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[Intervention Review]

Chlorpromazine versus placebo for schizophrenia

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ABSTRACT

Background

Chlorpromazine, formulated in the 1950s, remains a benchmark treatment for people with schizophrenia.

Objectives

To review the effects of chlorpromazine compared with placebo, for the treatment of schizophrenia.

Search methods

We searched the Cochrane Schizophrenia Group's Trials Register (15 May 2012). We also searched references of all identified studies for further trial citations. We contacted pharmaceutical companies and authors of trials for additional information.

Selection criteria

We included all randomised controlled trials (RCTs) comparing chlorpromazine with placebo for people with schizophrenia and non-affective serious/chronic mental illness irrespective of mode of diagnosis. Primary outcomes of interest were death, violent behaviours, overall improvement, relapse and satisfaction with care.

Data collection and analysis

We independently inspected citations and abstracts, ordered papers, re-inspected and quality assessed these. We analysed dichotomous data using risk ratio (RR) and estimated the 95% confidence interval (CI) around this. We excluded continuous data if more than 50% of participants were lost to follow-up. Where continuous data were included, we analysed this data using mean difference (MD) with a 95% confidence interval. We used a fixed-effect model.

Main results

We inspected over 1100 electronic records. The review currently includes 315 excluded studies and 55 included studies. The quality of the evidence is very low. We found chlorpromazine reduced the number of participants experiencing a relapse compared with placebo during six months to two years follow-up (n=512, 3 RCTs, RR 0.65 CI 0.47 to 0.90), but data were heterogeneous. No difference was found in relapse rates in the short, medium or long term over two years, although data were also heterogeneous. We found chlorpromazine provided a global improvement in a person's symptoms and functioning (n=1164, 14 RCTs, RR 0.71 CI 0.58 to 0.86). Fewer people allocated to chlorpromazine left trials early (n=1831, 27 RCTs, RR 0.64 CI 0.53 to 0.78) compared with placebo. There are many adverse effects. Chlorpromazine is clearly sedating (n=1627, 23 RCTs, RR 2.79 CI 2.25 to 3.45), it increases

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a person's chances of experiencing acute movement disorders (n=942, 5 RCTs, RR 3.47 CI 1.50 to 8.03) and parkinsonism (n=1468, 15 RCTs, RR 2.11 CI 1.59 to 2.80). Akathisia did not occur more often in the chlorpromazine group than placebo. Chlorpromazine clearly causes a lowering of blood pressure with accompanying dizziness (n=1488, 18 RCTs, RR 2.38 CI 1.74 to 3.25) and considerable weight gain (n=165, 5 RCTs, RR 4.92 CI 2.32 to 10.43).

Authors' conclusions

The results of this review confirm much that clinicians and recipients of care already know but aim to provide quantification to support clinical impression. Chlorpromazine's global position as a 'benchmark' treatment for psychoses is not threatened by the findings of this review. Chlorpromazine, in common use for half a century, is a well-established but imperfect treatment. Judicious use of this best available evidence should lead to improved evidence-based decision making by clinicians, carers and patients.

PLAIN LANGUAGE SUMMARY

Chlorpromazine versus placebo for schizophrenia

For previous plain language summary please see Appendix 3.

People with schizophrenia often hear voices or see things (hallucinations) and have strange beliefs (delusions). The main treatment for these symptoms of schizophrenia is antipsychotic drugs. Chlorpromazine was one of the first drugs discovered to be effective in the treatment of schizophrenia during the 1950s. It remains one of the most commonly used and inexpensive treatments even today. However, being an older drug ('typical' or first generation) it also has serious side effects, such as blurred vision, a dry mouth, tremors or uncontrollable shaking, depression, muscle stiffness and restlessness.

An update search was carried out in 2012 and the review now includes 55 studies that assess the effects of chlorpromazine in treating schizophrenia compared with no active treatment ('dummy' treatment or placebo). Evidence was, in the main, rated by the review authors as low quality. There is some evidence to suggest that chlorpromazine reduces relapse and improves people's mental health, symptoms and functioning. However, the side effects of chlorpromazine are severe and debilitating. Chlorpromazine causes sleepiness and sedation. It also causes movement disorders (such as tremors and uncontrollable shaking), considerable weight gain and lowering of blood pressure with accompanying dizziness.

Chlorpromazine is low-cost and widely available. Despite its many side effects, chlorpromazine is likely to remain a benchmark drug and one of the most widely used treatments for schizophrenia worldwide.

It should be noted that the quality of evidence from the 55 included studies was low and in addition to this, 315 studies were excluded because of flaws in the reporting of information or data and in research design and methods. Larger, better conducted and reported trials should focus on important outcomes such as quality of life, levels of satisfaction, relapse, hospital discharge or admission and number of violent incidents.

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SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

CHLORPROMAZINE versus PLACEBO for schizophrenia

Patient or population: patients with schizophrenia
Settings: hospital and community
Intervention: CHLORPROMAZINE versus PLACEBO

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	CHLORPROMAZINE versus PLACEBO				
Death Follow-up: 5 weeks	See comment	See comment	Not estimable	14 (1 study)	⊕◯◯◯ **very low**[1,2]	One study specifically reported mortality and there were no deaths in either the chlorpromazine or placebo group. There were no reports of death in any other study
Relapse Follow-up: 6 months to 2 years	**710 per 1000**	**461 per 1000** (334 to 639)	**RR 0.65** (0.47 to 0.90)	512 (3 studies)	⊕◯◯◯ **very low**[3,4]	2 trials report this outcome at 0-8 weeks follow-up, 3 trials at 6 months to 2 years, and 2 trials 2-5 years, none showed a significant difference
Global state: no overall improvement (psychiatrist - rated) Follow-up: 9 weeks to 6 months	**897 per 1000**	**637 per 1000** (520 to 772)	**RR 0.71** (0.58 to 0.90)	1164 (14 studies)	⊕◯◯◯ **very low**[5,6,7]	13 trials also reported on this outcome at 0-8 weeks follow-up and showed a significant result in favour of chlor-

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						promazine
Leaving the study early Follow-up: 9 weeks to 6 months	**200 per 1000**	**128 per 1000** (106 to 156)	**RR 0.64** (0.53 to 0.78)	1831 (27 studies)	⊕⊕◯◯ **low**[8]	17 trials reported on this outcome at 0-8 weeks follow-up and showed significant results in favour of chlorpromazine. 2 trials reported on this outcome at 6 months to 2 years follow-up, and 1 trial at 2-5 years, and there was no significant difference
Satisfaction with treatment - not reported	See comment	See comment	Not estimable	-	See comment	No studies reported on this outcome.
Behaviour: deteriorated/ disturbed/ uncooperative Follow-up: 9 weeks to 6 months	**471 per 1000**	**231 per 1000** (113 to 471)	**RR 0.49** (0.24 to 1.00)	1040 (8 studies)	⊕◯◯◯ **very low**[4,9]	2 trials reported on this outcome at 0-8 weeks follow-up and found no significant difference
Cost of care - not reported	See comment	See comment	Not estimable	-	See comment	No studies reported on this outcome.

*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: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Serious risk of bias: the study had an unclear risk of bias for random sequence generation, allocation concealment and other bias as the drugs were provided by a pharmaceutical company.

[2] Very serious imprecision: there are very few participants and no events for this outcome.

[3] Serious risk of bias: all studies had an unclear risk of bias for random sequence generation, allocation concealment, blinding of assessors and incomplete data. One also had an unclear risk of other bias as the drugs were provided by a pharmaceutical company.

[4] Very serious inconsistency: there was very high heterogeneity in the pooled results.

[5] Serious risk of bias: one study had a high risk of bias for random sequence generation and in eleven studies it was unclear. Twelve studies had an unclear risk of bias for allocation concealment. Blinding of participants and personnel was unclear in seven studies and blinding of assessors was unclear in twelve. Four studies also had a high risk of other bias as they were funded by industry.

[6] Serious inconsistency: there was high heterogeneity in the pooled results.

[7] Strongly suspected publication bias: the funnel plot suggests that there may be studies without statistically significant effects that have not been included in this analysis.

[8] Very serious risk of bias: twenty four of the studies had an unclear risk of bias for random sequence generation, and all but one for allocation concealment. Twelve studies had an unclear risk of bias for blinding of participants and personnel and in 23 studies it was unclear whether assessors were blinded. Six studies also had a high risk of other bias as they were partly funded by industry.

[9] Serious risk of bias: all studies had an unclear risk of bias for random sequence generation, and all but one for allocation concealment. Three studies had an unclear risk of bias for blinding of participants and personnel, and in all studies it was unclear whether assessors were blinded. Two studies also had a high risk of other bias as they were partly funded by industry.

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BACKGROUND

Description of the condition

Approximately 24 million people currently suffer from schizophrenia (WHO 1998), the majority of whom live in low- or middle-income countries. Chlorpromazine remains one of the most commonly used and inexpensive treatments for people with schizophrenia (Odejide 1982), despite its well-documented adverse effects and the advent of a new generation of antipsychotic drugs. It is one of the essential drugs listed by the World Health Organization (WHO 2003). Chlorpromazine is commonly prescribed in India, and in South East Asia, the older generation of antipsychotics are used to treat the majority of people with schizophrenia (Chong 2004). In 2003, chlorpromazine was the most frequently prescribed of the first generation 'typical' antipsychotic drugs in the UK at a time when the 'typical' group of antipsychotics accounted for 44% of all antipsychotic prescriptions (PPA, 2003).

Description of the intervention

Chlorpromazine, a drug developed in 1951 for reducing allergic reactions (an antihistamine) began to be used as part of a cocktail of drugs in order to induce a state of 'artificial hibernation' for surgical procedures (Laborit 1951). Its ability to reduce psychic stress led researchers to demonstrate its effectiveness for treating certain psychiatric disorders (Delay 1952). Chlorpromazine was hailed as a major discovery for schizophrenia, an illness for which few treatment options existed (Davis 1978). The impact of this drug has been so great, that according to one author, it has been heralded as the second revolution in psychiatry (the first being psychoanalysis) (Grozier 1973). Chlorpromazine is the first of many drugs to be classed as a 'neuroleptic' (literally translated: to grasp the nerve), a term coined by two of its first protagonists (Delay 1952). Early trials of chlorpromazine for schizophrenia indicated, that in comparison with placebo, it hastened clinical recovery, facilitated improvements in social functioning and was effective at preventing relapse.

How the intervention might work

The antipsychotic effect of chlorpromazine results from its action on particular areas within specific cells of the brain (Sedvall 1995). It is thought to affect how receptive these cells are to dopamine. However, chlorpromazine is not specific to one site of action within the body. Consequently, it is known to cause adverse effects ranging from dry mouth, blurred vision and urinary retention as well as restlessness, tremors, facial rigidity, shuffling gait and repetitive movements of the face and/or trunk which can be difficult to reverse (APA 1992). Chlorpromazine has also been linked to depressive symptoms that may be caused by the drug itself (neuroleptic dysphoria, Awad 1993). In addition, the use of chlorpromazine has been associated with a potentially fatal disturbance of blood pressure, temperature and muscle control (neuroleptic malignant syndrome, APA 1994).

Why it is important to do this review

There are questions relating to the differential response to drugs between certain groups of people with schizophrenia. For example, there may be differences in the effects of treatment for men and women (Hambrecht 1992; Kendler 1995; Szymanski 1995), for children, adults or the elderly (Kaplan 1990; Rosen 1990), or for people who are experiencing their first episode as opposed to those with a longer illness duration (Hill 1992; Szymanski 1996). When prescribing drugs for schizophrenia dosage is important in order to obtain optimal response with minimal adverse effects (Bollini 1994; Kane 1985). There also remains debate about the applicability of research findings to the 'real world' of clinicians (Jenicek 1990). For example, trials undertaken on highly selected groups of people with schizophrenia may be of very limited use in the 'everyday' situation. We attempted to investigate whether, for the primary outcomes of interest (see: Methods, Types of outcome measures), a real difference exists for those with diagnoses of schizophrenia made with operational 'checklists' as opposed to those with less rigorous diagnoses. A final question we posed was whether the effects of chlorpromazine were different between patients treated recently (1990-2002) to those treated in earlier decades (1951-1989).

New trials often use chlorpromazine as the 'benchmark' or 'control' drug rather than a placebo when a new treatment is being evaluated. The aim of this review is to evaluate this 'benchmark' in comparison to placebo. This is an update of a Cochrane Review first published in 1998, Issue 1 of The Cochrane Database of Systematic Reviews (Thornley 1998a) and updated in 2003 (Thornley 2003) and 2007 (Adams 2007).

OBJECTIVES

To review the effects of chlorpromazine compared with placebo, for the treatment of schizophrenia.

It was expected that several subgroup analyses could be undertaken within this review (see Subgroup analysis and investigation of heterogeneity).

METHODS

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Criteria for considering studies for this review

Types of studies

We sought all relevant randomised controlled trials. Where a trial was described as 'double blind' but it was implied that the study was randomised, we included these trials in a sensitivity analysis. If their inclusion did not result in a substantive difference, they remained in the analyses. If their inclusion did result in statistically significant differences, we did not add the data from these lower quality studies to the results of the better quality trials, but presented these within a subcategory. We excluded quasi-randomised studies, such as those allocating by alternate days of the week.

Types of participants

We included people with schizophrenia and other types of schizophrenia-like psychoses (schizophreniform and schizoaffective disorders) however diagnosed, irrespective of age, sex or severity of illness.

Types of interventions

1. Chlorpromazine: any dose or mode of administration (oral or by injection)

2. Placebo (active or inactive) or no treatment

Types of outcome measures

We categorised outcomes as short term (zero to eight weeks), medium term (nine weeks to six months) and long term (six months to two years).

Primary outcomes

We classified these outcomes as primary outcomes for the 2002 update to help minimise the potential for multiple statistical testing that could be undertaken within sensitivity analyses. We tried to choose these on the grounds of clinical importance and were helped in this by inclusion of a new co-reviewer, JR, who was not as familiar with the data as the previous authors. We have used the same outcomes but rearranged into new sub-headings for this 2012 update.

1. Death - suicide and natural causes

2. Relapse - as defined by each study

3. Global state

3.1 Overall improvement*

4. Leaving the study early

5. Satisfaction with treatment - participant/carer

6. Behaviour

6.1 Specific behaviours (e.g. aggressive or violent behaviour)

7. Economic

7.1 Cost of care

Secondary outcomes

1. Global state

1.1 Duration of hospital stay
1.2 Re-admission
1.3 Severity of Illness

2. Mental state

2.1 General symptoms
2.2 Specific symptoms
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. Behaviour

3.1 General behaviour
3.2 Social functioning
3.3 Employment status during trial (employed/unemployed)
3.4 Occurrence of violent incidents (to self, others or property)

4. Adverse effects

4.1 General
4.2 Specific
4.2.2 Movement disorders (extrapyramidal side effects, specifically tardive dyskinesia and neuroleptic malignant syndrome)
4.2.3 Sedation
4.2.4 Dry mouth

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5. 'Summary of findings' table

We used the GRADE approach to interpret findings (Schünemann 2008) and GRADE profiler (GRADEPRO) to import data from Review Manager 5 (Review Manager) to create a 'Summary of findings' table. These tables provide outcome-specific information concerning the overall quality of evidence from each included study in the comparison, the magnitude of effect of the interventions examined, and the sum of available data on all outcomes we rate as important to patient-care and decision making. We have selected the following main outcomes for inclusion in the 'Summary of findings' table.

1. Death - suicide and natural causes
2. Overall improvement
3. Relapse - as defined by each study
4. Leaving the study early
5. Satisfaction with treatment - participant/carer
6. Specific behaviours (e.g. aggressive or violent behaviour)
7. Cost of care

Search methods for identification of studies

Electronic searches

For previous searches please see Appendix 2.

1. Cochrane Schizophrenia Group Trials Register (May 2012)

The Trials Search Co-ordinator searched the Cochrane Schizophrenia Group's Trials Register (15 May 2012).
The Cochrane Schizophrenia Group's Trials Register is compiled by systematic searches of major databases, handsearches of relevant journals and conference proceedings (see group module).

Searching other resources

1. Reference searching

We inspected the references of all identified studies for further studies.

2. Personal contact

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

3. Pharmaceutical companies

In previous versions of this review, we contacted pharmaceutical companies for any unpublished and published trials. Approaches have been made to Rhone Poulenc Rorer, the original developers of chlorpromazine, for access to archive material. Dr R.A Pargiter of Hobart, Tasmania very kindly donated a series of reports from May and Baker (the pharmaceutical company which originally produced chlorpromazine) that listed presentations of work relevant to chlorpromazine and schizophrenia, dating from 1955 to 1973. We (BT, CEA and JR) handsearched these for further studies.

Data collection and analysis

Methods used in data collection and analysis for this 2012 update are below; for previous methods please see Appendix 3.

Selection of studies

For this 2012 update, the Cochrane Schizophrenia group provided Enhance Reviews a database of relevant abstracts; the Enhance Reviews team inspected full articles of the abstracts meeting the inclusion criteria.

Data extraction and management

1. Extraction

For this 2012 update, two members of the Enhance Reviews team extracted data from included studies. In addition, Jun Xia (JX) extracted data for all Chinese studies. We extracted data presented only in graphs and figures whenever possible. In the previous versions of the review, when further information was necessary, we contacted authors of studies in order to obtain missing data or for clarification. If studies were multi-centre, where possible, we extracted data relevant to each component centre separately.

2. Management

2.1 Forms

We extracted data onto standard, simple forms, created in a web-based software (www.systematic-review.ca).

2.2 Scale-derived data

We included 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 had not been written or modified by one of the trialists for that particular trial.
Ideally, the measuring instrument should either be i. a self-report or ii. completed by an independent rater or relative (not the therapist). We realise that this is not often reported clearly; we have noted whether or not this is the case in Description of studies.

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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 decided primarily to use endpoint data, and only use change data if the former were not available. We combined endpoint and change data in the analysis as we used mean differences (MD) rather than standardised mean differences throughout (Higgins 2011, Chapter 9.4.5.2).

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 aimed to apply the following standards to all data before inclusion:
a) standard deviations (SDs) and means are reported in the paper or obtainable from the authors;
b) when a scale starts from the finite number zero, the SD, when multiplied by two, is less than the mean (as otherwise the mean is unlikely to be an appropriate measure of the centre of the distribution (Altman 1996));
c) if a scale started from a positive value (such as the Positive and Negative Syndrome Scale (PANSS, Kay 1986) which can have values from 30 to 210), we modified the calculation described above to take the scale starting point into account. In these cases skew is present if 2 SD > (S-S min), where S is the mean score and S min is the minimum score.
Endpoint scores on scales often have a finite start and end point and these rules can be applied. We entered skewed endpoint data from studies of fewer than 200 participants in additional tables rather than into an analysis. Skewed data pose less of a problem when looking at the mean if the sample size is large; we entered such endpoint data into syntheses.
When continuous data are presented on a scale that includes a possibility of negative values (such as change data), it is difficult to tell whether data are skewed or not, we entered skewed change data into analyses regardless of the size of the study.

2.5 Common measure

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

Assessment of risk of bias in included studies

For this 2012 update, two members of the Enhance Reviews team worked independently by using criteria described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) to assess trial quality for the new included studies and all previously included studies. This new set of criteria is based on evidence of associations between overestimate of effect and high risk of bias of the article such as sequence generation, allocation concealment, blinding, incomplete outcome data and selective reporting.
Where inadequate details of randomisation and other characteristics of trials were provided, we did not contact authors of the studies in order to obtain additional information.
We have noted the level of risk of bias in both the text of the review and in the Summary of findings for the main comparison.

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 and that odds ratios tend to be interpreted as RR by clinicians (Deeks 2000).

