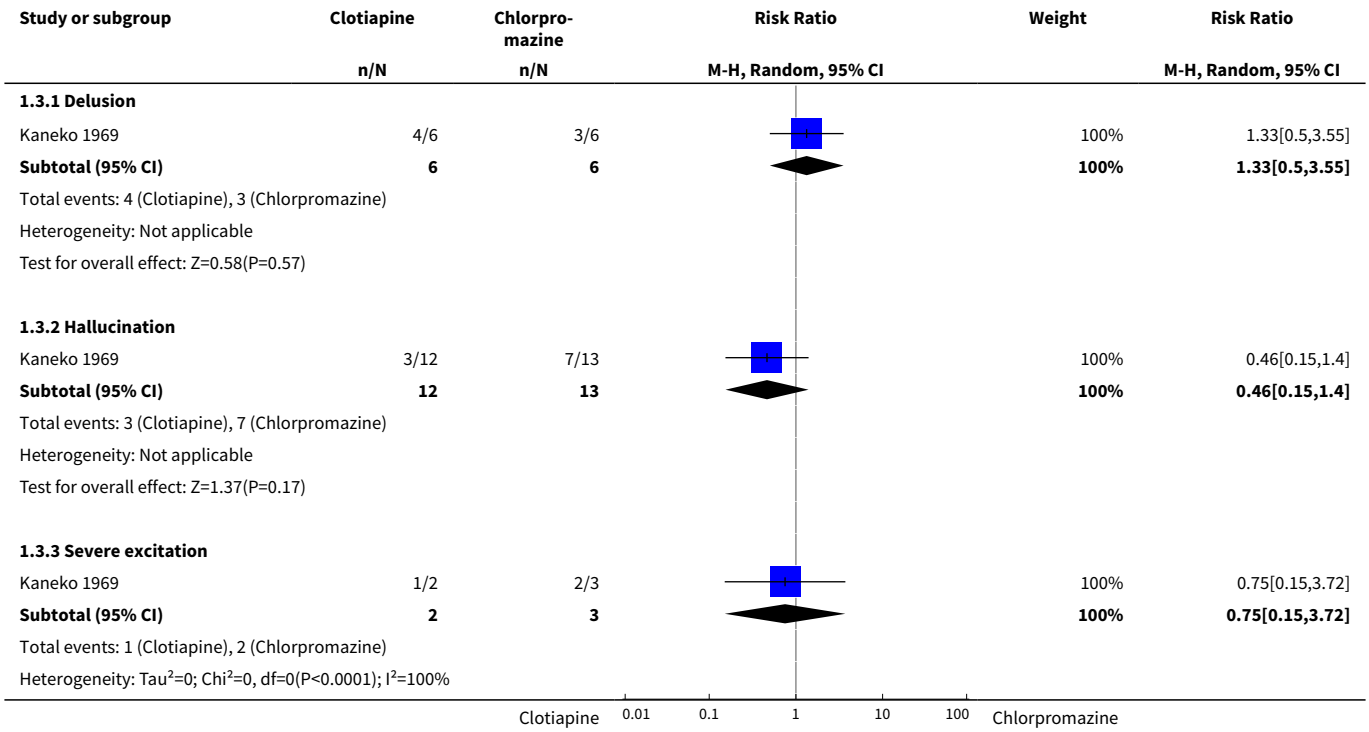
Analysis 1.1. Comparison 1 Chlorpromazine versus Clotiapine, Outcome 1 Mental state: 1a. General - average change scores (PANSS total, high = good).



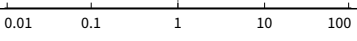
Analysis 1.2. Comparison 1 Chlorpromazine versus Clotiapine, Outcome 2 Mental state: 1b. General - average change scores (S-scale, high = poor).



Analysis 1.3. Comparison 1 Chlorpromazine versus Clotiapine, Outcome 3 Mental state: 2a. Specific - positive symptoms - frequency.