2. Continuous data

For continuous outcomes we estimated mean difference (MD) between groups. We would prefer not to calculate effect size measures (standardised mean difference (SMD)). However, if scales of very considerable similarity were used, we presumed 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.

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Unit of analysis issues

1. Cluster trials

Studies increasingly employ 'cluster randomisation' (such as randomisation by clinician or practice), but analysis and pooling of clustered data poses problems. Authors often fail to account for intra-class correlation in clustered studies, leading to a 'unit of analysis' error (Divine 1992) whereby P values are spuriously low, confidence intervals unduly narrow and statistical significance overestimated. This causes type I errors (Bland 1997; Gulliford 1999).
We did not include any cluster trials in this review. If we had, where clustering was not 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.
In subsequent versions of this review we will seek to contact first authors of studies to obtain intra-class correlation coefficients (ICC) 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 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 it was assumed to be 0.1 (Ukoumunne 1999).
If cluster studies have been appropriately analysed taking into account ICCs and relevant data documented in the report, synthesis with other studies would have been 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 of 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 the additional treatment arms in the comparisons. If data were binary, we simply added these and combined within the two-by-two table. If data were continuous, we combined data following the formula in section 7.7.3.8 (Combining groups) of the *Cochrane Handbook for Systemic reviews of Interventions* (Higgins 2011). Where the additional treatment arms were not relevant, we did not reproduce these data.

Dealing with missing data

1. Overall loss of credibility

At some degree of loss of follow-up, data must lose credibility (Xia 2009). We chose that, for any particular outcome, should more than 50% of data be unaccounted for, we did 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 marked such data with (*) to indicate that such a result may well be prone to bias.

2. Binary

In the case where attrition for a binary outcome was between 0% and 50%, we presented data for the total number of participants randomised for studies that used an intention-to-treat (ITT) analysis; where studies did not use an ITT analysis, we presented completer only data.

3. Continuous

3.1 Attrition

In the case 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 presented and used these data.

3.2 Standard deviations

If standard deviations (SDs) were not reported, we first tried to obtain the missing values from the authors. If not available, where there are missing measures of variance for continuous data, but an exact standard error (SE) and confidence intervals (CIs) available for group means, and either P value or T value available for differences in mean, we can calculate them according to the rules described in the *Cochrane Handbook for Systemic reviews of Interventions* (Higgins 2011). When only the SE is reported, SDs are calculated by the formula SD=SE * square root (n). Chapters 7.7.3 and 16.1.3 of the *Cochrane Handbook for Systemic reviews of Interventions* (Higgins 2011) present detailed formulae for estimating SDs from P values, T or F values, CIs, ranges or other statistics. If these formulae do not apply, we would calculate the SDs according to a validated imputation method which is based on the SDs of the other included studies (Furukawa 2006). Although some of these imputation strategies can introduce error, the alternative would be to exclude a given study's outcome and thus to lose information. We did not impute any SDs, if we had we would have examined the validity of the imputations in a sensitivity analysis excluding imputed values.

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3.3 Last observation carried forward

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

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 which we had not predicted would arise. When such situations or participant groups arose, we fully discussed these.

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. When such methodological outliers arose, we fully discussed these.

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 confidence interval for I^2). An I^2 estimate greater than or equal to around 50% accompanied by a statistically significant Chi^2 statistic was interpreted as evidence of substantial levels of heterogeneity (Higgins 2011). When substantial levels of heterogeneity were found in the primary outcome, we explored reasons for the heterogeneity (Subgroup analysis and investigation of heterogeneity). If data were heterogeneous we used a random-effects model.

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 of the *Cochrane Handbook for Systemic reviews of Interventions* (Higgins 2011). We are aware that funnel plots may be useful in investigating reporting biases but are of limited power to detect small-study effects. We did not use funnel plots for outcomes where there were 10 or fewer studies, or where all studies were of similar sizes. In other cases, where funnel plots were possible, we sought 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 the fixed-effect model for all analyses. The reader is, however, able to choose to inspect the data using the random-effects model.

Subgroup analysis and investigation of heterogeneity

1. Subgroup analyses - only primary outcomes

1.1 Clinical state, stage or problem

We proposed to undertake this review and provide an overview of the effects of chlorpromazine for people with schizophrenia in general. In addition, however, we tried to report data on subgroups of people in the same clinical state, stage and with similar problems. We also undertook subgroup analyses comparing the results for the following:

- men versus women; under 18 years of age versus 18-65 years old versus older than 65;
- acutely ill people (< one-month in duration) versus people who have been ill for longer;
- high dose (> 501 mg/day) versus low doses (1-500 mg/day);
- people diagnosed according to any operational criteria versus those who have not been diagnosed using operational criteria;
- studies published before 1990 versus studies published between 1990 and the present.

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2. Investigation of heterogeneity

If inconsistency was high, we have reported this. First, we investigated whether data had been entered correctly. Second, if data were correct, we visually inspected the graph and successively removed outlying to see if homogeneity was restored.
When unanticipated clinical or methodological heterogeneity was obvious we simply stated hypotheses regarding these for future reviews or versions of this review. We do not anticipate undertaking analyses relating to these.

Sensitivity analysis

We applied sensitivity analyses to the primary outcomes of this review.

1. Implication of randomisation

We aimed to include trials in a sensitivity analysis if they were described in some way so as to imply randomisation. For the primary outcomes we included these studies and if there was no substantive difference when the implied randomised studies were added to those with better description of randomisation, then we entered all data from these studies.

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 use our assumption/s and when we used data only from people who completed the study to that point. A sensitivity analysis was undertaken to test how prone results were to change when completer-only data only were compared to the imputed data using the above assumption. If there was a substantial difference, we reported results and discussed them but continued to employ our assumption.

3. Risk of bias

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

4. Imputed values

Had we included any cluster-randomised trials, we would have undertaken a sensitivity analysis to assess the effects of including data from trials where we used imputed values for ICC in calculating the design effect in cluster-randomised trials.
If we noted substantial differences in the direction or precision of effect estimates in any of the sensitivity analyses listed above, we did not pool data from the excluded trials with the other trials contributing to the outcome, but presented them separately.

RESULTS

Description of studies

Please see Characteristics of included studies and Characteristics of excluded studies.

Results of the search

The original searches in 1995 yielded over 600 references, and after initial appraisal we selected 201 studies for further inspection of the full papers. An additional 50 papers were also identified from the reference lists. We were able to include 45 relevant studies. For the July 2002 update, we found 106 citations and were able to include just one additional study, and four additional reports of already included studies. In addition, May and Baker's files of reports of chlorpromazine studies, kindly supplied by Dr Pargiter of Hobart, Tasmania, were handsearched by BT, CA and JR. These files yielded 37 more records that met the review criteria. Three of these reports were previously unknown studies that could be included. Thirty-four were excluded. We are very grateful to Dr Pargiter, who kept those files for so long and then, knowing that they could at last be usefully employed, donated them. For the January 2007 update search, we found 317 references from 142 studies. We were able to include one additional study (Xiong 1994).
The May 2012 update search identified a total of 21 new relevant studies. Five trials met the inclusion criteria for this review and there are now 55 studies included in the latest version of this review (see Figure 1). A total of 315 studies are now excluded. There are no studies awaiting assessment and no ongoing studies have been identified.

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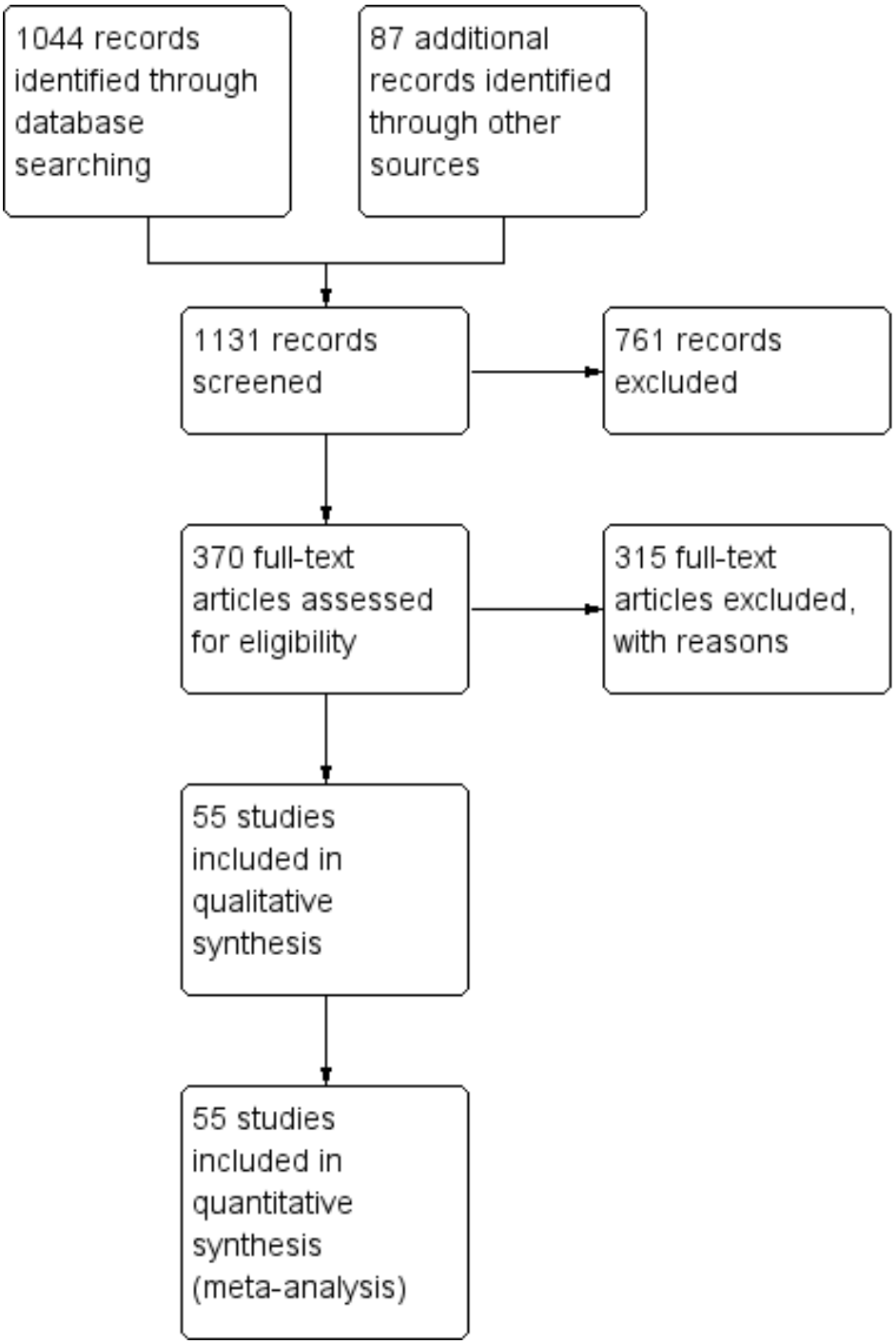
Figure 1. Study flow diagram.



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Included studies

We included 55 studies.

1. Methods

Four included studies were cross-over trials (Baker 1959; Letemendia 1967; Nishikawa 1982; Shepherd 1956), two had a factorial design (Hamilton 1960; Hogarty 1973), and the remainder were parallel studies. All studies were either stated to be randomised or implied randomisation.

2. Length of trials

The most common study length was six to 12 weeks but the range was considerable with two trials being just over 24 hours in duration, whilst the two longest were over a period of three years.

3. Participants

It was reported in all trials that the participants suffered from schizophrenia (with the exception of Vaughan 1955 who randomised people with mental illnesses who were 'chronic and intractable' with motor restlessness, psychomotor agitation, and excitement and Hankoff 1962 who did not clearly state the diagnoses but included psychiatric outpatients who were 'schizophrenic and non-schizophrenic', with the majority having schizophrenia). Only 14 of the 55 trials described the diagnostic criteria used, or the symptoms required for people to be included. Otherwise, entry to most included studies was on a clinical diagnosis of schizophrenia. A total of 5506 participants are now included in this review.

4. Setting

Most studies were hospital-based with only a few of the studies being undertaken in the community.

5. Study size

The mean number of participants was 99, ranging from 21 (Payne 1960) to 838 (Prien 1968).

6. Intervention

6.1 Chlorpromazine: The doses of chlorpromazine in these studies ranged from 25 mg/day (Reschke 1974) to 2400 mg/day (Dean 1958). The mean dose was 574 mg/day (SD 446).
6.2 Placebo: All trials compared chlorpromazine with placebo or no treatment. Kurland 1961 used a 'positive' placebo (phenobarbital) and a 'negative' placebo, the results of which were combined in this review. Clark 1968a randomised participants to placebo and a no-drug group, which were also combined in this review. Prien 1968, however, randomised to a placebo group and a 'routine conventional hospital treatment' group. These groups were not combined because the latter had the opportunity to receive any medication that the treating physicians felt appropriate (presumably including chlorpromazine). Prien 1968 also included two arms, one with lower doses and the other with higher doses. We pooled data from these arms in the main analysis and conducted subgroup analyses.
6.3 Other drug treatment arms: Thirty-eight of the trials also included at least one more drug treatment arm in addition to placebo and chlorpromazine. Data were not included from these treatment arms.

7. Outcomes

The following outcomes were reported by the included studies: death, relapse, global impression, mental state, behaviour, leaving the study early and adverse effects. None of the included studies attempted to quantify levels of satisfaction, or quality of life and there is no evidence of any direct economic evaluation of chlorpromazine. Most outcomes analysed were dichotomous, and presented as such, or were ordinal data that could be dichotomised.

7.1 Outcome scales

The following scales provided continuous data for the analysis.

7.1.2 Mental state

i. Brief Psychiatric Rating Scale (Overall 1962)
A brief rating scale used to assess the severity of a range of psychiatric symptoms, including psychotic symptoms. The original scale has 16 items, but a revised 18-item scale is commonly used. Each item is defined on a seven-point scale varying from 'not present' to 'extremely severe', scoring from zero to six or one to seven. Scores can range from zero to 126, with high scores indicating more severe symptoms. Tetreault 1969 reported data from this scale.
ii. Global impression
4.7.2.1 Clinical Global Impression (Guy 1976)
A rating instrument commonly used in studies on schizophrenia that enables clinicians to quantify severity of illness and overall clinical improvement. A seven-point scoring system is usually used with low scores indicating decreased severity and/or greater recovery. Borison 1991 reported data from this scale.

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7.1.3 Behaviour

i. Modified Rosenthal Rating Scale (Rosenthal 1963)
A scale for nurses to rate the behaviour of psychiatric patients. Lower scores indicate improved behaviour. Tetreault 1969 reported data from this scale.
ii. Parkside Behaviour Rating Scale (Schmidt 1957)
A rating scale in which six behavioural characteristics are rated on a five-point scale. The worst possible behaviour would carry a rating of six points, as against a maximum of 30 points for unproblematic behaviour. Baker 1959 reported data from this scale.
iii. Fergus Falls rating scale (Lucero 1951)
The L-M Fergus Falls Behavior Rating Scale is a method of rating the behaviour of patients in mental hospitals, which measures 11 aspects of behaviour, and the changes in one patient over a length of time. Ramu 1999a reported data from this scale.

7.1.4. Adverse effects

i. Extrapyramidal Bilan scale (Tetreault 1969a)
A nine-item rating scale for use by neurologists, to measure severity of symptoms such as facial mask, tremor, rigidity, akathisia, dystonia, dyskinesia and others. Each item can be scored from zero to three, such that the overall score can range from zero (no symptoms) to a possible 27 (severe symptoms of all types). Tetreault 1969 reported data from this scale.

Excluded studies

We have now excluded 315 studies. The studies listed in the 'Excluded studies' section had to be inspected in hard copy in order to make the final decision. Nearly half were not randomised, did not imply randomisation or did not describe the allocation procedure used. In several studies, participants were not suffering from schizophrenia. Another sizeable proportion of the trials did not compare chlorpromazine with placebo, but in combination with other treatments. A few were chlorpromazine withdrawal studies investigating the effects of instigation of treatment, which are not relevant to this review. We will include these withdrawal studies in a later review. Eighty-eight studies had no usable outcomes. Either data did not have clear clinical implications, for example EEG recordings, or genuinely relevant clinical data were not adequately reported. Frequently the numbers of participants in each group were not specified, means or standard deviations were not given or data were not reported from individual arms of cross-over studies.

Awaiting assessment

No studies are currently awaiting assessment.

Ongoing studies

We identified no ongoing studies.

Risk of bias in included studies

Please also see Figure 2 and Figure 3.

Figure 2. 'Risk of bias' graph: review authors' judgements about each 'Risk of bias' item presented as percentages across all included studies.

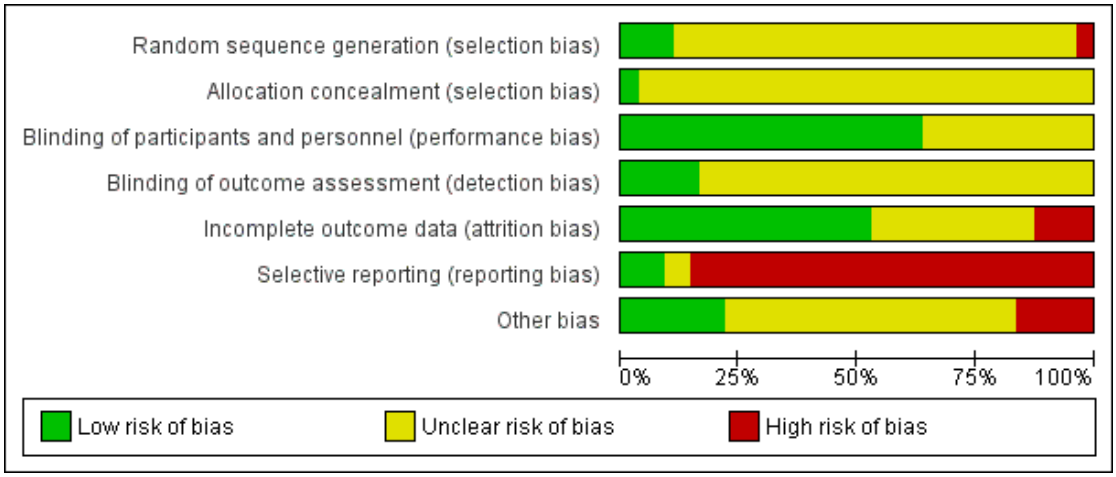

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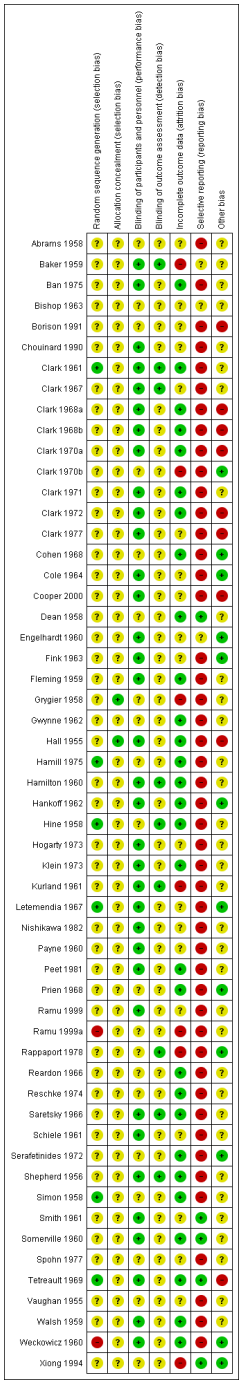
Figure 3. 'Risk of bias' summary: review authors' judgements about each 'Risk of bias' item for each included study.