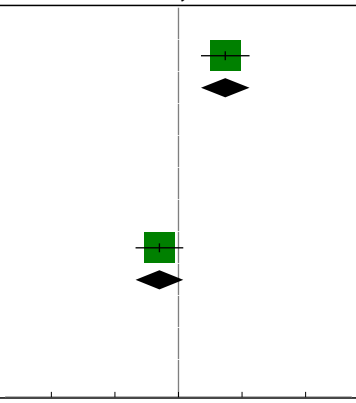
Study or subgroup	Clotiapine	Chlorpro-mazine	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
Test for overall effect: Z=0.35(P=0.72)					
Test for subgroup differences: Chi²=1.98, df=1 (P=0.37), I²=0%					



Clotiapine Chlorpromazine

Analysis 1.4. Comparison 1 Chlorpromazine versus Clotiapine, Outcome 4 Mental state: 2b Specific - positive symptoms - average change scores (PANSS positive subscale, high = good).

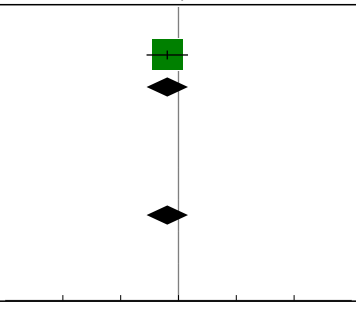
Study or subgroup	Clotiapine		Chlorpromazine		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI		Random, 95% CI
1.4.1 Delusion							
Kaneko 1969	5	17.7 (2.1)	6	10.4 (4.2)		100%	7.36[3.54,11.18]
Subtotal ***	**5**		**6**			**100%**	**7.36[3.54,11.18]**
Heterogeneity: Not applicable							
Test for overall effect: Z=3.78(P=0)							
1.4.2 Hallucination							
Kaneko 1969	7	9.7 (2.6)	9	12.7 (4.9)		100%	-3[-6.75,0.75]
Subtotal ***	**7**		**9**			**100%**	**-3[-6.75,0.75]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.57(P=0.12)							
Test for subgroup differences: Chi²=14.38, df=1 (P=0), I²=93.05%							



favours chlorpromazine favours clotiapine

Analysis 1.5. Comparison 1 Chlorpromazine versus Clotiapine, Outcome 5 Mental state: 2c. Specific - negative symptoms - average change scores (PANSS negative subscale, high = good).

Study or subgroup	Clotiapine		Chlorpromazine		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI		Random, 95% CI
1.5.1 Deficiency of initiative and apathy							
Kaneko 1969	10	4.6 (2)	11	5.6 (2.2)		100%	-0.97[-2.76,0.82]
Subtotal ***	**10**		**11**			**100%**	**-0.97[-2.76,0.82]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.06(P=0.29)							
Total ***	**10**		**11**			**100%**	**-0.97[-2.76,0.82]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.06(P=0.29)							



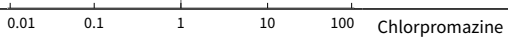
Clotiapine Chlorpromazine

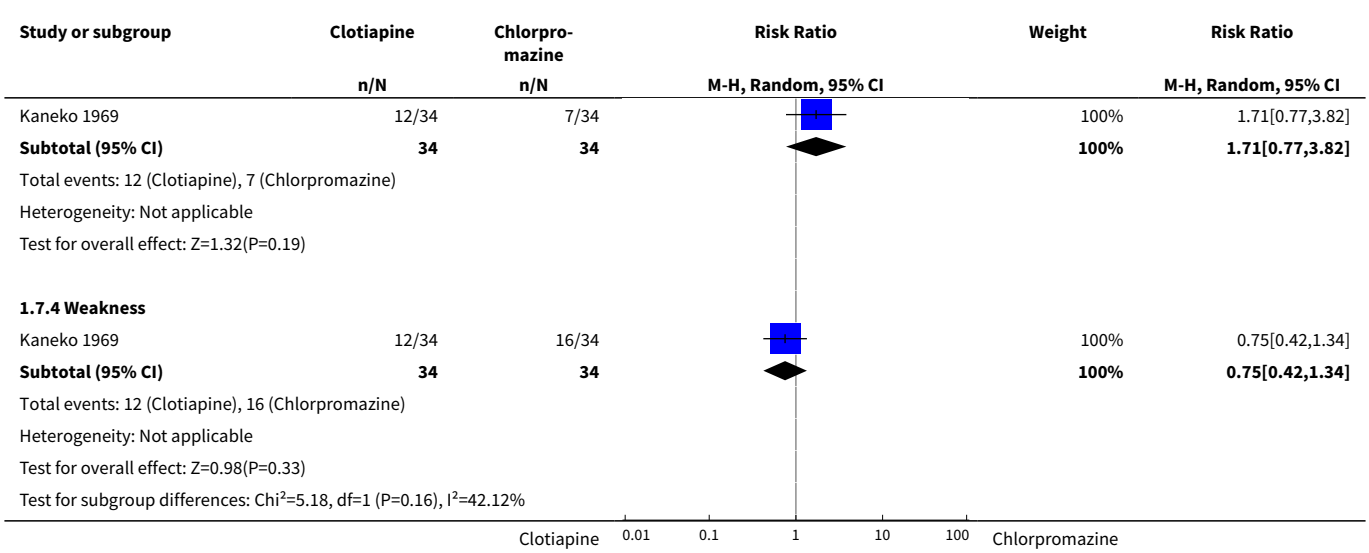
Analysis 1.6. Comparison 1 Chlorpromazine versus Clotiapine, Outcome 6 Mental state: 2d. Specific - various symptoms - average change score - (S-Scale, high = poor).

Study or subgroup	Clotiapine N	Clotiapine Mean(SD)	Chlorpromazine N	Chlorpromazine Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.6.1 Delusion							
Jacobsson 1974	17	0.8 (0.5)	21	0.8 (0.2)		100%	-0.06[-0.3,0.18]
Subtotal ***	**17**		**21**			**100%**	**-0.06[-0.3,0.18]**
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%							
Test for overall effect: Z=0.5(P=0.62)							
1.6.2 Hallucination							
Jacobsson 1974	17	0.4 (0.3)	21	0.6 (0.4)		100%	-0.24[-0.46,-0.02]
Subtotal ***	**17**		**21**			**100%**	**-0.24[-0.46,-0.02]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.11(P=0.03)							
1.6.3 Influence of thought							
Jacobsson 1974	17	0.7 (0.2)	21	0.5 (0.2)		100%	0.28[0.17,0.39]
Subtotal ***	**17**		**21**			**100%**	**0.28[0.17,0.39]**
Heterogeneity: Not applicable							
Test for overall effect: Z=4.92(P<0.0001)							
1.6.4 Splitting							
Jacobsson 1974	17	0.4 (0.2)	21	0.4 (0.1)		100%	0.01[-0.09,0.11]
Subtotal ***	**17**		**21**			**100%**	**0.01[-0.09,0.11]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.19(P=0.85)							
Test for subgroup differences: Chi^2=23.4, df=1 (P<0.0001), I^2=87.18%							