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Allocation

Only four studies described the methods used to generate random allocation. Two studies (Hine 1958; Letemendia 1967) randomised by the toss of a coin, and two used tables of random numbers (Hamill 1975; Tetreault 1969a). Two studies (Cole 1964; Hall 1955) described some form of allocation concealment (sealed envelopes). For the other 53 studies, readers are given little assurance that bias was minimised during the allocation procedure, yet 24 (24/53, 45%) reported that the participants allocated to each treatment group were very similar. One study, Cooper 2000, reported that participants were randomly assigned in blocks of six and Weckowicz 1960 reported that participants were divided into three matched groups. For the remaining studies it is improbable that such equal numbers could have been obtained unless block randomisation was used, yet 24 out of 53 studies (45%) had exactly the same numbers in the chlorpromazine and placebo groups.

Blinding

Thirty-five studies had a low risk of bias for performance bias and described the methods used to ensure blinding of participants and personnel. Twenty studies had an unclear risk of bias. Nine studies stated that outcome assessors were blinded and were rated a low risk of bias, the remainder had an unclear risk of bias. Two studies (Grygier 1958; Hall 1955) tested how successful their attempts at blinding were. Three studies (Clark 1970b; Hamill 1975; Simon 1958) gave no indication that blinding had been attempted.

Incomplete outcome data

Twenty-nine studies were rated as low risk of bias for incomplete outcome data and 19 studies had an unclear risk of bias. Seven studies were rated as having a high risk of bias.

Selective reporting

Only five studies had a low risk of bias for selective reporting. Three studies had an unclear risk of bias and 47 of the studies were rated as high risk of bias for selective reporting.

Other potential sources of bias

Eight trials were subject to other biases as they were either partly or fully funded by the pharmaceutical industry; in Borison 1991 two of the trialists are in prison for research fraud. Twelve studies were of low risk of bias for other potential sources of bias and the remainder had an unclear risk of bias.

Effects of interventions

See: **Summary of findings for the main comparison** CHLORPROMAZINE versus PLACEBO for schizophrenia

We used risk ratios (RR) for dichotomous data and mean differences (MD) for continuous data, with their respective 95% confidence intervals (CIs) throughout.

1. Comparison: CHLORPROMAZINE versus PLACEBO

We categorised outcomes as short term (up to eight weeks), medium term (nine weeks to six months) and long term (six months to two years).

1.1 Death

We found only one small trial (n=14) that specifically reported mortality (Baker 1959); there were no deaths in either the chlorpromazine or placebo group (Analysis 1.1). We found no reports of death in any study and currently over 5506 people have been included in trials relating to this review (of which 1741 were given chlorpromazine).

1.2 Relapse

We found short-term (n=74, 2 RCTs) and medium-term (n=809, 4 RCTs) data did not show a significant difference in rates of relapse (Analysis 1.2), but with significant heterogeneity (I^2=78% and 96%, respectively). Removing the studies with results that were causing this heterogeneity, as judged by visual inspection (Prien 1968; Spohn 1977) eliminates this heterogeneity. We found longer-term data (six months to two years) favoured the chlorpromazine group (n=512, 3 RCTs, RR 0.65 CI 0.47 to 0.90), but the two long-term studies lasting two to five years (Hogarty 1973; Nishikawa 1982) showed no difference (n=394, 2 RCTs), again with significant heterogeneity (I^2 = 72% and 84%, respectively). In this case, the larger trials (Hogarty 1973; Prien 1968) show a better effect for chlorpromazine and it may well be that the smaller trials are the outlying ones. However, Prien 1968 includes a high-dose treatment arm (2000 mg/day of chlorpromazine), which may explain some of the heterogeneity in the results, see the subgroup analysis (Analysis 1.23) below.

1.3 Global state

1.3.1 No overall improvement

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We found short-term global state data ('no overall improvement' - psychiatrist-rated ; Analysis 1.3) significantly favoured chlorpromazine (n=728, 13 RCTs, RR 0.61 CI 0.46 to 0.82) compared with placebo. Medium-term data up to six months also favoured chlorpromazine (n=1164, 14 RCTs, RR 0.71 CI 0.58 to 0.86). There was significant heterogeneity at both short term and medium term (I^2=69% and 81%, respectively). There were no obviously outlying trials for this outcome at short term, so none were removed from the analysis. For medium term, removal of the largest trial, Prien 1968, restores homogeneity, an effect that does not appear in the subgroup analysis for high versus low dose, see the subgroup analysis (Analysis 1.23) below, and again, it may be the smaller trials that are outliers.

Nurse-rated global state 'no overall improvement' scores (Analysis 1.4) were equivocal at short-term assessment in one small study (Weckowicz 1960) (n=29, RR 0.91 CI 0.65 to 1.27). However, scores from one research group (Clark 1970a; Clark 1972; Clark 1977) favoured chlorpromazine at medium-term assessment (n= 84, 3 RCTs, RR 0.48 CI 0.35 to 0.64). Similar data were recorded in continuous form in only one small study (Borison 1991) and results were equivocal (n=19, 1 RCT; Analysis 1.5).

1.3.2 Severity of illness

We found estimates by psychiatrists for the severity of illness (Analysis 1.6) were equivocal at short-term assessments (n=44, 1 RCT) however, medium-term data showed significantly greater improvement in the chlorpromazine group (n=694, 3 RCTs, RR 0.80 CI 0.74 to 0.86) compared with placebo. Nurse-rated severity of illness scores (Analysis 1.7) also favoured the chlorpromazine group (medium term, n=66, 2 RCTs, RR 0.63 CI 0.45 to 0.90) compared with placebo.

1.4 Leaving the study early

People allocated to chlorpromazine are more likely to remain in the study than participants given placebo (Analysis 1.8), in both short- (n=1065, 17 RCTs, RR 0.76 CI 0.63 to 0.92) and medium-term studies (n=1831, 27 RCTs, RR 0.64 CI 0.53 to 0.78). The short-term studies showed some heterogeneity (I^2 = 51%). When we analyse the data using random-effects, the result becomes non-significant (n=1065, 17 RCTs, RR 0.80 CI0.58 to 1.10). Removing the study with results that were causing this heterogeneity, as judged by visual inspection (Cole 1964, which used very high doses of chlorpromazine in one arm of the trial) eliminates this heterogeneity. However, we did not find any significant differences in attrition rates from the comparatively large studies (Engelhardt 1960, Hogarty 1973, n=492), which were conducted for up to two years. Also, longer-term data (Hogarty 1973) did not demonstrate a significant difference in retention rates.

1.5 Mental state

There are only a few studies with usable data relating to mental state.

1.5.1 Improved (50% reduction in BPRS)

We found no short-term difference in mental state using a cut-off point of at least a 50% decline in score to indicate 'improvement' (Cooper 2000, n=106; Analysis 1.9).

1.5.2 Average endpoint score (BPRS)

What continuous data there are favour chlorpromazine at short- (n=49, 2 RCTs, MD -4.82 CI -8.48 to -1.15) and medium-term assessments (Tetreault 1969, n=30, MD -7.70 CI -14.77 to -0.63) (Analysis 1.10).

1.5.3 Average change score (BPRS)

See Table 1.

1.6 Behaviour

1.6.1 Deteriorated/disturbed/un-cooperative

We found participants did not differ significantly in experiencing a worsening in their behaviour (Analysis 1.11) at short-term assessment (n=87, 2 RCTs), although data are heterogeneous (I^2=65%). Medium-term data also did not differ significantly (n= 1040, 8 RCTs), but again, data are heterogeneous (I^2 =90%). There are no obviously outlying studies as all confidence intervals overlap. Removing the possibly outlying studies, either Prien 1968 or Hall 1955, does not restore homogeneity, nor does their removal change the results.

1.6.2 Unchanged

Both short-term (Schiele 1961, n=40) and medium-term (n=68, 2 RCTs) dichotomous data did not reveal any significant differences between chlorpromazine and placebo when assessing change in participants behaviour (Analysis 1.12).

1.6.3 Rosenthal Rating Scale

Tetreault 1969 provided data from the Rosenthal Rating Scale (Analysis 1.13) and we found short-term data were not significantly different (n=30, 1 RCT) between chlorpromazine and the placebo group. Medium-term data were also not significantly different (n= 30, 1 RCT).

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1.6.4 Parkside Behaviour Rating Scale

Baker 1959 used the Parkside Behaviour Rating Scale (Analysis 1.14) to assess behaviour and we found that those given chlorpromazine had a significantly better rating in their behaviour compared with the placebo group (n=14, MD 6.00 CI 1.97 to 10.03).

1.6.5 Fergus Falls Behavioural Rating Scale

Ramu 1999a used the Fergus Falls Behavioural Rating Scale (Analysis 1.15) to assess change in behaviour of participants and we found that behaviour was not significantly different (n=42, 1 RCT) between chlorpromazine and the placebo group.

1.7 Adverse effects

1.7.1 Extrapyramidal symptoms

There is evidence that chlorpromazine increases a person's chances of experiencing acute movement disorders (dystonia) (n=942, 5 RCTs, RR 3.47 CI 1.50 to 8.03), parkinsonism (n=1468, 15 RCTs, RR 2.11 CI 1.59 to 2.80), tremor (n=392, 7 RCTs, RR 1.66 CI 1.01 to 2.73) and rigidity (n=412, 7 RCTs, RR 2.24 CI 1.42 to 3.54). Akathisia (subjective feeling of restlessness that may lead to agitation) was dominated by one trial (Prien 1968) and did not occur more frequently in the chlorpromazine group than placebo (n=1164, 9 RCTs), nor did tardive dyskinesia (Clark 1977, n= 18) nor ataxia (Hankoff 1962, n=97). We found extrapyramidal adverse effects were equivocal at both short- and medium-term assessments from one small scale study (n=30) by Tetreault 1969. (See Analysis 1.16; Analysis 1.17).

1.7.2 Central nervous system

Chlorpromazine is clearly sedating (n=1627, 23 RCTs, RR 2.79 CI 2.25 to 3.45). There is also evidence that chlorpromazine increases a person's chances of experiencing fits (n=695, 3 RCTs, RR 3.11 CI 1.05 to 9.18) and weakness (n=92, 3 RCTs, RR 3.33 CI 1.02 to 10.88). Convulsions did not occur more frequently in the chlorpromazine group than placebo (Gwynne 1962, n=52; Analysis 1.18).

1.7.3 Blood, skin, liver and eyes

We found no significant differences in blood problems such as agranulocytosis and leucopenia (n=394, 7 RCTs), or rashes and itching (n=1313, 13 RCTs). Liver problems, mainly jaundice were also not significant (n=249, 4 RCTs). Further data from early trials suggest that chlorpromazine may well cause photosensitivity (n= 799, 6 RCTs, RR 6.04 CI 3.22 to 11.32), and eye opacities or pigment problems (n=657, 2 RCTs, RR 3.09 CI 1.87 to 5.11) when large dosages of chlorpromazine are used. (See Analysis 1.19).

1.7.4 Other

Chlorpromazine clearly causes a lowering of blood pressure with accompanying dizziness (n=1488, 18 RCTs, RR 2.38 CI 1.74 to 3.25). Chlorpromazine is constipating, when compared with placebo (n=1117, 10 RCTs, RR 2.05 CI 1.33 to 3.15). We found data that urinary problems (n=926, 5 RCTs), and also blurred vision were not significantly different between chlorpromazine and placebo. We found that chlorpromazine does cause dry mouth (n=1015, 7 RCTs, RR 4.56 CI 2.35 to 8.85). Chlorpromazine increases participants' weight (n=165, 5 RCTs, RR 4.92 CI 2.32 to 10.43). We found significantly more participants given chlorpromazine experienced nausea (n=1024, 5 RCTs, RR 2.07 CI 1.14 to 3.73). Salivation occurred significantly more frequently in the chlorpromazine group (n=830, 3TCTs, RR 3.37 CI 1.07 to 10.57). We found no clear evidence that chlorpromazine precipitates the frequency of amenorrhoea, menorrhagia or lactation problems. (See Analysis 1.20).

2. Subgroup analyses

2.1 Men versus women

Few studies reported outcomes for only men or women. The only primary outcome for which data were available for comparison is 'Behaviour deteriorated/disturbed/uncooperative' (Analysis 1.21). Schiele 1961 included only men (n=40) and three studies report the same outcome for women alone (Clark 1970b; Fleming 1959; Somerville 1960, total n=158). Results of randomised trials were equally significant for the subgroups.

2.2 Under 18 years of age versus 18-65 years old versus older than 65

We could not perform this subgroup analysis as data were only available for people between the ages of 18 and 64 years.

2.3 Acutely ill people (< one month in duration) versus people who have been ill for longer

Limited data were available for a few primary outcomes (Analysis 1.22). We found that people who were chronically ill were more likely to have improved for short- and medium-term global improvement, and disturbed behaviour compared with those whose illnesses were acute. No difference was found for rates of relapse between acute and chronic participants. Results of randomised trials were equally significant for all subgroups. However, these analyses are severely limited by the lack of studies in the acutely ill groups and no firm conclusion can be made.

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2.4 High dose (> 501 mg/day) versus low doses (1-500 mg/day)

For the outcome of relapse between nine weeks and six months, the high-dose arm of Prien 1968 reports statistically significantly more favourable results for the chlorpromazine group, compared with the low-dose group of studies (P < 0.005). However, for the low-dose subgroup there remains significant heterogeneity that is not explained by the exclusion of the high-dose arm of Prien 1968. For the short- and medium-term outcome 'no global improvement', there is no clear difference between studies using high-dose chlorpromazine to low dose. Higher dosages of chlorpromazine did not confer an advantage in reducing behavioural disturbances, compared with the low-dose group (Analysis 1.23).

2.5 People diagnosed according to any operational criteria versus those who have not been diagnosed using operational criteria

For relapse in short-term studies, the any operational criteria group had a better outcome but the sample size is too small to enable conclusions to be made. Relapse in medium-term studies favoured participants diagnosed with operational criteria (P < 0.04). Global impression 'not improved' revealed no differences in the short and medium term. There were no apparent differences for severity of illness and behaviour (Analysis 1.24).

2.6 Studies published before 1990 versus studies published between 1990 and the present

Data were available for the outcomes of 'no overall improvement' in the short term and medium term, and 'behaviour deteriorated/disturbed/uncooperative' (Analysis 1.25). Few studies were available in the 1990 to 2007 group limiting the analysis. Results of randomised trials were equally significant for all subgroups.

3. Sensitivity analyses

3.1 Implication of randomisation

For the outcome 'no overall improvement' in the medium term, there were no differences in the results for one study (Ramu 1999a) that only implied randomisation and studies that explicitly stated that they were randomised (Analysis 1.26).

3.2 Assumptions for lost binary data

Two studies made assumptions regarding people lost to follow-up for the outcome 'no overall improvement' in the short term; no differences were found (Analysis 1.27).

3.3 Risk of bias

None of the studies had a high risk of bias for allocation concealment, or blinding of participants and outcome assessors (see Figure 2). Those that had a high risk of bias for randomisation were included in the sensitivity analysis above (Analysis 1.26).

3.4 Imputed values

We did not undertake a sensitivity analysis to assess the effects of including data from trials where we used imputed values for ICC as there were no cluster-randomised trials included in the review.

3.5 Dishonest researchers

It has come to our attention that Dr Richard Borison and Dr Bruce Diamond have been convicted of theft, making false statements and violations of state racketeering law in the USA. At this point, it seems that the crimes were to do with criminal diversion of funds, rather than falsifying study data (http://www.the-scientist.com/yr1998/oct/notebook˙981026.html). Nevertheless, we temporarily removed studies with either of these authors from the analyses to see if this made a substantive difference to the findings. Borison 1991 presented usable data on mental state (average endpoint score on BPRS), the removal of this study did not result in a substantive change in the findings. Borison 1991 is the reports one unique outcome for global state (average endpoint score on Clinical Global Impression (CGI)), so removal of the study results in the deletion of the complete outcome.

DISCUSSION

Summary of main results

The summary below reflects the outcomes chosen for the Summary of findings for the main comparison, and considered the main findings of this review that can support evidence-based decision making.

1. Death

It may be surprising that there were no more deaths reported among over 5000 people with schizophrenia who were randomised to chlorpromazine or placebo. The lifetime incidence of suicide for people suffering from schizophrenia is 10% to 13% (Caldwell 1992). Furthermore, the use of large doses of neuroleptic has been associated with sudden death (Jusic 1994), but there are no records of such events within this review. The fact that there are none may reflect the fact that either trial-care is more vigilant than routine care or that death is an under-reported outcome.

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2. Relapse

Chlorpromazine reduced the number of participants experiencing a relapse compared with placebo during six months to two years follow-up, but not in the short, medium or long term over two years, although data were heterogeneous. The removal of Prien 1968 and Spohn 1977 did restore homogeneity in the short- and medium-term studies. The Prien 1968 study was different because of the very large dosages of chlorpromazine that were employed, although it had two arms, one with lower doses and another with higher doses, and these two arms were pooled in the analysis. An 86% efficacy was found for the high-dose arm in preventing relapse and a 68% efficacy for the low-dose arm; the confidence intervals only minimally overlap, so there is a potential impact of Prien 1968 on this outcome.

3. Global state

The best-quality data would need to be reported from six months onwards, and trials only reported on this outcome at short- and medium-term follow-ups. The efficacy of chlorpromazine for improving global state is 39% for short-term data and 29% for medium term, but the data are heterogenous. Considering that there was very little antipsychotic treatment that preceded the advent of chlorpromazine, such an efficacy can be considered nothing less than revolutionary for those with very serious mental illnesses.

4. Leaving the study early

The finding that using chlorpromazine results in more people staying in the study could be seen as heartening. Perhaps a genuine decrease in the distressing symptoms of schizophrenia leads to an increased concordance with medication despite the unpleasant side effects of this drug. On the other hand, this apparent willingness to comply may be due partly to sedation and hypotension. These effects (the former being linked to emotive terms such as the 'chemical straitjacket') may decrease a person's ability to make his/her own decisions.

5. Mental state

In spite of 45 years of research on this benchmark anti-psychotic treatment, very little can be said from trials regarding its direct effect on mental state in general or specific symptoms of schizophrenia.

6. Satisfaction with care

No studies reported on this outcome, so it is not possible to make any conclusions as to participants' satisfaction with chlorpromazine treatment.

7. Behaviour

There are more data regarding behaviour. No difference in the occurrence of behaviour judged to be disturbed or deteriorated was found in both short- and medium-term analyses, but the medium-term result is based on heterogeneous data (I^2=90%). Other measures of behaviour 'unchanged' and the modified Rosenthal scale and the Fergus Falls scale did not result in any significant differences. Continuous endpoint data (Baker 1959) derived from the Parkside Behaviour Rating Scale did favour chlorpromazine but there were only seven participants in each group and we can have no real confidence in this finding.

8. Adverse effects

Clinicians will not be surprised that chlorpromazine produces acute movement disorders, parkinsonism, fits, tremor, rigidity, weakness and sleepiness. This Cochrane review, however, is a rare report of the best available and quantitative data on this compound that is now over half a century old. Estimates of the incidence of movement disorders such as tardive dyskinesia, however, are not available from this review, as these necessitate a long follow-up period that was only attempted in a few trials. Evidence supporting a link between chlorpromazine and akathisia is much less convincing than that for acute movement disorders, such as oculogyric crisis, and parkinsonism. This suggests that chlorpromazine may be less potent a cause of this unpleasant adverse effect than other compounds.

Taking chlorpromazine commonly causes people to become sleepy. This is an effect that, at times, may be welcomed by clinicians, but not necessarily by those with schizophrenia. Short-term sedation can be advantageous for clinicians trying to manage people with very disturbed behaviour. Sedation often helps to bring a difficult and dangerous situation under control and gives time for antipsychotic measures to be effective.

In addition, chlorpromazine has a tendency to cause other adverse effects such as jaundice, photosensitivity, eye opacities, low blood pressure, constipation, urinary retention, blurred vision and dry mouth. The worrying data regarding eye opacities is all derived from one trial (Prien 1968). This large trial, however, used up to two grams of chlorpromazine a day and it is likely that the lower doses more usual in current practice would result in less risk of this adverse effect. Chlorpromazine frequently causes weight increase.