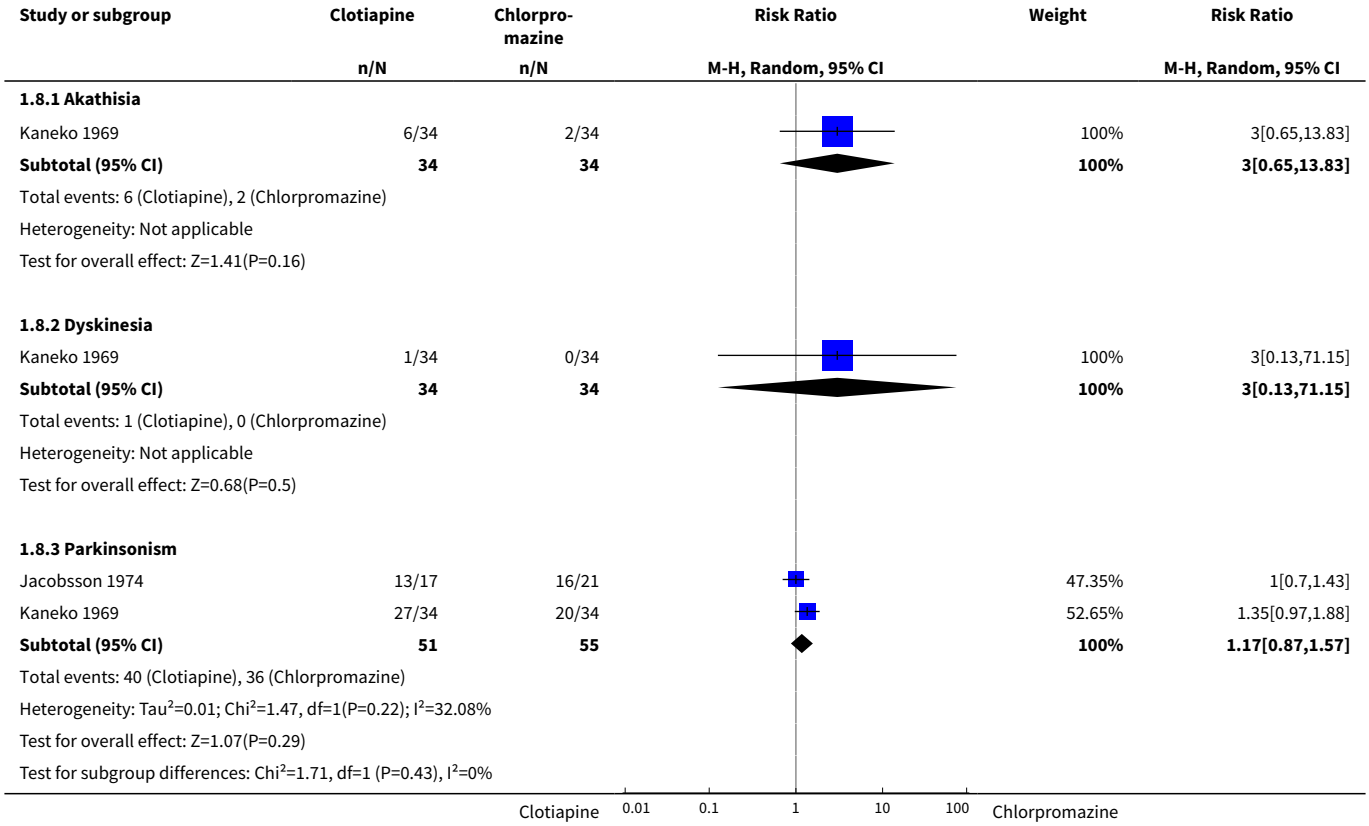
Analysis 1.7. Comparison 1 Chlorpromazine versus Clotiapine, Outcome 7 Adverse effects: 1. Central nervous system - short term.

Study or subgroup	Clotiapine n/N	Chlorpro-mazine n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.7.1 Drowsiness					
Kaneko 1969	17/34	9/34		100%	1.89[0.98,3.63]
Subtotal (95% CI)	**34**	**34**		**100%**	**1.89[0.98,3.63]**
Total events: 17 (Clotiapine), 9 (Chlorpromazine)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.91(P=0.06)					
1.7.2 Somnipathy					
Kaneko 1969	11/34	8/34		100%	1.38[0.63,2.99]
Subtotal (95% CI)	**34**	**34**		**100%**	**1.38[0.63,2.99]**
Total events: 11 (Clotiapine), 8 (Chlorpromazine)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.8(P=0.42)					
1.7.3 Unsteadiness					

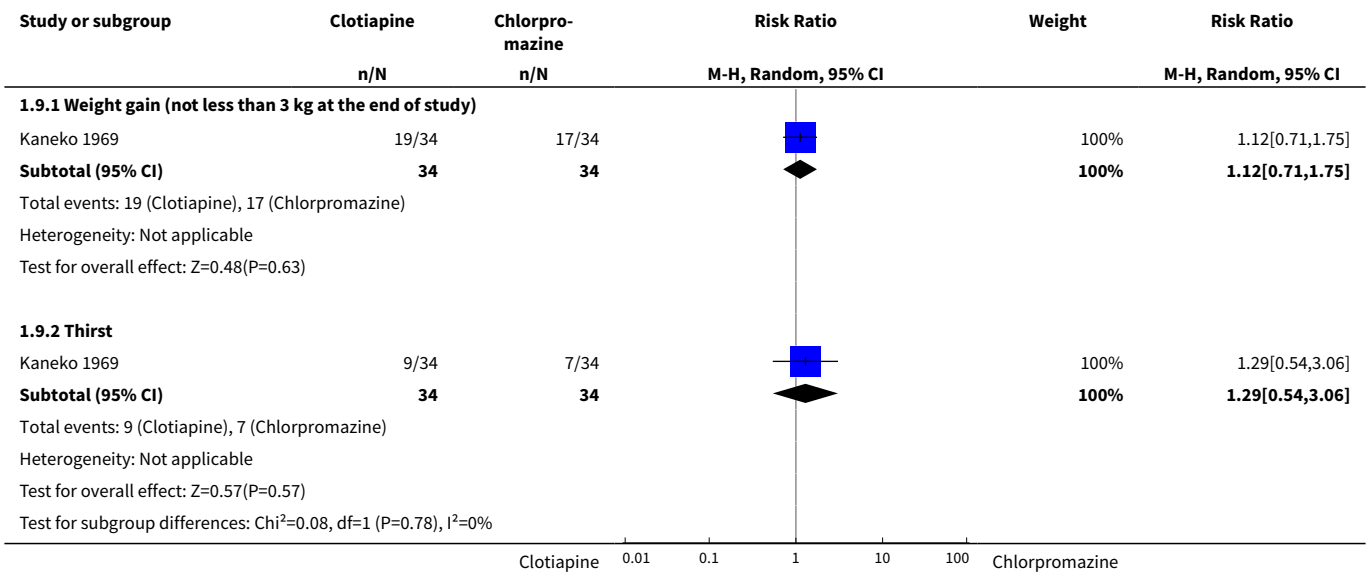




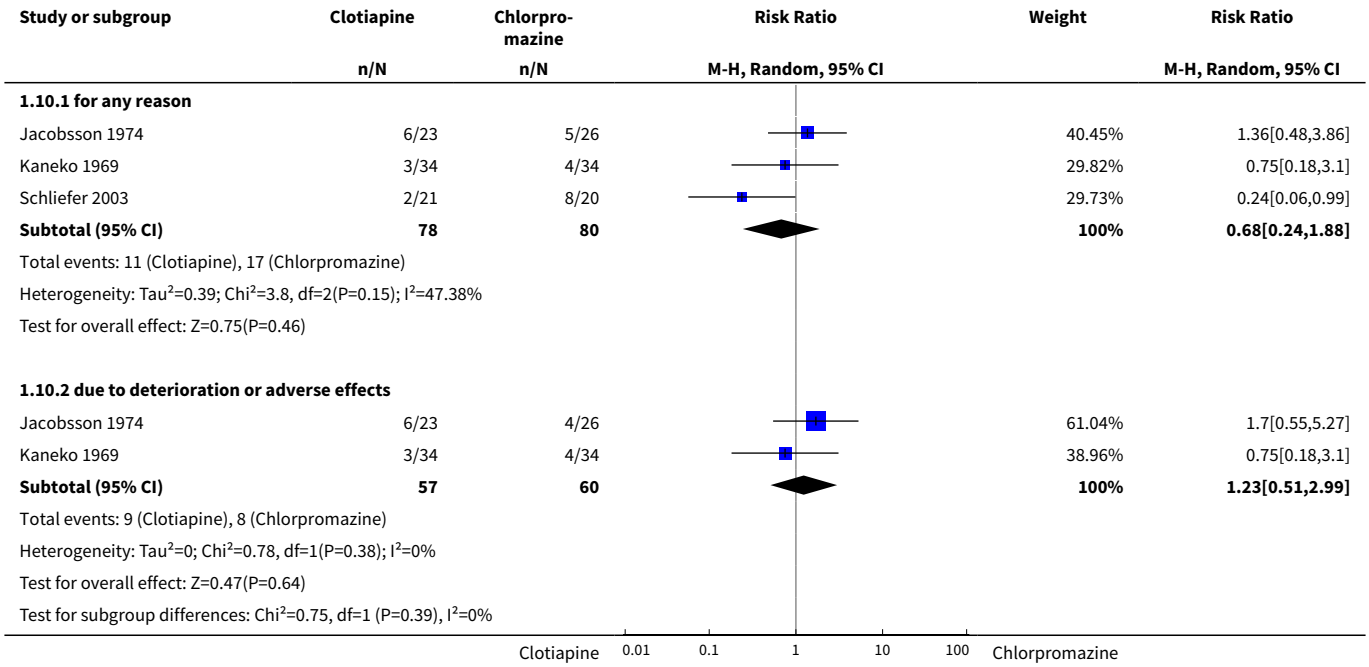
Analysis 1.8. Comparison 1 Chlorpromazine versus Clotiapine, Outcome 8 Adverse effects: 2. Movement disorders - short term.