9. Cost of care

Again, no studies reported on this outcome, so it is not possible to make any conclusions about the cost of chlorpromazine treatment.

10. Subgroup analyses

As was likely from the start, the power to detect a real difference between studies in any one of the subgroup analyses was very low.

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Only subsets of already limited lists of trials were available. The wide confidence intervals could be hiding true differences in effect between the groups. The only suggestions of statistically significant differences were for acutely ill versus chronically ill for the outcomes of global improvement and behaviour, and for high-dose versus low-dose studies (relapse between nine weeks and six months). It is important to remember that this is now a non-randomised comparison between studies, rather than within a study, and that this is one of many statistical tests that were undertaken on this dataset. Further complicating matters is the fact that the other outcomes within this particular subgroup analysis did not clearly support or refute this difference between high and low doses. Prien 1968 is an unusual study. Using two grams of chlorpromazine per day would be unacceptable in most situations today, a view supported by some of the findings of this review (n=657, 2 RCTs, RR eye opacities from two grams chlorpromazine per day, 3.09 CI 1.9 to 5.1).

Overall completeness and applicability of evidence

Applicability

The 55 included studies in this version of this review include many people who would be recognisable in everyday practice. There are those with strictly diagnosed illnesses, very likely to suffer from schizophrenia, and people whose illness was diagnosed using less rigorous criteria. The results of the subgroup analyses on diagnostic rigour (see Effects of interventions section 2.5) also support the assertion that the results are widely applicable.

The dose of chlorpromazine in the studies included in this review could be considered high (mean 574.1 mg/day SD 445) but, again, these levels are probably common for people with persistent schizophrenia across the globe.

Although the outcomes that have been used in this review are accessible to both clinicians and recipients of care, generalising to treatment in community settings, could be problematic. Most studies were undertaken in hospital, whereas the great majority of people with schizophrenia are in the community.

Homogeneity

Some results are difficult, or impossible, to interpret because of heterogeneity. The test for homogeneity is based on I^2 analysis, and is often fairly weak, as the number of studies is small. However, the results of such tests, when statistically significant, suggest caution when adding trial data together.

Quality of the evidence

The quality of the current evidence is very low based on GRADE (Schünemann 2008). The majority of studies did not report the method of randomisation, and only two trials described method of allocation concealment. Although most studies were reported to be double blind, it was not clear in many whether or not the assessors were blinded to treatment group of participants. Forty-eight out of the 55 included studies were rated as high risk of bias for selective reporting. Studies frequently presented both dichotomous and continuous data in graphs, or just reported statistical measures of probability (P values). This often made it impossible to acquire raw data for synthesis. It was also common to use P values as a measure of association between intervention and outcomes instead of showing the strength of the association. Although P values are influenced by the strength of the association, they also depend on the sample size of the groups. It is sometimes possible to extract raw data from P values, but their exact values are needed. In the reviewed studies this was not possible, because they were reported as 'P < 0.05' or 'P > 0.05'. Frequently, continuous data were presented without providing standard deviations or standard errors (33/55 trials) or no data were presented at all (11/55 trials). In this way a lot of potentially informative data were lost. In some studies it seemed that attempts had been made to use the original trials as vehicles for answering a host of other questions about schizophrenia. As a consequence, data from the randomised parts of the studies became buried beneath copious subgroup analyses.

Potential biases in the review process

1. Adding the old to the new

This work includes studies that span nearly five decades of evaluative studies within psychiatry. It is possible that the rigour of these experiments has changed over time, as have the participants and even the formulation of the drug; it was thought that introduction of impurities in early formulations of chlorpromazine led to jaundice. There is some empirical evidence that the quality of schizophrenia trial reporting has not changed much over time (Thornley 1998) or, if it has changed, it may even have declined (Ahmed 1998). We have found no time-related differences in reporting of studies within this review and no suggestion of a change of the effect size over time. Synthesis of the results of studies seems justified.

2. Failing to identify old trials

We identified trials by meticulous searching, including hand-searching old files (2002 update) that covered the drug's development over its first two decades. Nevertheless, for this compound formulated so long ago, publication biases may be difficult to avoid. We did not detect any overt asymmetry of the funnel plots.

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The strength of this review is that it presents up-to-date quantitative data for a benchmark treatment for schizophrenia that is used throughout the world.

3. Sensitivity analyses on dishonest researchers

We felt that it would be harsh to immediately delete all trial data associated with Drs Borison and Diamond without empirical data. That removal of their data makes no discernable difference to any outcome is reassuring.

Agreements and disagreements with other studies or reviews

We do not know of any other systematic reviews on this topic.

AUTHORS' CONCLUSIONS

Implications for practice

1. For people with schizophrenia

Many people with schizophrenia and their non-professional carers recognise psychotic symptoms as phenomena generated by a damaging and pernicious illness and may see the effect of chlorpromazine, as demonstrated within this review, as positive. Others may consider these data as supporting well-publicised objections to the use of drugs: drugs potent in their ability to cause unpleasant adverse effects, and to potentially erode a person's ability to make informed decisions.

2. For clinicians

This review will confirm much that clinicians already know, but it does provide some quantification to support clinical impression. Chlorpromazine is a sedating drug, prone to cause a variety of movement problems and increased weight. Evidence suggests that chlorpromazine reduces relapse and facilitates global improvement.

The adverse effect of sedation can, in certain clinical situations (especially in the short term), be a useful adjunct to any antipsychotic properties that chlorpromazine may have. For example, someone acutely disturbed and violent, perhaps because of false beliefs, may well benefit from a certain amount of sedation while the antipsychotic effects of treatment begin to work.

Chlorpromazine is a low-cost and widely available choice for the clinician. Despite its many adverse effects chlorpromazine is likely to remain one of the most widely used treatments for schizophrenia worldwide.

3. For managers or policy makers

Chlorpromazine is widely available and inexpensive. It is understandable that it remains one of the essential drugs listed by the WHO for treating people with serious mental illnesses. However, some of chlorpromazine's adverse effects could be expensive in terms of human suffering and cost of treatment. It could, therefore, prove better to use a more costly drug if the latter was equally potent, but had a more favourable adverse effects profile.

Implications for research

1. More trials comparing chlorpromazine with placebo?

Even though chlorpromazine has been used as an antipsychotic drug for decades, there are still a surprisingly small number of well-conducted randomised, placebo-controlled trials measuring its efficacy and potential to cause adverse effects. The use of chlorpromazine for millions of people is based on clinical experience rather than the poorly reported trials that involve, in total, only a few thousand participants. Clinicians and researchers are mainly satisfied with the current levels of understanding, and, therefore new studies evaluating chlorpromazine versus placebo will be very rare. However the chlorpromazine story is incomplete. Questions remain regarding the effect of this drug on mental state, long-term movement disorders and vision. One or more large, methodologically sound randomised, placebo-controlled trials could help answer these questions. With the advent of new drugs, however, the day for studies comparing chlorpromazine with placebo has passed.

2. Placebo-controlled studies of other treatments

Having shown that chlorpromazine is a benchmark treatment of psychotic symptoms, and knowing that allowing schizophrenia to go untreated may be damaging (Birchwood 1997), the question may well be raised as to whether any placebo-controlled studies of new antipsychotic drugs are justified. However, the marked level of improvement in the placebo groups in this review would seem to indicate that short-term studies of those with schizophrenia using a placebo group are justified and would be unlikely to be damaging to those with psychotic illnesses. Using a placebo comparison in the longer term would seem more problematic and difficult to justify.

3. Future trials

So much more could have been learnt about the effects of chlorpromazine if the studies in this review had clearly described the method of allocation, the integrity of blinding, especially for the more subjective outcomes, and the reasons for early withdrawal.

Concrete and simple outcomes are of interest. For example, clearly reporting improvement, 'number of violent incidents', 'relapse'

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(giving some description of criteria), 'hospital discharge or admission', and 'presence of delusions or hallucinations' would have been helpful, and simple reporting of levels of satisfaction and quality of life would have been most informative. Chlorpromazine has been in use for decades, yet clinicians still have no trial-based data indicating how people with schizophrenia perceive the value of this drug in the short, medium and long term.

If rating scales are to be employed, a concerted effort should be made to agree on which measures are the most useful. Studies within this review reported on so many scales that, even if results had not been poorly reported, they would have been difficult to synthesise in a clinically meaningful way.

Further information on the standardisation of trial reporting can be found in the CONSORT statement (Moher 2001).

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Jun Xie screened full texts and extracted data for all Chinese studies.

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* *Indicates the major publication for the study*

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CHARACTERISTICS OF STUDIES

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

Abrams 1958

Methods	Allocation: 'divided at random' - no further description. Blinding: medications 'same size, shape and colour'. Duration: 4 months. Design: parallel. Country: not reported.
Participants	Diagnosis: schizophrenia. History: in hospital 2+ years, 'treatment resistant'. N=40. Sex: 40 F. Age: range 20-55 years. Setting: hospital.
Interventions	1. Chlorpromazine: dose 200 mg/day rising to 600 mg/day. N=20. 2. Placebo. N=20. Medication given in fixed-dose regimen.
Outcomes	Leaving study early. Unable to use - Mental state: MSRPP (no SD). Adverse effects (no usable data). Cognitive functioning: Weschler Bellvue Intelligence Scale, Rorschach tests (no SD)
Notes	MSRPP reported with SE of differences. SDs calculated but data implausible

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Divided, at random, into two groups" no further details reported
Allocation concealment (selection bias)	Unclear risk	No information reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"The experimental group received chlorpromazine under the name of "Thoraxine A", "The control group, received a placebo, the same size, shape and colour as the chlorpromazine. As a differentiation from the chlorpromazine, the placebo was known as "Thorazine B"

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Abrams 1958 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information reported.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	"During the course of the experiment several patients had to be eliminated from both groups for various reasons so that the final chlorpromazine group consisted of 18 patients while the final placebo group consisted of 16 patients". Reasons for leaving the study early not reported
Selective reporting (reporting bias)	High risk	No SDs reported for MSRPP, Weschler Bellvue Intelligence Scale or Rorschach tests. No useable data for adverse effects
Other bias	Unclear risk	Source of funding not reported.

Baker 1959

Methods	Allocation: 'order determined by random selection'. Blinding: double, matching tablets in envelopes. Design: cross-over - first arm data used. Duration: 5 weeks (preceded by 1 week washout). Country: UK.
Participants	Diagnosis: psychosis (schizophrenia N=21, involutional melancholia N=2, manic depressive N=1, senile psychosis N=1). History: 'chronic', in hospital 2+ years. N=25*. Sex: 25 F. Age: range 33-79 years. Setting: hospital.
Interventions	1. Chlorpromazine: dose mean 200 mg/day, range 150-300 mg/day. N=7. 2. Placebo (lactulose): dose 1.95 g/day to 3.9 g/day. N=7. 3. Ethylcrotonylurea: dose range 600-1200 mg/day. N=8. Medication given in fixed-dose regimen.
Outcomes	Leaving study early. Death. Behaviour. BPRS Adverse effects. Unable to use - Mental state: BPRS (no usable data). Physiological measures (no usable data).

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Baker 1959 (*Continued*)

Notes	*three participants not accounted for. Only data for those with schizophrenia and senile psychosis used (N=22)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Order determined by random selection" no further details reported
Allocation concealment (selection bias)	Unclear risk	No information reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Matching tablets" were used.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"The total number of tablets for each five-week period (378) were put in a separate envelope, labelled "A", "B", or "C" and a code was kept showing which tablets any patient was taking during any given period [...] It was thus possible to keep the handling and the knowledge of the identity of the tablets under the control of a person other than the psychiatric assessor of results until the trial was completed."
Incomplete outcome data (attrition bias) All outcomes	High risk	"There were no deaths in this group, but one patient (Case 120) was so uncooperative in taking tablets that it was decided to abandon the attempt, in her case". Three participants are not accounted for in the analysis
Selective reporting (reporting bias)	Unclear risk	Unable to use BPRS data.
Other bias	Unclear risk	"These three substances were supplied in matching tablets by Messrs. Smith & Nephew, the sponsors of the new drug"

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Ban 1975

Methods	Allocation: randomly assigned - no further description. Blinding: double, 'capsules identical in appearance, taste and smell'. Duration: 12 weeks (preceded by 2 weeks drug-free washout). Design: parallel. Country: not reported.
Participants	Diagnosis: chronic (50%) & acute (50%) schizophrenia (criteria not specified). N=30. Sex: 22 M, 8 F. Age: mean 28 yrs, range 17-46. Setting: hospital.
Interventions	1. Chlorpromazine: dose 200-800 mg/day (dose discretionary). N=10. 2. Placebo. N=10. 3. Thiothixine: dose 10-40 mg/day (dose discretionary). N=10
Outcomes	Leaving study early. Global impression. CGI. Unable to use - Adverse effects (not given per individual). Mental state: BPRS (no mean/SD).
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomised" no further details reported.
Allocation concealment (selection bias)	Unclear risk	No information reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Double-blind" "All medication was supplied in capsules identical in appearance, taste and smell"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"Double-blind" no further details reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were no losses to follow-up.
Selective reporting (reporting bias)	High risk	No means and SDs reported for BPRS.
Other bias	Unclear risk	Supported in part by PHS Grant from the National Institute of Mental Health, Rockwell, Maryland

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Ban 1975 (*Continued*)

		Drugs supplied by Pfizer (Canada) Inc, Montreal, Canada.

Bishop 1963

Methods	Allocation: randomly assigned, stratified by age, sex, history - no further description. Blinding: double - no further description. Duration: 10 weeks (preceded by 60 days washout). Design: parallel. Country: not reported.
Participants	Diagnosis: schizophrenia (criteria not specified). History: 'chronic'. N=30. Sex: both (proportions not given). Age: unknown. Setting: hospital.
Interventions	1. Chlorpromazine: dose 800 mg/day max. (dose discretionary). N=10. 2. Placebo. N=10. 3. Benzquinamide (Quantril): dose 1200 mg/day max. (dose discretionary). N=10
Outcomes	Leaving study early. Global impression. Unable to use - Mental state: Lorr Scale, BPRS (no data reported). Psychological tests: Tulane Research Battery (no data reported)
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Divided at random" no further details reported.
Allocation concealment (selection bias)	Unclear risk	No information reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"Double blind" no further details reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"Double blind" no further details reported.

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Bishop 1963 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No losses to follow-up in the chlorpromazine or placebo groups
Selective reporting (reporting bias)	Unclear risk	No data reported for the BPRS, Lorr scale or Tulane Research Battery
Other bias	Unclear risk	Study supported by PHS Grant MY-3701 (Psychopharmacology Service Centre - NIMII). Benzquinamide supplied by Charles Pfizer and Company, Inc, New York

Borison 1991

Methods	Allocation: randomly assigned - no further description. Blinding: double - no further description. Duration: 4 weeks (preceded by 1 week placebo washout). Design: parallel. Country: USA.
Participants	Diagnosis: schizophrenia (DSM-III criteria). History: acutely ill, physically healthy. N=30. Sex: 30 M. Age: mean 35.6 yrs, range 22-58. Setting: hospital.
Interventions	1. Chlorpromazine: dose 400-1600 mg/day (variable dose regimen). N=9. 2. Placebo. N=10. 3. Rimcazole: dose 20-400 mg/day (variable dose regimen). N=11
Outcomes	Global impression. CGI. Mental state. BPRS. Unable to use - Adverse effects: SAS (no data).
Notes	Those leaving early 'analysed [in paper] using last observation carried forward'

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Subjects were assigned on a double-blind, random basis" no further details reported
Allocation concealment (selection bias)	Unclear risk	No information reported.

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Borison 1991 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"Double blind" no further details reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"Double blind" no further details reported.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	"Early terminators from treatment were analysed using last observation carried forward"
Selective reporting (reporting bias)	High risk	Use of SAS not pre-specified in methods. No data reported for adverse effects
Other bias	High risk	Borison and Diamond in prison for research fraud.

Chouinard 1990

Methods	Allocation: randomly assigned - no further description. Blinding: double, identical capsules. Duration: 4 weeks (preceded by 3-7 days washout). Design: parallel. Country: Canada.
Participants	Diagnosis: schizophrenia (DSM-III criteria & >18 on BPRS). History: newly admitted. N=62. Sex: 39 M, 23 F. Age: mean 39.7 yrs, range 19-62. Setting: hospital inpatients, admitted through emergency room
Interventions	1. Chlorpromazine: dose 300-1200 mg/day (variable dose regimen). N=21. 2. Placebo. N=21. 3. Remoxipride: dose 150-600 mg/day (variable dose regimen). N=20 Chloral hydrate/clonazepam for sedation as requested; procyclidine for parkinsonism as requested
Outcomes	Leaving study early. Global improvement (> 50% reduction of BPRS score). Adverse effects (as measured by requiring procyclidine). Requiring sedation. Unable to use - Mental state: BPRS (no SD). Global impression: CGI (no SD) Adverse effects (no usable data).

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Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Randomly assigned" no further details reported.
Allocation concealment (selection bias)	Unclear risk	No information reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Double blind", "The trial drugs were provided in the form of identical white opaque gelatin capsules"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"Double blind" no further details reported.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Patients that did not complete the four week trial "were included in the statistical analyses by using their endpoint scores at time of discontinuation" "Four chlorpromazine-treated patients failed to complete the trial: 3 on account of side effects (1 case of leucopenia and 2 of hypotension) and 1 on account of inefficacy. Seven placebo-treated patients did not complete the clinical trial (1 case of abnormal liver function, 5 of inefficacy, and 1 patient for administrative reasons)." Last observation carried forward method used
Selective reporting (reporting bias)	High risk	No SDs reported for BPRS and CGI. No useable data reported for adverse effects
Other bias	Unclear risk	Source of funding not reported.

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Clark 1961

Methods	Allocation: randomly assigned, matched by OBRS scores into ”triplets“ - no further description. Blinding: double, identical capsules. Duration: 24 weeks (preceded by 8-week placebo washout). Design: parallel. Country: USA.
Participants	Diagnosis: schizophrenia (Diagnostic Manual of APA, 1952). History: 'chronic', in hospital > 5 years, physically healthy. N=60. Sex: 60 F. Age: mean 43 yrs, range 26-52. Setting: hospital.
Interventions	1. Chlorpromazine: dose 200-800 mg/day. N=20. 2. Placebo (lactose): dose 6-8 capsules per day. N=20. 3. Phenobarbital: dose 120-480 mg/day. N=20 Medication given in variable dose regimen.
Outcomes	Global improvement. Adverse effects. Unable to use - Behaviour: OBRS (no data). Psychological tests (no usable data).
Notes	One in CPZ group withdrawn (agranulocytosis, week 12). Her other 'triplets' also withdrawn, therefore, N=57 except side effects (N=60)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Participants ”individually matched into triplets. Random assignment of triplet members to treatment groups“, ”drawn by a table of random numbers“
Allocation concealment (selection bias)	Unclear risk	No information reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	”Double-blind“, ”neither the patients nor the personnel involved in the care or evaluation of the subjects were informed of any individual's medication until the end of the study. Medications were dispensed in individually labeled bottles so that identification by code was not possible“

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Clark 1961 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Double-blind", ""neither the patients nor the personnel involved in the care or evaluation of the subjects were informed of any individual's medication until the end of the study"
Incomplete outcome data (attrition bias) All outcomes	Low risk	One participant in the chlorpromazine group was withdrawn due to agranulocytosis, along with the other two participants in her "triplet"
Selective reporting (reporting bias)	High risk	No data reported for OBRS, and no useable data reported for psychological tests
Other bias	Unclear risk	Supported, in part, by USPHS Grant M-1600 from the National Institute of Mental Health, National Institutes of Health, Department of Health, Education, and Welfare Medications supplied by Dr Fred Alexander of Smith, Kline, and French Laboratories

Clark 1967

Methods	Allocation: randomised - table of random numbers. Blindness: double - identical capsules. Duration: 10 weeks.* Design: parallel. Setting: inpatients. Country: USA.
Participants	Diagnosis: schizophrenia. History: duration ill > 5 years. N=72. Sex: 72 F. Age: 25-55 years. Setting: hospital.
Interventions	1. Chlorpromazine: dose mean 678 mg/day. N=51. 2. Placebo. N=21.
Outcomes	Leaving the study early. Unable to use - Mental state: BPRS, PRS (no data). Behaviour: OBRS (no data). Cognitive function: Perdue Pegboard test, Digit Symbol Test (no data). Physiological measures (no usable data).

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Notes	* Two identical 10-week studies are reported. Same women allocated within second - potential for cross-over effects. Data not included

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Assigned at random" no further details reported.
Allocation concealment (selection bias)	Unclear risk	No information reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Double-blind procedure in which neither the investigators nor the subjects knew who was receiving chlorpromazine. Medications were dispensed in identical-appearing capsules from individual stock bottle labeled only with the patient's name."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Double-blind procedure in which neither the investigators nor the subjects knew who was receiving chlorpromazine"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	"Seventy subjects meeting all physical and selection criteria completed both cycles of study 1 year apart. During the course of the second cycle, 2 subjects were found to be abnormal in regard to cholesterol metabolism [...] and their data were deleted from this report" "11 subjects taking chlorpromazine were unable to tolerate the full 800 mg over the 10-week trial"
Selective reporting (reporting bias)	High risk	No data reported for BPRS, PRS, OBRS, Perdue Pegboard test, Digit Symbol Test and physiological measures
Other bias	Unclear risk	Chlorpromazine and placebo were supplied by Smith Kline & French Laboratories, Philadelphia, Pa Supported by Grant MH-04260 from the US Public Health Service

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Clark 1968a

Methods	Allocation: randomly assigned - no further description. Blinding: double, identical capsules. Duration: 14 weeks (preceded by 12 week washout). Design: parallel. Country: USA.
Participants	Diagnosis: chronic schizophrenia (criteria not specified). History: >2 yrs of illness. N=72. Sex: 72 F. Age: mean 42 yrs, range 20-60. Setting: hospital.
Interventions	1. Chlorpromazine: dose 1000 mg/day max. N=18. 2. Placebo. N=18. 3. Trifluperidol: dose 10 mg/day max. N=18. 4. No drug group. N=18. Barbiturates or chloral hydrate for sedation as required.
Outcomes	Leaving study early. Global improvement. Adverse effects. Unable to use - Behaviour: Oklahoma Rating Scale (no SD). Psychological tests (no SD). Physiological tests (no data).
Notes	Groups 3 and 4 combined for purposes of review.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomly assigned" no further details reported.
Allocation concealment (selection bias)	Unclear risk	No information reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Identically appearing capsules from each subject's individually labelled stock bottle to meet the double-blind requirements of the study"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"Double-blind" no further details reported.

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Clark 1968a (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	"Sixty six patients completed the study. Two patients were dropped from the CPZ group because of skin rashes and a third because of a severe behavioural reaction", "Three were dropped form the no drug group [...] one patient in TRP group completed only 13 weeks before undergoing surgery"
Selective reporting (reporting bias)	High risk	No SDs reported for Oklahoma Rating Scale and psychological tests. No data reported for physiological tests
Other bias	High risk	Supported by grants from the National Institute of Mental Health, US Public Health Service and McNeil Laboratories Inc, Fort Washington, Pennsylvania

Clark 1968b

Methods	Allocation: randomised - no further details. Blinding: double - identical tablets. Duration: 16 weeks. Design: parallel. Country: USA.
Participants	Diagnosis: schizophrenia. History: duration ill ~20 years, in hospital ~16 years. N=69. Sex: all women. Age: 20-60 years, mean 45. Setting: hospital.
Interventions	1. Chlorpromazine: dose max 1000 mg/day. N=23. 2. Placebo: dose 10 tablets. N=23. 3. Butaperazine: dose max 100 mg/day. N=23. Barbiturates, chloral hydrate, benztropine as required.
Outcomes	Leaving the study early. Adverse effects. Unable to use - Global improvement (no usable data). Behaviour: OBRS (no usable data). Personality inventory: IMPS (modified, no usable data). Cognitive function: Perdue Pegboard, Digit Symbol test (no usable data). Physiological tests (no data).
Notes	

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Clark 1968b (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Randomly assigned" no further details.
Allocation concealment (selection bias)	Unclear risk	No information reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind", "All medications were identical in appearance"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Double-blind" no further details reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	"Sixty seven patients completed the study. One patient was dropped from the CPZ group because of agranulocytosis; one was lost form the BPZ group when she eloped. "
Selective reporting (reporting bias)	High risk	No useable data was reported for global improvement, OBRS, IMPS, Perdue Peg-board, Digit Symbol test and physiological tests
Other bias	High risk	Supported by grants from US Public Heath Service and AH Robins Company

Clark 1970a

Methods	Allocation: randomly assigned 'by sex'. Blinding: double, identical capsules. Duration: 12 weeks (preceded by 12-week washout). Design: parallel. Country: USA.
Participants	Diagnosis: schizophrenia (criteria not specified). History: 'chronic'. N=44. Sex: 7 M, 37 F. Age: mean 39.7 yrs, range 22-55. Setting: hospital.

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Clark 1970a (*Continued*)

Interventions	1. Chlorpromazine: dose 200-1000 mg/day. N=15. 2. Molindone: dose 20-100 mg/day. N=15. 3. Placebo: dose 2-10 capsules/day. N=14. Medication given in variable dose regimen.
Outcomes	Leaving study early. Global improvement. Severity of illness. Cooperativeness (those who agreed to EEG tests). Adverse effects. Unable to use - Mental state: BPRS (no SD). Behaviour: NOSIE (no SD). Various psychological tests (no SD).
Notes	Drugs to combat EPS not used.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Randomly assigned by sex" no further details reported.
Allocation concealment (selection bias)	Unclear risk	No information reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Identically appearing capsules", "double-blind, with medications dispensed from individual stock bottles labelled only with the patient's name"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"Double-blind" no further details reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	"One subject was dropped form the CPZ group because of abnormal liver function tests; another subject on CPZ was terminated 2 weeks early because of surgery"
Selective reporting (reporting bias)	High risk	No SDs reported for BPRS, NOSIE and the various psychological tests
Other bias	High risk	Supported in part by US Public Health Service Grant, Research Scientist Development Award from National Institute of Mental Health. Endo Laboratories provided the medication and partial support

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Clark 1970b

Methods	Allocation: randomly assigned by block - no further description. Blinding: not described. Duration: 24 weeks (preceded by 12 week washout). Design: parallel. Country: USA.
Participants	Diagnosis: schizophrenia - criteria not specified. History: "chronic". N=71. Sex: 71 F. Age: mean 43.7 yrs, range 21-60. Setting: hospital.
Interventions	1. Chlorpromazine: dose 150 mg/day. N=17.* 2. Chlorpromazine: dose 300 mg/day. N=18.* 3. Chlorpromazine: dose 600 mg/day. N=18.* 4. Placebo. N=18.* Medication given in fixed dose regimen; benztropine for EPS, chloral hydrate, phenobarbitone or sodium amytal for sedation, as required
Outcomes	Leaving study early. Adverse effects. Behavioural disturbance (requiring more medication on >5 occasions) Unable to use - Global Impression: CGI (no SD). Mental state: BPRS, IMPS (no SD). Behaviour: OBRS (no SD).
Notes	* Withdrawals partially described (N=4) - initial group unclear. Assumed one from each group (these amended numbers appear above)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Subjects were assigned by block randomisation" no further details reported
Allocation concealment (selection bias)	Unclear risk	No information reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information reported.

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Clark 1970b (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	High risk	"During the course of the study one subject was dropped because of rash and anaemia, one because of agranulocytosis, two because of elopement from the hospital, and two because of requisite surgery". Study does not report which from groups the losses to follow-ups occurred
Selective reporting (reporting bias)	High risk	No SDs reported for CGI, BPRS, IMPS, and OBRS.
Other bias	Low risk	Supported by USPHS grant and Research Scientist Development Award

Clark 1971

Methods	Allocation: randomly assigned, blocks of 4 - no further description. Blinding: double, identical capsules. Duration: 4 weeks. Design: parallel. Country: USA.
Participants	Diagnosis: schizophrenia (minimum of 2 symptoms from list). History: mean no. admissions CPZ group=2.4, placebo group=3.6. N=86. Sex: male and female (numbers unclear). Age: mean 33 years, range 21-45. Setting: hospital.
Interventions	1. Chlorpromazine: dose 200-1000 mg/day. N=23. 2. Placebo (lactulose). N=21. 3. Fluphenazine: dose 2-10 mg/day. N=20. 4. Thioridazine: dose 200-1000 mg/day. N=22. Medication given in variable dose regimen; usual night-time sedation permitted
Outcomes	Leaving study early. Global impression. CGI. Adverse effects. Unable to use - Mental state: BPRS (no SD). Behaviour: NOSIE (no SD). Psychological tests (no SD).
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

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Clark 1971 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	"Patients were assigned to treatment randomly in blocks of four" no further details reported
Allocation concealment (selection bias)	Unclear risk	No information reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Double-blind", "identical appearing medication was administered from a bottle labelled only with the patient's name"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"Double-blind" no further details reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	"Of the 75 subjects completing the study, one placebo subject was terminated because of behavioural deterioration after only three weeks observation and one subject taking fluphenazine was discharged from the hospital as markedly improved after only two weeks observation. In both instances, final measures were obtained and their data were retained for the final analysis. Eleven additional subjects were started in the study but were dropped without obtaining final measures for a variety of reasons: in the placebo group there was one subject absent without permission (AWOL), one on convalescent leave, and one subject transferred to another hospital; in the thioridazine group there were two AWOL subjects and one with medication intolerance; in the chlorpromazine group there was one AWOL and two subjects who refused oral medication; in the fluphenazine group there was one administrative transfer and one AWOL."
Selective reporting (reporting bias)	High risk	No SDs reported for BPRS, NOSIE and the psychological tests.
Other bias	Unclear risk	Supported by Public Health Service grant and Research Scientist Award. Medication provided by Smith Kline & French Laboratories, Sandoz Inc and ER SQuibb & Sons

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Clark 1972

Methods	Allocation: randomly assigned - no further description. Blinding: double, identical capsules. Duration: 12 weeks (preceded by 12 weeks washout). Design: parallel. Country: USA.
Participants	Diagnosis: schizophrenia (criteria not specified). History: 'chronic', 2+ yrs ill. N=55. Sex: 24 M, 31 F. Age: CPZ group mean 42 yrs, placebo group mean 40 yrs, range 21-60. Setting: hospital.
Interventions	1. Chlorpromazine: dose 1000 mg/day. N=19. 2. Placebo. N=18. 3. Loxapine: dose 10 mg/day. N=18. Medication increasing to fixed dose; antiparkinson medication as required
Outcomes	Leaving study early. Global impression. CGI. Global severity of illness. CGI. Adverse effects. Unable to use - Mental state: BPRS (no SD). Behaviour: NOSIE (no SD). Weight gain (no SD). Physical tests: EKG, urine, blood (no data reported).
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Allocation to treatment was random, but provided for balancing of groups by sex and age" no further details reported
Allocation concealment (selection bias)	Unclear risk	No information reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Double-blind", identical appearing medication in capsule form was administered orally to each subject rom his individual stock bottle labelled only with his name"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"Double-blind" no further details reported.

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Clark 1972 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	"Five patients were lost from the study: 2 from the PL group because of a grand mal seizure in one, and a cardiac arrhythmia in the second; 2 from the CPZ group because of abnormal liver function in one and a severe allergic reaction dermatitis with photo-sensitivity on the other; 1 from the LOX group because of a hip fracture"
Selective reporting (reporting bias)	High risk	No SDs reported for BPRS, NOSIE and weight gain. No data reported for physical tests
Other bias	High risk	Supported by a grant from USPHS and a grant-in-aid from Lederle Laboratories

Clark 1977

Methods	Allocation: randomly assigned 'by sex' - no further description. Blinding: double, identical capsules. Duration: 12 weeks (preceded by 8 week wash-out). Design: parallel. Country: USA.
Participants	Diagnosis: schizophrenia (criteria not specified). History: 'chronic'. N=27. Sex: 13 M, 14 F. Age: mean 43.2 yrs, range 23-61. Setting: hospital.
Interventions	1. Chlorpromazine: dose 1000 mg/day. N=9. 2. Placebo. N=9. 3. Butaclamol: dose 50 mg/day. N=9. Medication increasing to fixed dose; antiparkinson medication for EPS as required; sodium amytal and chloral hydrate for behaviour control as required
Outcomes	Leaving study early. Global impression. CGI. Adverse effects. Unable to use - Mental state: BPRS (no SD). Global impression: CGI (no SD). Behaviour: NOSIE (no SD). Physical tests: EKG, urine, blood (no data).
Notes	

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Clark 1977 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Allocation to treatment by sex was random" no further details reported
Allocation concealment (selection bias)	Unclear risk	No information reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Placebo tablets identical to the white butaclamol and to the brown CPZ preparations were taken by all subjects during the dry-out period and by the placebo group during treatment" "Each patient received his/her medication from individual stock bottles" "Double-blind".
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"Double-blind" no further details reported.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	"Of the 27 subjects who started, three failed to complete the full 12 weeks of study: one female subject in the butaclamol group became excited and agitated during the 4th week of treatment, exacerbated a labile hypertension, and was dropped at the end of the 4th week as treatment failure. Two male subjects in the placebo group also manifested clinical deterioration, one at the 8th week and one at the 11th week of treatment, and were terminated as treatment failures. In each instance, final rating were obtained and their data were retained in the analysis". Last observation carried forward method used
Selective reporting (reporting bias)	High risk	No SDs reported for BPRS, CGI and NOSIE, and no data reported for physical tests
Other bias	High risk	Supported in part by a USPHS grant and a grant-in-aid from Ayerst Laboratories, NY

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Cohen 1968

Methods	Allocation: randomised. Blinding: "using a double-blind procedure". Duration: 3 months. Design: parallel. Country: USA.
Participants	Diagnosis: schizophrenia. History: participants had symptoms of schizophrenia for at least 1-year. N=126. Sex: 54 M 72 F. Age: range 18-42. Setting: community outpatients clinic.
Interventions	1. Chlorpromazine: dose 180 mg/day. N=42. 2. Placebo. N=42. 3. Promazine: dose 180 mg/day. N=42.
Outcomes	Leaving the study early. Unable to use - Mean change in social aggression (no SD). Manifest anxiety state (no SD).
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomly assigned" no further details reported.
Allocation concealment (selection bias)	Unclear risk	No information reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"Double-blind" no further details reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"Double-blind" no further details reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up reported.
Selective reporting (reporting bias)	High risk	No SDs reported for social aggression and manifest anxiety state
Other bias	Low risk	Supported by grants from the National Institute of Mental Health, Public Health

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Cohen 1968 (*Continued*)

		Service

Cole 1964

Methods	Allocation: randomly assigned, sealed envelopes, stratified by sex and race (no further description). Blinding: double, oral medication 'prepared as standard No. 2 pink capsules', IM from '1 cc glass ampules' with sterile saline for placebo. Duration: 6 weeks. Design: parallel. Country: USA.
Participants	Diagnosis: schizophrenia (presence of specific symptoms/behaviours). History: newly admitted, recent onset illness. N=463. Sex: male and female (proportions not given). Age: 16-45 yrs. Setting: hospital. Exclusions: childhood autism or schizophrenia, brain syndrome, learning disability, alcoholism, epilepsy, drug abuse
Interventions	1. Chlorpromazine: dose 200-1600 mg/day or 50-400 mg/day (IM). N=112. 2. Placebo: dose 2-16 doses/day or 2-16 injections/day (IM). N=125. 3. Fluphenazine: dose 2-16 mg/day or 1-8 mg/day (IM). N=115. 4. Thioridazine: dose 200-1600 mg/day or 50-400 mg/day (IM). N=111 Medication given in discretionary dose regimen; antiparkinsonian medication for EPS as required
Outcomes	Leaving study early. Adverse effects. Unable to use - Global impression: Global Rating of Severity of Mental Illness & Global Rating of Improvements (data not reported by group). Mental state: IMPS (data not reported by group). Behaviour: Burdock Ward Behaviour Rating Scale (data not reported by group)
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Stratified by sex with randomised assignment to drug treatment within each sex group" no further details reported
Allocation concealment (selection bias)	Unclear risk	No information reported.

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Cole 1964 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Double-blind" oral medication "prepared as standard No. 2 pink capsules", IM from "1 cc glass ampules" with sterile saline for placebo
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"Double-blind" no further details reported.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	119 out of 463 participants were lost to follow-up. Reasons for loss to follow-up were balanced across groups, apart from treatment failure where "the majority of patients who were dropped because of treatment failure were on placebo"
Selective reporting (reporting bias)	High risk	Data was not reported by group for Global Rating of Severity of Mental Illness & Global Rating of Improvements, IMPS and Burdock Ward Behaviour Rating Scale
Other bias	Low risk	Supported by NIMH grants.

Cooper 2000

Methods	Allocation: randomly assigned in blocks of 6 - no further description. Blinding: "double dummy technique ... used to maintain blinding". Duration: 8 weeks. Design: parallel. Country: Multi-centre (Belgium, UK., Ireland and Poland)
Participants	Diagnosis: schizophrenia (DSM-III-R & > moderately ill on CGI). History: acute exacerbation or sub chronic/chronic. N=159. Sex: 115 M, 44 F. Age: mean ~39 yrs, range 18-65. Setting: inpatients and outpatients.
Interventions	1. Chlorpromazine: dose 600 mg/day. N=53. 2. Placebo. N=53. 3. Zotepine: dose 300 mg/day. N=53. Benzodiazepines or chloral hydrate for sleeplessness as required; anticholinergic medication for EPS as required
Outcomes	Leaving study early. Global improvement (50% reduction in BPRS). Global impression: CGI (no improvement psychiatrist rated). Unable to use -

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	Adverse effects (unclear if data includes withdrawals). Mental state: BPRS, SANS (unsure of data). Global impression: CGI (unsure of data). Adverse effects: AIMS, COSTART, EPMS, Simpson and Angus (no means, SD)
Notes	Unclear if data for 'leaving study early' and 'improvement' include 1 person omitted from 'ITT' analysis. Author contacted, replied, and further data awaited

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"All eligible patients were allocated a study number and randomly assigned in blocks of six" no further details reported
Allocation concealment (selection bias)	Unclear risk	No information reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Double-blind" "A double-dummy technique was used to maintain blinding because of differences in capsule and tablet appearances, i.e. patients received active zotepine plus placebo chlorpromazine or placebo zotepine plus active chlorpromazine or double placebo."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"Double-blind" no further details reported.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	"ITT analysis" "A total of 89 patients completed the full 8-week study." "Sixty-nine patients withdrew from the study" Reasons for leaving the study not fully described
Selective reporting (reporting bias)	High risk	For adverse effects it is unclear if data includes withdrawals. We are unsure of the data reported for BPRS, SANS, CGI, AIMS, COSTART and EPMS. No means and SDs were reported for Simpson and Angus
Other bias	High risk	Funded by Knoll Pharmaceuticals. Data analysis was by Knoll in conjunction with Dr Cooper

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Dean 1958

Methods	Allocation: randomised. Blinding: double blind. Duration: 15 weeks. Design: parallel. Country: USA.
Participants	Diagnosis: schizophrenia. History: chronic schizophrenia. N=18. Sex: female. Age: mean 37, range 26-47. Setting: hospital.
Interventions	1. Chlorpromazine: dose mean 2400 mg/day, 2000-3000 mg/day . N=9. 2. Placebo. N=9.
Outcomes	Leaving the study early. Adverse effects (jaundice, skin reactions). Unable to use - Ward evaluation (unpublished scale).
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information reported.
Allocation concealment (selection bias)	Unclear risk	No information reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"Those patients on placebo were given tablets which were identical in appearance with chlorpromazine." "Until the patients were receiving 1000 mg of chlorpromazine a day, the hospital pharmacist was was the only person who knew which patients were receiving placebos. At the 1000 mg level the ward physician checked the master list to determine who was on the placebos"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were no losses to follow-up.