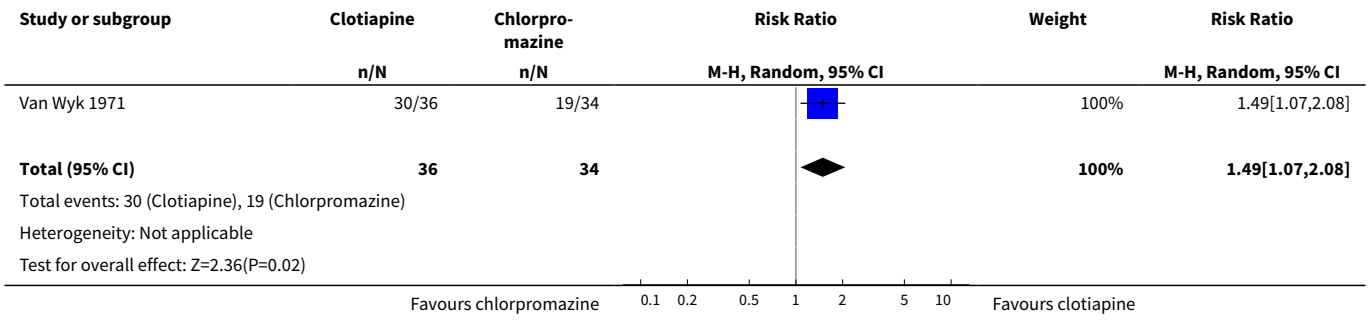
Analysis 1.9. Comparison 1 Chlorpromazine versus Clotiapine, Outcome 9 Adverse effects: 3. Various other - short term.



Analysis 1.10. Comparison 1 Chlorpromazine versus Clotiapine, Outcome 10 Leaving the study early - short term.



Analysis 1.11. Comparison 1 Chlorpromazine versus Clotiapine, Outcome 11 Service use: discharge from hospital - short term (12 weeks).



ADDITIONAL TABLES

Table 1. The Cochrane chlorpromazine for people with schizophrenia reviews

Review title	Reference
Acetophenazine versus chlorpromazine	Bazrafshan 2015
Chlorpromazine dose for people with schizophrenia	Liu 2009
Cessation of medication for people with schizophrenia already stable on chlorpromazine	Almerie 2007
Chlorpromazine versus atypical antipsychotic drugs for schizophrenia	Saha 2013
Chlorpromazine versus clotiapine for schizophrenia	Current review
Chlorpromazine versus haloperidol for schizophrenia	Leucht 2008
Chlorpromazine versus metiapine for schizophrenia	Zare 2015
Chlorpromazine versus penfluridol for schizophrenia	Khalili 2015
Chlorpromazine versus piperacetazine for schizophrenia	Eslami 2015
Chlorpromazine versus placebo for schizophrenia	Adams 2014
Chlorpromazine for psychosis induced aggression or agitation	Ahmed 2010

Table 2. Mental state: improvement for positive symptoms

Outcome or subgroup	Studies	Participants	Statistical method	Effect estimate
Mental state: average scores for improvement of positive symptoms (high score = improvement)	1	27	Mean difference (IV, random, 95% CI)	2.17 [-7.98, 12.33]

Table 2. Mental state: improvement for positive symptoms *(Continued)*

1. Hallucination	1	16	Mean difference (IV, random, 95% CI)	-3.00 [-6.75, 0.75]
2. Delusion	1	11	Mean difference (IV, random, 95% CI)	7.36 [3.54, 11.18]
Mental state: Improved positive symptoms (frequency of marked effects)	1	42	Risk ratio (M-H, random, 95% CI)	0.82 [0.41, 1.62]
1. Hallucination	1	25	Risk ratio (M-H, random, 95% CI)	0.46 [0.15, 1.40]
2. Delusion	1	12	Risk ratio (M-H, random, 95% CI)	1.33 [0.50, 3.55]
3. Severe excitation	1	5	Risk ratio (M-H, random, 95% CI)	0.75 [0.15, 3.72]