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Dean 1958 (*Continued*)

Selective reporting (reporting bias)	Low risk	All expected outcomes reported.
Other bias	Unclear risk	Chlorpromazine supplied by Smith Kline & French Laboratories Source of funding not reported.

Engelhardt 1960

Methods	Allocation: randomly assigned - no further description. Blinding: double, identical capsules. Duration: 18 months. Design: parallel. Country: USA.
Participants	Diagnosis: schizophrenia (criteria not specified). History: illness >1 yr. N=173. Sex: not reported. Age: range 18-40 yrs. Setting: outpatients department.
Interventions	1. Chlorpromazine: dose 50-800 mg/day (variable dose regimen). N=62. 2. Placebo. N=56. 3. Promazine: dose 50-800 mg/day (variable dose regimen). N=55
Outcomes	Leaving study early. Relapse (hospitalisation).
Notes	Above data extracted from Engelhardt (JAMA 1960;173:147-9). Other reports have greater 'N' (of which the 173 above are assumed to be an unbiased sub-sample) but no data is usable from these papers

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Drug assignment was random" no further details reported.
Allocation concealment (selection bias)	Unclear risk	No information reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Double-blind" "The medication was in the form of pink capsules containing either placebo, promazine hydrochloride or chlorpromazine hydrochloride" "The treating psychiatrist did not know

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Engelhardt 1960 (*Continued*)

		which agent the patient received"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"Double-blind" no further details reported.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	"The overall drop-out rate was 36.4% (63 out of 173 patients), while for individual agents the rates were as follows: placebo, 33.9%; and chlorpromazine, 40.3%". Reasons for loss to follow-up not reported
Selective reporting (reporting bias)	Unclear risk	No outcomes pre-specified in methods. Other reports have greater 'N' (of which the 173 above are assumed to be an unbiased sub-sample) but no data is usable from these papers
Other bias	Low risk	Study supported in part by a grant from National Institute of Mental Health, US Public Health Service

Fink 1963

Methods	Allocation: randomly assigned - no further description. Blinding: used "40 cc of highly flavoured liquid". Duration: 6 weeks, follow-up 2-3 yrs. Design: parallel. Country: USA.
Participants	Diagnosis: schizophrenia, affective disorders, personality disorders, neuroses, organic mental disorders* History: voluntary inpatients, 'middle-class, well educated'. N=311 (schizophrenia N=142). Sex: male and female (proportions unknown). Age: mean 31.1 yrs.. Setting: hospital.
Interventions	1. Chlorpromazine: dose 1200 mg/day. N=51. 2. Placebo. N=44. 3. Imipramine: dose 300 mg/day. N=47. Medication increasing to fixed dose; group 1 given procyclidine to prevent EPS: dose max. 15 mg/day
Outcomes	Global improvement. Leaving the study early (Belmont 1963, N=19) Unable to use - Mental state: MSRPP (no usable data).

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Fink 1963 (*Continued*)

	Memory: Rorschach tests (no SD).
Notes	*Review uses schizophrenia data only. Another 33 participants in Klein, Honigfeld, and Feldman report (1968) but no data. Belmont 1963 reported data on a subgroup of 19 people with schizophrenia

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomly assigned" no further details reported.
Allocation concealment (selection bias)	Unclear risk	No information reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Double-blind" "Each medication was dissolved in a highly flavoured liquid vehicle and each patient received 40ml per day from individually labelled bottles"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"Double-blind" no further details reported.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	"Of the 173 patients starting medication, 19 did not complete the study because of psychiatric reasons [...] 5 for medical complications [...] 5 patients received an active placebo in a methodological substudy and are not included in this analysis
Selective reporting (reporting bias)	High risk	No useable data reported for the MSRPP and no SDs reported for Rorschach tests
Other bias	Low risk	Partly funded by National Institute of Mental Health, USPHS

Fleming 1959

Methods	Allocation: randomly assigned - no further description. Blinding: double, identical capsules. Duration: 6 months (preceded by 'several weeks' washout). Design: parallel. Country: Ireland.

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Fleming 1959 (*Continued*)

Participants	Diagnosis: schizophrenia (criteria not specified). History: 'chronic', mean duration ill 21 yrs. N=63. Sex: 63 F. Age: mean 57.6 yrs. Setting: hospital.
Interventions	1. Chlorpromazine: dose 75 mg/day increasing to 300 mg/day max. N=21. 2. Placebo. N=21. 3. Promazine: dose 75 mg/day increasing to 300 mg/day max. N=21
Outcomes	Leaving study early. Disturbed behaviour ("noisy, aggressive or disturbed incidents"). Adverse effects. Unable to use - Mental state: Powick Psychiatric Rating Scale (no SD).
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Patients were sub-divided, upon a random basis, into 3 equal groups" no further details reported
Allocation concealment (selection bias)	Unclear risk	No information reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Double-blind" "the tablets of the 3 treatments were identical in appearance, the hospital dispenser alone knowing to which treatment any particular patient had been assigned at the outset"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"Double-blind" no further details reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	"12 patients who failed to complete the trial was as follows: 6 patient received ECT; 2 patients developed severe extrapyramidal symptoms (chlorpromazine); 1 patient developed agranulocytosis (chlorpromazine); and 3 patients were withdrawn for miscellaneous physical considerations (promazine)"

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Fleming 1959 (*Continued*)

		"The loss of patients was equally distributed"
Selective reporting (reporting bias)	High risk	No SD reported for Powick Psychiatric Rating Scale.
Other bias	Unclear risk	John Wyeth & Bro. supplied the promazine, Messrs, May & Baker Ltd supplied chlorpromazine and placebo tablets

Grygier 1958

Methods	Allocation: randomly assigned - pairs matched (on age, duration of illness, intelligence, and aptitude for OT), and 'pharmacist decided at random' - no further description. Blinding: not described but raters asked to guess which participants were on which medication. Duration: 24 weeks. Design: parallel. Country: UK.
Participants	Diagnosis: chronic schizophrenia (criteria not specified). History: 'chronic', mean duration ill 19.6 yrs. N=30. Sex: 30 F. Age: mean 49.8 yrs, SD 10.7 yrs. Setting: hospital.
Interventions	1. Chlorpromazine: dose 150 mg/day. N=15. 2. Placebo. N=15.
Outcomes	Global improvement. Unable to use - Behaviour: Albany Behavioral Rating Scale (no SD). Leaving study early (both members of a pair removed from analysis when one left). Adverse effects (both members of a pair removed from analysis when one developed a serious side effect e.g. granulocytosis, jaundice)
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"selected two groups, matching them as closely as possible", "pharmacist decided at random" no further details reported

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Grygier 1958 (*Continued*)

Allocation concealment (selection bias)	Low risk	"The pharmacist decided at random which group would receive chlorpromazine and which inert tablets, and only she had this information at any time"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"At the end of the experiment both raters were asked to "guess" the composition of the chlorpromazine group" no further details reported, implies assessors were blind for treatment allocation
Incomplete outcome data (attrition bias) All outcomes	High risk	"if any patient had to discontinue the program, her "pair" could also be omitted" "Three pairs were lost: one due to death from unassociated causes; two due to major side-effects". Both members of a pair removed from analysis when one left
Selective reporting (reporting bias)	High risk	No SDs reported for Albany Behavioral Rating Scale.
Other bias	Unclear risk	Source of funding not reported.

Gwynne 1962

Methods	Allocation: randomised. Blinding: unclear. Duration: 4 months. Design: parallel. Setting: inpatients. Country: not reported.
Participants	Diagnosis: schizophrenia. N=78. Age: average 49 years. Sex: M 38 F 38. History: Hospital record diagnosis of schizophrenia for a least 5 years, history of withdrawal for at least one year. Exclusions: not reported. Setting: hospital.
Interventions	1. Chlorpromazine: dose 7 days on 100 mg/day, 200 mg/day, 300 mg/day, and 400 mg/day until maximum improvement or side-effects intervened. N=26. 2. Trifluoperazine: dose 7 days on 10 mg/day, 20 mg/day, 30 mg/day, and 40 mg/day

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	until maximum improvement or side-effects intervened. N=26. 3. Placebo. N=26. Benztropine methanesulfonate (2 mg) as required.
Outcomes	Adverse effects*. Leaving the study early. Unable to use - Mental state: MRSPP (no means and SDs reported)
Notes	*N not reported, assumed to be N randomised.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Three groups of 26 patients each (13 males and 13 females) were formed by random selection from the basic group" no further details reported
Allocation concealment (selection bias)	Unclear risk	No information reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"All drugs and placebo were identical in appearance and taste." No further details reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	In the placebo group, one participant left the study early due to adverse effects and two due to unmanageability. There were no losses to follow-up in the chlorpromazine group
Selective reporting (reporting bias)	High risk	No means and SDs reported for MSRPP.
Other bias	Unclear risk	Drugs provided by Smith, Kline and French, and Merck, Sharp & Dohme Source of funding not reported.

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Hall 1955

Methods	Allocation: randomly assigned - 'code letters ... assigned at random to these batches [of drugs]. In turn, these code letters ... assigned in serial fashion to patients on each ward, thus insuring randomised and unknown assignment of drug and placebo'. Blinding: double, identical capsules and blindness tested (see notes). Duration: 66 days (preceded by 32 day washout). Design: parallel. Country: USA.
Participants	Diagnosis: schizophrenia (criteria not specified). History: 'chronic', 'semi-disturbed'. N=175. Sex: 54 M, 121 F. Age: range 20-59 yrs. Setting: hospital.
Interventions	1. Chlorpromazine: dose variable up to 750 mg/day (discretionary). N=87. 2. Placebo (terra alba). N=88.
Outcomes	Leaving study early. Global improvement. Behaviour. Modified Fergus Falls Behavior Rating Sheet. Adverse effects. Unable to use - Specific symptoms (no usable data). Liver biopsy data (non-random subset of participants).
Notes	Blindness testing. Psychiatrists guessed 22/50 CPZ group correctly, and 56/61 placebo group correctly. Psychologists guessed 31/50 CPZ group correctly, and 53/63 placebo group correctly - side effects=main source of unblinding

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Randomised selection" no further details reported.
Allocation concealment (selection bias)	Low risk	"The drug manufacturer supplied the material in 10 coded batches. Half of the batches contained drug, and half placebo (terra alba), and code letters were assigned at random to these batches. In turn, these codes letters were assigned in serial fashion to
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Double-blind" "identical-appearing placebo"

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Hall 1955 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"Double-blind", "the participating technicians, psychiatrists and psychologist recorded their judgments as the whether the patient received drug or placebo", "the psychiatrists and psychologist were neither completely "blind" nor completely "unblind"
Incomplete outcome data (attrition bias) All outcomes	Low risk	"The three patients who developed jaundice were eliminated from the project"
Selective reporting (reporting bias)	High risk	There were no useable data for specific symptoms and liver biopsy data was only reported for a non-random subset of participants
Other bias	High risk	Smith, Kline & French Laboratories provided chlorpromazine, partly supported the study with a grant for statistical analysis and provided other assistance

Hamill 1975

Methods	Allocation: assigned 'using a table of random numbers'. Blinding: unclear. Duration: 5 days. Design: parallel. Country: USA.
Participants	Diagnosis: schizophrenia (presence of > 2 symptoms from checklist). History: newly admitted. N=44. Sex: 33% M, 67% F. Age: range 18-55 yrs. Setting: hospital.
Interventions	1. Chlorpromazine: dose 306-475 mg/day. N=22. 2. Placebo. N=22. Medication given in variable dose regimen.
Outcomes	Leaving study early. Unable to use - Mental state: BPRS (no mean, N, or SD). Global improvement: CGI (no SD). Behaviour: NOSIE (no mean, N, or SD).
Notes	

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Hamill 1975 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Assignment of patients to the chlorpromazine or the placebo group was determined using a table of random numbers"
Allocation concealment (selection bias)	Unclear risk	"Patients were given a number from 1 to 44 according to the randomisation and without the participation of the research psychiatrist"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	"Of the 44 patients evaluated, 11 were dropped from the study during the 5 day period. OF the 111 dropped patients, 6 were in the drug group and 5 in the placebo group." Reasons for leaving the study early balanced across groups
Selective reporting (reporting bias)	High risk	No useable data reported for the BPRS and NOSIE and no SDs reported for CGI
Other bias	Unclear risk	Source of funding not reported. Placebo provided by Smith Kline & French Laboratories, Philadelphia, Pa

Hamilton 1960

Methods	Allocation: block randomisation into six groups. Blinding: double, 'placebo tablets .... indistinguishable from the active drugs'. Design: factorial (2 x 3). Duration: 8 weeks. Country: UK.
Participants	Diagnosis: schizophrenia (no specified criteria). History: 'chronic'; all liable to overactivity/aggression. N=54. Sex: 54 M. Age: mean 38 yrs.

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Hamilton 1960 (*Continued*)

	Setting: hospital.
Interventions	1. Chlorpromazine: dose 300 mg/day. N=18. 2. Placebo. N=18. 3. Thiopropazate: dose 30 mg/day. N= 18. Medication given in fixed dose regime; factored to: A. Occupational therapy. N=27. B. No occupational therapy.N=27.
Outcomes	Leaving study early. Adverse effects. Unable to use - Mental state: Lorr (no mean, SD). Behaviour: nurse-rated scale (no mean, SD).
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"The patients were randomly allotted to 6 groups of 9 patients each" "Each of these 3 groups was randomly coupled with another group, and the names of the patients in the 3 pairs of groups given to the hospital pharmacist. He randomly selected one pair of no further details reported
Allocation concealment (selection bias)	Unclear risk	"Pharmacist [...] randomly selected" groups, no further details reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Form the point of view of the patients, nurses and physicians, there were 27 patients receiving one kind of tablet and 27 patients receiving the other kind, but only the pharmacist knew which of the patients were receiving active and which inert tablets. All the tablets were sugar-coated nad the placebo tablets were indistinguishable from the active drugs. "
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Form the point of view of the patients, nurses and physicians, there were 27 patients receiving one kind of tablet and 27 patients receiving the other kind, but only the pharmacist knew which of the patients were receiving active and which inert

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Hamilton 1960 (*Continued*)

		tablets." "The patients were assessed on Behaviour in the ward by the charge nurses and on Symtoms by the physician"
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were no losses to follow-up.
Selective reporting (reporting bias)	High risk	No means and SDs reported for mental state and a nurse-rated behaviour scale
Other bias	Unclear risk	Source of funding not reported.

Hankoff 1962

Methods	Allocation: randomised. Blinding: double. Duration: 2 weeks. Design: parallel. Country: USA.
Participants	Diagnosis: schizophrenia and non-schizophrenia. N=174. Age: mean 39 years. Sex: M 70, F 64 History: not reported. Exclusions: not reported. Setting: community.
Interventions	1. Chlorpromazine: dose 150 mg/day. N=25. 2. Chlordiazepoxide: dose 30 mg/day. N=27. 3. Meprobamate: dose 600 mg/day. N=27. 4. Placebo. N=72. Doses adjusted at one week intervals as necessary.
Outcomes	Global improvement. Leaving the study early. Adverse effects. Unable to use - Manifest Anxiety (no SDs reported). Affect Adjective Checklist (no SDs reported).
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

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Hankoff 1962 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	"Patients were randomly assigned to treatment groups" no further details reported
Allocation concealment (selection bias)	Unclear risk	No information reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Double-blind" "All the drugs and their placebos were administered in pink No.2 capsules"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"Double-blind" no further details reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	"Of 174 patients starting in the project, 134 completed the two-week drug trial. The 40 patients who failed to complete the study usually did not return for appointments. An occasional patient in this total of 40 was dropped for reasons of protocol violation"
Selective reporting (reporting bias)	High risk	No SDs reported for Manifest Anxiety and Affect Adjective Checklist
Other bias	Low risk	Supported by a grant from the US Public Health Service.

Hine 1958

Methods	Allocation: matched on level of withdrawal symptoms and assigned at 'the toss of a coin'. Blinding: double, 'corresponding tablets or solution'. Duration: 20 weeks (preceded by 11 week baseline period). Design: parallel. Country: USA.
Participants	Diagnosis: schizophrenia (criteria unspecified). History: 'chronic', 'more withdrawn than usual', continuously hospitalised for > 5 yrs. N=22. Sex: 22 F. Age: range 30-50 yrs. Setting: hospital.
Interventions	1. Chlorpromazine: dose increasing to max. tolerable level or 750 mg/day. N=11. 2. Placebo. N=11.
Outcomes	Leaving study early. Adverse effects. weakness, skin rash. Improvement. change in hospital status, such as grounds privileges

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Hine 1958 (*Continued*)

	Unable to use - Withdrawal: Southeast Louisiana Hospital Behavior Rating Scale (no data)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Matched pairs" based on withdrawal symptoms "and one member of this pair was assigned to the treatment group by the toss of a coin
Allocation concealment (selection bias)	Unclear risk	No information reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"Double-blind" "The results of this assignment were not known to the judges, raters or other ward personnel" "corresponding placebo tablets or solution" no further details reported
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Double-blind" "The results of this assignment were not known to the judges, raters or other ward personnel"
Incomplete outcome data (attrition bias) All outcomes	Low risk	"It was necessary to discontinue medication during the third week on one patient in the treatment group because of the development of severe angioneurotic edema. This patient was eliminated from the project"
Selective reporting (reporting bias)	High risk	No data reported for the Southeast Louisiana Hospital Behavior Rating Scale
Other bias	Unclear risk	Drugs provided by Smith Kline & French Laboratories

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Hogarty 1973

Methods	Allocation: stratified by sex and randomly assigned - no further description. Blinding: double, "identical looking tablets". Design: factorial (2 x 2). Duration: 3 years (preceded by 2 months CPZ-stabilisation period) Country: USA.
Participants	Diagnosis: schizophrenia (no specified criteria). History: recently discharged. N=374. Sex: 43% M, 57% F. Age: mean 34 yrs, range 18-53. Setting: community.
Interventions	1. Chlorpromazine: dose variable min. 100 mg/day, mean 270 mg/day. N=192. 2. Placebo. N=182. Factored to: A. Major role therapy. N=190. B. Rehabilitation counseling. N=184.
Outcomes	Leaving study early. Relapse. Unable to use - Death (N given, but not by group). Trouble with police (N given, but not by group). Mental state: BPRS, Symptom Checklist, IMPS, Springfield Symptom Inventory (no SD). Social functioning: Major Role Adjustment Inventory, Katz Adjustment Scale, Casework Evaluation Schedule (no SD). Carer morbidity: Family Distress Scale (no SD).
Notes	Assumption re 'leaving study early': One report states - 27 people 'terminated' during month 1-10, 3 due to side effects of CPZ. No data on remaining 24 - group of allocation unknown. However, by 2 yrs 'terminations'=31 (Table 3, 'II. Two-year relapse rates' paper), 13 from CPZ, 18 from placebo group. This allowed calculation of group of allocation of the original 24 at 10 months (10 + 3 already known=CPZ group, 14= placebo group)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Randomly assigned" no further details reported.
Allocation concealment (selection bias)	Unclear risk	No information reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Assigned on a double-blind basis to identical looking 100 mg or 50 mg tablets of chlorpromazine or placebo"

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Hogarty 1973 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"Double-blind" no further details reported.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Losses to follow-up not clearly reported. Reasons for leaving the study early reported, but not according to group
Selective reporting (reporting bias)	High risk	Number of deaths and number of participants in trouble with police not reported by group No SDs reported for BPRS, Symptom Checklist, IMPS, Springfield Symptom Inventory, Major Role Adjustment Inventory, Katz Adjustment Scale, Casework Evaluation Schedu
Other bias	Unclear risk	Supported by grants from the Psychopharmacology Research Branch, National Institute of Mental Health (NIMH) Chlorpromazine was supplied by Smith Kline & French Laboratories, Philadelphia

Klein 1973

Methods	Allocation: randomly assigned - no further description. Blinding: double, used 'highly flavoured liquid placebo', a constant 40 ml per day from individually labelled bottles. Duration: 6 weeks. Design: parallel. Country: USA.
Participants	Diagnosis: schizophrenia (specified criteria). N=88. Sex: 51% M, 49% F. Age: mean 26.7 yrs, range 17-61. Setting: hospital.
Interventions	1. Chlorpromazine: dose increased by 300 mg/day/week to max. 1200 mg/day, week 4-6. N=46. 2. Placebo. N=42. Chlorpromazine combined with procyclidine for EPS: dose max. 15 mg/day
Outcomes	Leaving study early. Unable to use - Mental state: MSRPP (no SD).
Notes	

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Klein 1973 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Randomly assigned" no further details reported.
Allocation concealment (selection bias)	Unclear risk	No information reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Double-blind" "Medication was administered in a highly flavoured liquid placebo, and each patient received a constant 40 ml/day from individually labelled bottles"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"Double-blind" no further details reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were no losses to follow-up.
Selective reporting (reporting bias)	High risk	No SDs reported for MSRPP.
Other bias	Unclear risk	Supported in part by grants from the Public Health Service of the National Institue of Mental Health Smith Kline & French Laboratories and Wellcome and Co supplied the drugs

Kurland 1961

Methods	Allocation: assigned by "predetermined random selection". Blinding: double, "standard unmarked capsules", "coloured pink to mask all identifying consistencies and colours of drugs". Duration: 6 weeks. Design: parallel. Country: USA.
Participants	Diagnosis: 'predominantly schizophrenic in character'. History: newly admitted, target symptoms of hyperactivity, anxiety, tension, overt aggression. N=277. Sex: 1:2 ratio M:F. Age: mean 31 yrs, range 18-61. Setting: hospital.

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Kurland 1961 (*Continued*)

Interventions	1. Chlorpromazine: dose 25 mg/day IM (days 1-2) then min. 300 mg/day (no max.). N=33. 2. 'Positive' placebo (phenobarbital): dose 65 mg/day IM (days 1-2) then min. 97.5 mg/day (no max.). N=37. 3. 'Negative' placebo (saline/lactose): dose IM (days 1-2) then oral. N=37. 4. Promazine: dose 50 mg/day IM (days 1-2) then min. 300 mg/day (no max.). N=32. 5. Mepazine: dose 25 mg/day IM (days 1-2) then min. 75 mg/day (no max.). N=34. 6. Triflupromazine: dose 25 mg/day IM (days 1-2) then min. 75 mg/day (no max.). N=36. 7. Prochlorperazine: dose 5 mg/day IM (days 1-2) then min. 30 mg/day (no max.). N=32. 8. Perphenazine: dose 5 mg/day (days 1-2) then min. 24 mg/day (no max.). N=36
Outcomes	Leaving study early. Adverse effects. Global improvement. Unable to use - Mental state: MSRPP, Psychotic Reaction Profile, Psychiatric Scale of Target Symptoms (no SD)
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"The choice of the particular drug to be used in any case was based on a predetermined random selection" no further details reported
Allocation concealment (selection bias)	Unclear risk	No information reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Double-blind" "The drugs were dispensed in standard unmarked capsules [...] coloured pink to mask all identifying consistencies and colours of the drugs"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Double-blind" "Ratings were blind, in that raters did not know which drug the patients was receiving"
Incomplete outcome data (attrition bias) All outcomes	High risk	"Those patients whom data were incomplete, together with those not receiving medication for at least ten days, were excluded from the study"

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Kurland 1961 (*Continued*)

		"Of the 238 patients who met all population restrictions, 187 remained in the project at least 10 days [...] Fifty-nine patients completed the prescribed six-week treatment course."
Selective reporting (reporting bias)	High risk	No SDs reported for the MSRPP, Psychotic Reaction Profile and Psychiatric Scale of Target Symptoms
Other bias	Unclear risk	Funded by a research grant from the National Advisory Mental Health Council, National Institute of Health, US Public Health Service Drugs provided by Smith Kline & French Laboratories, Squibb Laboratories, Shering Corporation and Warner-Chilcott Laboratories

Letemendia 1967

Methods	Allocation: matched (age, length of hospitalisation & severity) then assigned by toss of a coin. Blinding: double, "medication dispensed in uniform amber-coloured capsules". Design: cross-over. Duration: 9 months per arm of cross-over. Country: UK.
Participants	Diagnosis: schizophrenia (N=26 - criteria not specified), deluded (N=2), concurrent learning difficulties (N=2). History: > 5 yrs continuous hospitalisation, physically healthy. N=28. Sex: 28 M. Age: < 65 years. Setting: hospital.
Interventions	1. Chlorpromazine: dose 300 mg/day. N=14. 2. Placebo. N=14.
Outcomes	Leaving study early. Unable to use - Mental state & behaviour (authors' own scale - no SD).
Notes	2 people dropped out - unsure if before/after randomisation.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

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Letemendia 1967 (*Continued*)

Random sequence generation (selection bias)	Low risk	Groups matched according to age, length of hospital stay and severity, "The designation of the two groups was determined by tossing a coin"
Allocation concealment (selection bias)	Unclear risk	No information reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Double-blind" "Neither patients, doctors, nor nurses knew which patients were being given chlorpromazine and which placebo. All medication was dispensed in uniform amber-coloured capsules. Each patient was supplied from a separated bottle, replenished weekly according to the design by an independent party"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"Double-blind" no further details reported.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	"Of the 30 patients who initially fulfilled out conditions, one died from a cerebrovascular accident during the period of preliminary observations, and a second was eliminated because of slow phasic changes in mental state". Two losses to follow-up, but unclear is before or after randomisation
Selective reporting (reporting bias)	High risk	No SDs reported for mental state and behaviour scale
Other bias	Low risk	Supported by a grant from the Rockefeller foundation.

Nishikawa 1982

Methods	Allocation: randomly assigned - no further description. Blinding: double, drug appearance (colour, taste, volume) identical. Design: cross-over, data reported for first arm only. Duration: up to 3 years (or relapse, if sooner). Country: Japan.
Participants	Diagnosis: schizophrenia (criteria not specified). History: remitted illness, but > 1 relapses. N=55. Sex: 37 M, 18 F. Age: mean 33.3 yrs, SD 8.0.

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Nishikawa 1982 (*Continued*)

	Setting: outpatients department.
Interventions	1. Chlorpromazine: dose 75 mg/day. N=10. 2. Placebo. N=10. 3. Diazepam: dose 15 mg/day. N=13. 4. Imipramine: dose 50 mg/day. N=12. 5. Haloperidol: dose 3 mg/day. N=10. Medication given in fixed-dose regimen; nitrazepam 10 mg/day for insomnia as required; biperiden 3 mg/day for EPS as required
Outcomes	Relapse. Unable to use - Symptom-free days (survival data not supported by RevMan).
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Randomly assigned" no further information reported.
Allocation concealment (selection bias)	Unclear risk	No information reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Double-blind" "Drug appearance, with respect to powder colour, taste and volume, was made identical by adding a kind of stomachics
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"Double-bind" no further details reported.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	"Then nine patients were dropped from the study for various reasons. These reasons included: failure to report to the hospital for scheduled appointments (N=3); admissions to other hospitals (N=2); strong requests from the patient not to change the previous drugs (N=3); and a suicide after admission to the hospital (N=1)". Number of participants and reasons for leaving the study early not reported by groups
Selective reporting (reporting bias)	High risk	Not all expected outcomes reported.
Other bias	Unclear risk	Drugs provided by SMP (Sankyo, Japan).

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Payne 1960

Methods	Allocation: "double blind technique employed". Blinding: double blind. Duration: 6 weeks. Design: parallel. Country: Canada.
Participants	Diagnosis: schizophrenia. History: chronic, hospitalised for an average of 12.7 years. N=21. Sex: 21 M. Age: 23-73 (41.9 average). Setting: hospital.
Interventions	1. Chlorpromazine: dose 25 mg/tds increasing to 100 mg/tds. N=7. 2. Placebo. N=7. 3. Vesprin: dose 25 mg/tds increasing to 100 mg/tds . N=7.
Outcomes	Adverse effects. Unable to use - Categories of improved, much improved and unimproved (no usable data)
Notes	Withdrawals not described.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"The patients were divided into three groups of seven persons" no further details reported
Allocation concealment (selection bias)	Unclear risk	No information reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Double-blind" "All three types of tablet were exactly the same colour, size and shape. Each patient's medication was supplied to the wards in identical containers bearing the patient's name only. The physician and ward personnel were unaware of which patient was receiving which tablet; the latter being known only to the pharmacist and not divulged until the completion of the investigation"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"Double-blind" no further information reported.

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Payne 1960 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Did not report any losses to follow-up.
Selective reporting (reporting bias)	High risk	Results for categories of 'improved', 'much improved' and 'unimproved' not fully reported
Other bias	Unclear risk	Drugs supplied by ER Squibb and Sons of Canada, Limited. Source of funding not reported.

Peet 1981

Methods	Allocation: randomly assigned - no further description. Blinding: double, used 'capsules of identical external appearance'. Duration: 3 months. Design: parallel. Country: UK.
Participants	Diagnosis: schizophrenia (Feighner's criteria). History: unclear. 'with a diagnosis of chronic schizophrenia'. N=53. Sex: 40 M, 13 F. Age: mean 51.3 yrs. Setting: hospital. Exclusions: heart disease, asthma, liver disease, diabetes, alcoholism, drug abuse, other regularly prescribed psychotropic drugs
Interventions	1. Chlorpromazine: dose max. 400 mg/day. N=16. 2. Placebo: dose max. 8 capsules/day. N=18. 3. Propranolol: dose max. 640 mg/day. N=19. Medication given in discretionary dose regimen; diazepam used as required
Outcomes	Leaving study early. Relapse. Adverse effects. tremor, drowsiness. Unable to use - Mental state: BPRS (no mean, N, or SD). Behaviour: NOSIE (no mean, N, or SD).
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Randomly assigned" no further details reported.

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Peet 1981 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	No information reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Double-blind" "Capsules of identical appearance"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"Double-blind" no further details reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	6 patients left the study early from the propanolol and chlorpromazine groups, and 9 from the placebo group. Reasons for loss evenly distributes across groups
Selective reporting (reporting bias)	High risk	No means or SDs reported for IMPS, NOSIE and Discharge Readiness Inventory
Other bias	Unclear risk	Source of funding not reported.

Prien 1968

Methods	Allocation: randomly assigned - no further description. Blinding: double - no further description. Duration: 24 weeks (preceded by 8 weeks 'routine hospital medication') Design: parallel. Country: USA.
Participants	Diagnosis: schizophrenia (specified criteria). History: 'chronic'. N=838. Sex: male and female (proportions not given). Age: mean 41 yrs, range 19-55. Setting: hospital.
Interventions	1. Chlorpromazine: dose 2000 mg/day ("high dose"). N=208. (Permanent dose reduction to 1500 mg permitted to control side effects). 2. Chlorpromazine: dose 300 mg/day ("low dose"). N=208. 3. Placebo. N= 212. 4. 'Routine conventional hospital treatment'. N=210.
Outcomes	Leaving study early. Behaviour deterioration. Global improvement (own 7-point rating scale). Global severity of illness (own 7-point rating scale). Adverse effects. Relapse.

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Prien 1968 (*Continued*)

	Unable to use - Mental state: IMPS (no mean or SD). Behaviour: NOSIE (no mean or SD). Social function: Discharge Readiness Inventory (no mean or SD)
Notes	Blood problems reported from just one centre (N=58). Tardive dyskinesia side-effects- extracted from a sub-study by Crane (1968)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Randomly assigned" no further details reported.
Allocation concealment (selection bias)	Unclear risk	No information reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"Double-blind" no further details reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	"The placebo group had the highest percentage of dropout (38%), followed by the high dose group (25%), and the low dose group (15%). Terminations due to side effects were most frequent in the high dose group, while the placebo group had the highest incidence of dropouts due to deteriorated behavior." Losses to follow-up balanced across intervention groups, with similar reasons for missing data
Selective reporting (reporting bias)	High risk	No SD for IMPS, NOSIE, Discharge Readiness Inventory.
Other bias	Low risk	The study appears to be free of other sources of bias.

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Ramu 1999

Methods	Allocation: randomised. Blinding: double. Duration: 2 months. Design: parallel. Country: India.
Participants	Diagnosis: schizophrenia (in accordance with National Institute of Mental Health, Psychopharmacological service centre, collaborative study group) N=136. Age: 15-45 years. Sex: male and female. History: significant hospitalisation during previous 12 months. Acute episode of chronic schizophrenia. Exclusions: stuporous and exclusively withdrawn patients. Setting: outpatients.
Interventions	1. Chlorpromazine: dose 200 mg/day in month 1 and 300 mg/day in month 2. N=27*. 2. Placebo. N=27*. 3. Brahmadiyoga. N=27*. 4. Tagara. N=27*.
Outcomes	Global impression: no global improvement. Adverse effects. Unable to use - Psychotic rating scale (unclear whether a validated scale). Spiral after effect (not a validated scale).
Notes	*N randomised to each group not reported; N after losses to follow-up

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Randomly allocated" no further details reported.
Allocation concealment (selection bias)	Unclear risk	No information reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Double-blind" "The medicines and placebo were administered in the form of identical tablets"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"Double-blind" no further details reported.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	"Out of 136 patients 108 who have completed the treatment for a period of 2 months were taken for final assessment.

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Ramu 1999 (*Continued*)

		The remaining 28 were dropouts for reasons of escape and leaving without medical advice". Number randomised to each group not reported. Number lost from each group not reported
Selective reporting (reporting bias)	High risk	Not all expected outcomes reported. Unclear which rating scales are reported in the results tables
Other bias	Unclear risk	Source of funding not reported.

Ramu 1999a

Methods	Allocation: not stated. Blinding: double. Duration: 11 weeks. Design: parallel. Country: India.
Participants	Diagnosis: schizophrenia (WHO glossary of mental disorders) N=78. Age: average ~32 (SD 7) for chlorpromazine and placebo groups. Sex: M 30, F 35. History: Chronic schizophrenia between 2 and 6 years. Exclusions: not reported. Setting: not reported.
Interventions	1. Chlorpromazine: dose 300 mg/day up to day 30 and 450 mg/day up to day 75. N=22*. 2. Brahmyadiyoga: 12 g/day up to day 30 and 16 g/day up to day 75. N=23*. 3. Placebo. N=20*.
Outcomes	No global improvement. Behaviour: Fergus Falls rating scale**. Adverse effects: drowsiness**. Unable to use - Psychiatric symptoms rating scale (not a validated scale).
Notes	*N randomised to each group not reported; N after losses to follow-up. **N not reported, assumed to be the number reported in each group after losses to follow-up

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

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Ramu 1999a (*Continued*)

Random sequence generation (selection bias)	High risk	No information reported.
Allocation concealment (selection bias)	Unclear risk	No information reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"Double-blind" "Sugar coated uniform tablets of the trial drugs" no further details reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"Double-blind" no further details reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	"78 cases were taken for the study. Of them, 13 cases were dropped out for various reasons" N randomised to each group not reported. Reasons for losses and number of losses to follow-up per group not reported
Selective reporting (reporting bias)	High risk	N not reported for psychiatric rating scale. Total scores not reported for final assessment of psychiatric rating scale N reported for global improvement differs from N reported in each group
Other bias	Unclear risk	Drugs supplied by M/s Eros Pharma, Bangalore.

Rappaport 1978

Methods	Allocation: randomly assigned - no further description. Blinding: single, staff 'remained blind as to whether the patient was receiving medication or placebos'. Duration: unclear, mean hospitalisation=43 days, follow up at 1-36 months after discharge Design: parallel. Country: USA.
Participants	Diagnosis: schizophrenia (no specified criteria). History: 'acute' illness. N=127. Sex: 127 M. Age: range 16-40 yrs. Setting: hospital.
Interventions	1. Chlorpromazine: dose variable 300-900 mg/day. N=53. 2. Placebo.N=74.

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Rappaport 1978 (*Continued*)

Outcomes	Leaving study early. Relapse (rehospitalisation).
Notes	N's at allocation unbalanced - integrity of randomisation unclear. Unclear when outcomes recorded - assumed 'medium-term' in all cases (to reflect mode outcome period in review)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Assigned randomly" no further details reported.
Allocation concealment (selection bias)	Unclear risk	No information reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"physician [...] and the nursing staff remained blind as to whether the patient was receiving medication or placebos" no further details reported
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Ratings were made by a trained research assistant who was unaware as to what the patient's medication condition was while he was hospitalised"
Incomplete outcome data (attrition bias) All outcomes	High risk	"The 80 patients in this study represented 63% of the total sample (127) studied while in the hospital. It was noted that during the follow-up period, there was a significantly larger attrition of subjects from the group assigned to placebo while in the hospital than the group assigned to chlorpromazine (45% vs 26%)."
Selective reporting (reporting bias)	High risk	Unclear when outcomes recorded. Not all expected outcomes reported
Other bias	Low risk	Supported California Department of Mental Hygiene and the National Institute of Mental Health and from the Wickes Foundation and Esalen Institute

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Reardon 1966

Methods	Allocation: randomly assigned - no further description. Blinding: 'neither the ward personnel nor the investigator knew which drug the patient received'. Duration: min. 4 weeks, max. 12 weeks. Design: parallel. Country: USA.
Participants	Diagnosis: paranoid schizophrenia (Bleuler criteria). History: 'acute' illness. N=34. Sex: 22 M, 12 F. Age: not stated. Setting: hospital.
Interventions	1. Chlorpromazine: dose 300 mg/day (week 1), 600 mg/day thereafter. N=11. 2. Placebo: dose 2-4 cc/day (week 1), 5-10 cc/day thereafter. N=12. 3. Trifluoperazine: dose 20 mg/day (week 1), 40 mg/day thereafter. N=11 Medication given in fixed-dose regimen; artane: 10 mg/day given to all to reduce side effects
Outcomes	Leaving study early. Global improvement (lack of previously observed delusions and hallucinations) Unable to use - Mental state: MMPI (no means or SD).
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomly assigned" no further details reported.
Allocation concealment (selection bias)	Unclear risk	"Randomly assigned trifluoroperazine, chlorpromazine or placebo by the pharmacy" no further details reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"Neither the ward personnel nor the investigator knew which drug the patient received" no further details reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"Neither the ward personnel nor the investigator knew which drug the patient received" no further details reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	"Six patients had to be excluded from the investigation as they were given ECT. Of these subjects two were on trifluoroper-

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Reardon 1966 (*Continued*)

		azine, one on chlorpromazine and three were controls" "An additional three subjects, one from each group, had to be removed from the study because of transfer or home leave"
Selective reporting (reporting bias)	High risk	No means or SDs reported for the MMPI. Not all expected outcomes reported
Other bias	Unclear risk	Smith Kline and French provided drugs. Source of funding not reported.