Table 3. Suggestions for design of future study

Methods	Allocation: randomised, with sequence generation and concealment of allocation clearly described Blindness: double, tested Duration: 12 months beyond end of intervention at least Raters: independent
Participants	Diagnosis: people with schizophrenia - however diagnosed* Age: any Sex: both History: any N = 300**
Interventions	1. Clotiapine: ˜100 mg/day. N = 150 2. Chlorpromazine: ˜400 mg/day. N = 150
Outcomes	Global state - relapse, clinically important change Mental state - general - clinically important change in mental state, average change in negative symptoms Adverse effects - incidence of serious adverse events/effects, clinically important extrapyramidal symptoms Leaving the study early - for any reason Cost of care Service outcomes: admitted, number of admissions, length of hospitalisation, discharge, contacts with psychiatric services Compliance with drugs Economic evaluations: cost-effectiveness, cost-benefit
Notes	*This could be diagnosed by clinical decision. If funds were permitting all participants could be screened using operational criteria, otherwise a random sample should suffice. **Size of study with sufficient power to highlight about a 10% difference between groups for primary outcome

CONTRIBUTIONS OF AUTHORS

Shahrzad Mazhari (SM): designing the review, development and writing the review, reliability checking for trial selection, reliability checking for data extraction and report writing.

Saeed Esmailian (SE): development and writing of protocol, trial selection and review writing.

Armita Shah-Esmaili (ASE): provided general advice, reliability checking for trial selection, draft checking.

Ali Shahsavari Goughari (ASG) : development and writing of protocol, trial selection, reliability checking data extraction and review writing

Azam Bazrafshan (AB): data extraction, statistical analysis and review writing.

Morteza Zare (MZ): data extraction, statistical analysis and review writing.

DECLARATIONS OF INTEREST

Shahrzad Mazhari: None known

Saeed Esmailian: None known
Armita Shah-Esmaili: None known
Ali Shahsavari: None known
Azam Bazrafshan: None known
Morteza Zare: None known

SOURCES OF SUPPORT

Internal sources

- Kerman University of Medical Sciences, Kerman, Iran.

  all review authors are students at this university

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We have updated some of the text in the methods to reflect changes made to the template since publication of the protocol. As these changes did not affect our data collection and analyses for these studies we felt we could add to the methods section, so they are published before the next update of this review.

1. Areas of text changed

1.1 Use of scales

We added this sentence to clarify use of sub-scale data:

- the instrument was a global assessment of an area of functioning and not sub-scores which were not, in themselves, validated or shown to be reliable. However there would be exceptions, we would include sub-scores from mental state scales measuring positive and negative symptoms of schizophrenia.

1.2 Selection of studies

We added this sentence to clarify our selection of studies for inclusion and exclusion.

We included studies that met our inclusion criteria and reported useable data. We would have excluded studies that either did not meet our inclusion criteria or met our inclusion criteria but did not report useable data.

1.3 Outcome title change

We have, changed 'service utilisation outcome' to 'service use' and added discharge from hospital. Data were reported for this outcome in a trial and we felt it was of interest to reproduce these data for the review. Excluding would mean the trial would have no useable data.

2. Additional authors

Two new authors have joined the team (Asam Bazrafshan and Morteza Zare) since protocol publication.

INDEX TERMS

Medical Subject Headings (MeSH)

Antipsychotic Agents [adverse effects] [*therapeutic use]; Chlorpromazine [adverse effects] [*therapeutic use]; Dibenzothiazepines [adverse effects] [*therapeutic use]; Dyskinesia, Drug-Induced [epidemiology]; Intention to Treat Analysis; Patient Dropouts [statistics & numerical data]; Randomized Controlled Trials as Topic; Risk; Schizophrenia [*drug therapy]

MeSH check words

Humans