Reschke 1974

Methods	Allocation: randomly assigned - no further description. Blinding: double - no further description. Duration: approximately 25 hours. Design: parallel. Country: not reported.
Participants	Diagnosis: schizophrenia (no specified criteria). History: severe agitation. N=50. Sex: 2 M, 48 F. Age: mean 35.9 yrs, range 19-57. Setting: hospital.
Interventions	1. Chlorpromazine: dose 25 mg IM. N=10. 2. Placebo. N=11. 3. Haloperidol: dose 5 mg IM. N=10. 4. Haloperidol: dose 2 mg IM. N=11. 5. Haloperidol: dose 1 mg IM. N=8. Max. of 4 injections administered at min. intervals of 30 minutes
Outcomes	Leaving study early. Global improvement (own 5-point rating scale). Adverse effects. Unable to use - Mental state: BPRS and own target symptoms scale (no mean or SD)
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Randomly assigned" no further details reported.

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Reschke 1974 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	No information reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"Double-blind" no further details reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"Double-blind" no further details reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were no losses to follow-up.
Selective reporting (reporting bias)	High risk	No means and SDs reported for BPRS.
Other bias	Unclear risk	Source of funding not reported.

Saretsky 1966

Methods	Allocation: randomly assigned - no further description. Blinding: double, 'two kinds of pills ... identical in size, shape, colour, and taste'. Duration: 3 months. Design: parallel. Country: USA.
Participants	Diagnosis: schizophrenic reaction (no criteria stated). History: newly admitted. N=40. Sex: 40 M. Age: < 55 yrs. Setting: hospital.
Interventions	1. Chlorpromazine: dose 400 mg/day. N=20. 2. Placebo (lactose): dose 4 pills/day. N=20. Medication given in fixed-dose regimen.
Outcomes	Leaving study early. Unable to use - Mental state: MSRPP (mean appears erroneous).
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

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Saretsky 1966 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	"Randomly assigned" no further details reported.
Allocation concealment (selection bias)	Unclear risk	No information reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The drugs were packaged in individual bottles with only the patient's name printed on them as a means of identification." "Throughout the experiment, whether the patient received the drug or a placebo was not known to anyone connected with the experiment." "The two kinds of pills were identical in size, shape, colour, and taste."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Throughout the experiment, whether the patient received the drug or a placebo was not known to anyone connected with the experiment."
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were no losses to follow-up.
Selective reporting (reporting bias)	High risk	Not all expected outcomes reported.
Other bias	Unclear risk	Source of funding not reported.

Schiele 1961

Methods	Allocation: randomly assigned - no further description. Blinding: double - no further description. Duration: 16 weeks. Design: parallel. Country: USA.
Participants	Diagnosis: schizophrenia (no criteria stated). History: all had been hospitalised for an average of 10 years. N=80. Sex: 80 M. Age: 40.6 years (average). Setting: hospital.
Interventions	1. Chlorpromazine: dose 200-1000 mg/day. N=20. 2. Placebo: N=20. 3. Thioridazine: dose 200-1000 mg/day. N=20. 4. Trifluoperazine: dose 10-50 mg/day. N=20.

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Schiele 1961 (*Continued*)

Outcomes	Leaving the study early. Mental state. MMPI. Global estimate of clinical change - via ward staff. Adverse effects. Unable to use - Behaviour: MBS (no SD).
Notes	Withdrawals described.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Randomly assigned" no further details reported.
Allocation concealment (selection bias)	Unclear risk	No information reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"During the first 16 weeks, the study was carried out under strict double-blind conditions. Each patient had his individual bottle of medication; the capsules were identical in appearance, and only the hospital pharmacist had the code for determining which patient was receiving each kind of medication"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"Double-blind" no further details reported.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	"Only 2 patients were dropped [...] because their psychiatric condition became and remained worse." "During the thirteenth week. a third patient who was in the trifluoperazine group eloped from the hospital." Only 43 participants took the MMPI three times
Selective reporting (reporting bias)	High risk	No SD reported for the MBS.
Other bias	Unclear risk	Source of funding not reported.

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Serafetinides 1972

Methods	Allocation: randomly assigned - no further description. Blinding: double, used 'identically appearing capsules'. Duration: 12 weeks (preceded by 12 week dry-out period). Design: parallel. Country: USA.
Participants	Diagnosis: schizophrenia (criteria not specified). History: > 2 yrs ill. N=57*. Sex: 25 M, 32 F. Age: range 21-61 yrs. Setting: hospital.
Interventions	1. Chlorpromazine: dose max. 1000 mg/day. N=14. 2. Placebo: dose max. 10 capsules/day. N=13. 3. Haloperidol: dose max. 15 mg/day. N=14. 4. Clopenthixol: dose max. 250 mg/day. N=15. Medication given in variable dose regimen' medication for EPS or insomnia as required
Outcomes	Leaving study early. Global improvement. CGI. Adverse effects. Liver function. Unable to use - Global improvement: CGI (discrepancy with group totals). Mental state: BPRS, Venables-O'Conner scale (no SD). Behaviour: NOSIE, OBRS (no SD). Psychological function: test battery (no data).
Notes	*One participant not accounted for.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Randomly assigned" no further details reported.
Allocation concealment (selection bias)	Unclear risk	No information reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"All medications were prepared in identically appearing capsules" no further details reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information reported.

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Serafetinides 1972 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	"Four of the 57 subjects, three on CPZ, and one on PL,failed to complete the 12 weeks of study. The PL subject and one CPZ subject were terminated because of behavioural deterioration after 4 and 8 weeks respectively. The other two CPZ subjects developed intestinal obstruction secondary to massive fecal impactions and were terminated in the 7th week of study."
Selective reporting (reporting bias)	High risk	No SDs were reported for the CGI, NOSIE and the OBPRS. No data was reported for the psychological function tests.
Other bias	Low risk	Supported in part by a US Public Health Service Grant.

Shepherd 1956

Methods	Allocation: randomly assigned - no further description. Blinding: unclear, medication identical and 'nobody but ... doctor and ... dispenser [knew who was] receiving drugs [or] placebo'. Design: cross-over (Latin square, slightly modified) - data extracted for first arm only. Duration: 6 weeks (each individual arm). Country: UK.
Participants	Diagnosis: schizophrenia (apathetic and deteriorated). History: duration of hospitalisation, mean 15.8 yrs, range 7-29. N=24. Sex: 24 F. Age: mean 40 yrs, range 27-52. Setting: hospital.
Interventions	1. Chlorpromazine: dose 300 mg/day. N=8. 2. Placebo. N=8. [see notes]. 3. Reserpine: dose 15 mg (reduced to) 10 mg/day. N=8. [see notes] Medication given in fixed-dose regimen.
Outcomes	Improvement. Leaving study early. Unable to use - Adverse effects (not reported for individual arm of cross-over)
Notes	Before first cross-over reserpine group inadvertently given 0.75 mg/day (not 15 mg/day) . This group therefore regarded as placebo group by trialists and reviewers (hence N for placebo=16)

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Shepherd 1956 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	The 24 patients were divided into three groups of eight (A,B, and C) by random selection" no further details reported
Allocation concealment (selection bias)	Unclear risk	No information reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Two kinds of inert substances were employed, one indistinguishable from reserpine, the other from chlorpromazine. Nobody but the ward doctor allocating the drugs and the dispenser knew which patients were receiving drugs and which patients were on placebo"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Weekly clinical assessments were carried out by one of us (DCW) who was unaware of the nature of individual prescriptions"
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were no losses to follow-up.
Selective reporting (reporting bias)	High risk	Adverse effects were not reported for each individual arm.
Other bias	Unclear risk	Messrs Ciba supplied serpasil and dummy tablets, Messrs May and Baker supplied dummy tablets

Simon 1958

Methods	Allocation: by list of random numbers. Blinding: unclear. Duration: 30 days. Design: parallel. Country: USA.
Participants	Diagnosis: schizophrenia (78), schizoaffective (2). History: treatment naive, duration treated ~33 days. N=80 Sex: not reported. Age: mean ~31 years. IQ: mean ~ 103. Setting: hospital.

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Simon 1958 (*Continued*)

Interventions	1. Chlorpromazine: dose mean 400 mg/day, range 200-1200 mg/day. N=20. 2. Reserpine: dose mean mg/day, range 2-mg/day. N=20. 3. Clinical judgement: any treatment - could include chlorpromazine. N=20. 4. Hospital routine: admission but no specific treatment, no drugs. N=20
Outcomes	Leaving the study early. Unable to use - Personality profile: MMPI (no means, no SD). Social functioning: Scale of Occupational Adjustment (no data reported)
Notes	Withdrawals described.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Assigned to one of 4 treatment groups on a random basis [...] the staff was kept ignorant of the order within the random list"
Allocation concealment (selection bias)	Unclear risk	No information reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were no losses to follow-up.
Selective reporting (reporting bias)	High risk	Means and SDs were not reported for the MMPI. No data was reported for the Scale of Occupational Adjustment
Other bias	Unclear risk	Source of funding not reported.

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Smith 1961

Methods	Allocation: divided into 3 matched groups on the basis of age, illness duration and symptom. Blinding: double. Duration: 14 weeks. Design: parallel. Country: not reported.
Participants	Diagnosis: schizophrenia. History: chronic. N=41. Sex: male and female. Age: 42.21 years (average). Setting: research unit.
Interventions	1. Chlorpromazine: dose 150-600 mg/day. N=13. 2. Placebo. N=15. 3. Chlordiazepoxide: dose 150-700 mg/day. N=13.
Outcomes	Behaviour rating scale. Unable to use- Leaving the study early (no usable data).
Notes	Withdrawals described but unclear.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The 45 patients were divided into three matched groups on the basis of age, illness duration and predominant symptomatology" no further details reported
Allocation concealment (selection bias)	Unclear risk	No information reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The medication used during the study was prepared in identical capsules" "Neither the patients nor the attending physicians knew what medication was being given. An identifying code was available but not broken until the end of the study."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"Neither the patients nor the attending physicians knew what medication was being given." no further details reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Two participants lost to follow-up in the chlorpromazine group and two in the clordiazepoxide group, reasons for leaving the

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Smith 1961 (*Continued*)

		study early not reported. Unclear whether there were any losses in the placebo group
Selective reporting (reporting bias)	Low risk	All expected outcomes reported.
Other bias	Unclear risk	Source of funding not reported.

Somerville 1960

Methods	Allocation: matched on symptoms, age, and duration of illness, then allocated 'by random choice' - no further description. Blinding: 'the two placebos were identical in appearance with the respective active tablets'. Duration: 6 weeks. Design: parallel. Country: Australia.
Participants	Diagnosis: schizophrenia or 'paraphrenic psychoses' (N=56); manic depression (N=4). History: duration of illness, mean 9.5 yrs, range 0.4-29. N=60. Sex: 60 F. Age: mean 41 yrs, range 24-58. Setting: hospital.
Interventions	1. Chlorpromazine: dose 200-800 mg/day. N=15. 2. Placebo. N=30. 3. Thioridazine: dose 200-800 mg/day. N=15.
Outcomes	Leaving study early. Clinical improvement (own 5-point rating scale). Behaviour. Fergus Falls Rating Scale. Adverse effects.
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Random choice" matched on symptoms, age, and duration of illness, no further details reported
Allocation concealment (selection bias)	Unclear risk	"A doctor who had no duties connected with the ward concerned allotted each of the groups to a particular therapy" no further details reported

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Somerville 1960 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The two placebos were identical in appearance with the respective active tablets."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were no losses to follow-up.
Selective reporting (reporting bias)	Low risk	All expected outcomes reported.
Other bias	Unclear risk	Sandoz Australia Proprietary Limited and May & Baker (Australia) Proprietary Limited supplied drugs Source of funding not reported.

Spohn 1977

Methods	Allocation: randomly assigned - no further description. Blinding: double, used 'chlorpromazine facsimile" placebo. Duration: "at least six weeks" (preceded by abrupt medication withdrawal & 6 week washout) Design: parallel. Country: USA.
Participants	Diagnosis: chronic schizophrenia ('official hospital diagnosis'). N=40. Sex: 28 M, 12 F. Age: range 18-55 yrs. Setting: hospital.
Interventions	1. Chlorpromazine: dose discretionary min. 200 mg/day. N=20. 2. Placebo. N=20. Antiparkinsonian medication for EPS as required; chloral hydrate for insomnia as required
Outcomes	Relapse. Unable to use - Global severity of illness: Global Severity Scale (no means or SD). Global improvement: Global Improvement Scale (no means or SD). Behaviour: Ward Behavior Rating Scale (no means or SD).
Notes	
Risk of bias	

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Spohn 1977 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Random assignment" no further details reported.
Allocation concealment (selection bias)	Unclear risk	No information reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"During the drug treatment period, patients, project personnel, and hospital personnel were "blind" to the patients' drug status" no further details reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"During the drug treatment period, patients, project personnel, and hospital personnel were "blind" to the patients' drug status" no further details reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Losses to follow-up not reported.
Selective reporting (reporting bias)	High risk	Means and SDs were not reported for the Global Severity Scale, Global improvement Scale and the Ward Behaviour Rating Scale
Other bias	Unclear risk	Supported by a Public Health Service research grant and a research scientist award from the National Institute of Mental Health and by the Ittleson Family Foundation Chlorpromazine supplied by Smith Kline and French Laboratories

Tetreault 1969

Methods	Allocation: randomly assigned - according to a 'random number table'. Blinding: double, identical capsules. Duration: 12 weeks (preceded by 19-day wash-out). Design: parallel. Country: Canada.
Participants	Diagnosis: schizophrenia (no specified criteria). History: 'chronic', mean duration of hospitalisation 16.3 yrs. N=45. Sex:45 F. Age: mean 50.5 yrs. Setting: hospital.

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Tetreault 1969 (*Continued*)

Interventions	1. Chlorpromazine: dose 300 mg increasing to 600 mg/day. N=15. 2. Placebo: dose 3 capsules increasing to 6 capsules/day. N=15. 3. TPS-23 (Mesoridazine): dose 150 mg increasing to 300 mg/day. N=15 Chlorpromazine (50 mg im), chloral hydrate (650 mg), ethchlorvynol (500 mg), procyclidine (5 mg IM) as required 'in case of emergency'
Outcomes	Leaving study early. Mental state. BPRS. Behaviour. Modified Rosenthal Rating Scale. Extrapyramidal adverse effects. Adverse effects.
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Patients received one of the tested drugs according to a random number table"
Allocation concealment (selection bias)	Unclear risk	No information reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"TPS-23 (50mg, chlorpromazine (100 mg) and placebo presented in identical white capsules; they were distributed on the ward in containers on which only the patient's name appeared. The double-blind technique was followed throughout the experiment"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"Double-blind" no further details reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were no losses to follow-up.
Selective reporting (reporting bias)	Low risk	All expected outcomes reported.
Other bias	High risk	Partly supported by a grant-in-aid from Sandoz (Canada) Ltd. who supplied the drugs

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Vaughan 1955

Methods	Allocation: randomly assigned - no further description. Blinding: 'the hospital pharmacist alone knowing which patients were receiving CPZ and which the placebo'. Duration: not specified. Design: parallel. Country: UK.
Participants	Diagnosis: not specified; all participants had motor restlessness, psychomotor agitation, and excitement, were 'chronic and intractable', and had a poor prognosis. History: mean duration of hospitalisation 9.6 yrs. N=48. Sex: 48 F. Age: mean 43 yrs. Setting: hospital.
Interventions	1. Chlorpromazine: dose variable 75-450 mg/day. N=24. 2. Placebo. N=24.
Outcomes	Global improvement.
Notes	Reviewers assume short-term outcome - in keeping with other studies of that period

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"By random selection" no further details reported.
Allocation concealment (selection bias)	Unclear risk	No information reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"The hospital pharmacist alone knowing which patients were receiving chlorpromazine and which the placebo" no further details reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"The hospital pharmacist alone knowing which patients were receiving chlorpromazine and which the placebo" no further details reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Losses to follow-up not reported.
Selective reporting (reporting bias)	High risk	Not all expected outcomes reported.
Other bias	Unclear risk	Messrs May & Baker supplied the placebo tablets. Source of funding not reported.

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Walsh 1959

Methods	Allocation: randomly assigned - 'allocation of a preparation to a group was purely arbitrary' - matched on age, hospitalisation, adjustment, psychotic behaviour, and activity/withdrawal. Blinding: unclear, no. & size of placebo tablets altered when active preparations altered. Duration: 8 weeks. Design: parallel. Country: not reported
Participants	Diagnosis: schizophrenia (no specified criteria). History: 'chronic', mean duration of hospitalisation 13 yrs, range 1-28. N=66. Sex: 66 F. Age: mean 40 yrs, range 27-50. Setting: hospital.
Interventions	1. Chlorpromazine: dose 75 mg/day increasing to 300 mg/day. N=22. 2. Placebo. N=22. 3. Trifluprom azine: dose 75 mg/day increasing to 300 mg/day. N=22
Outcomes	Clinical improvement (4-point rating scale). Adverse effects. Unable to use - Mental state: Rowell 'Psychoticism' Rating Scale (no SD). Behaviour: Venables Activity-Withdrawal Rating Scale (no SD)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Allocation of a preparation to a group was purely arbitrary", participants matched on age, hospitalisation, adjustment, psychotic behaviour, and activity/withdrawal. No further details reported
Allocation concealment (selection bias)	Unclear risk	No information reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	As this involved periodic changes in the number and/or size of the tablets, the number and/or size of the tablets given to the placebo group was altered simultaneously. Neither the doctor nor the ward staff were aware of the nature of the preparation being given to a particular patient. A separate bottle was assigned to each patient and in this supplies of the specific preparation

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Walsh 1959 (*Continued*)

		were issued at weekly intervals"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"Neither the doctor nor the ward staff were aware of the nature of the preparation being given to a particular patient" no further details reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were no losses to follow-up.
Selective reporting (reporting bias)	High risk	No SDs were reported for Rowell 'Psychoticism' Rating Scale and the Venables Activity-Withdrawal Rating Scale
Other bias	Unclear risk	ER Squibb and Sons Ltd, London provided drugs. Source of funding not reported.

Weckowicz 1960

Methods	Allocation: not stated. Blinding: double blind. Duration: 8 weeks. Design: parallel. Country: Canada.
Participants	Diagnosis: schizophrenia (criteria not reported). N=48 Age: average was 48 to 51 in each group. Sex: F 48. History: Disturbed chronic schizophrenic patients. Exclusions: not reported. Setting: hospital.
Interventions	1. Chlorpromazine: dose 50 mg/day for 2 days, 100 mg/day for 3 days and 150 mg/day for the remaining 28 days. N=16. 2. Placebo. N=16. 3. RO5-0690. dose 50mg/day for 2 days, 100 mg/day for 3 days and 150 mg/day for the remaining 28 days. N=16
Outcomes	Global impression: no global improvement (rated by nurse). Adverse effects. Unable to use - Weyburn Assessment Scale (no SDs reported).
Notes	

Risk of bias

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Weckowicz 1960 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	"On the basis of rating they were divided into three matched groups" no further details reported
Allocation concealment (selection bias)	Unclear risk	No information reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Double-blind" "The patients in the three groups received respectively from bottles marked "A", "B" and "C" 50mg tablets which looked exactly the same"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"Double-blind" no further details reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	For the outcome global impression "the number [of participants] is less than 16 in the groups, because some patients refused to take their medication"
Selective reporting (reporting bias)	High risk	N and SD not reported for the Weyburn assessment scale.
Other bias	Low risk	Funded by the Rockefeller Foundation and the Federal Fund.

Xiong 1994

Methods	Allocation: randomly divided. Blinding: double. Duration: 9 weeks. Design: parallel. Country: China.
Participants	Diagnosis: chronic schizophrenia (DSM III-R). History: not reported. N=48*. Sex: all male. Age: range 27-46, mean 35 years. Setting: hospital.
Interventions	1. Chlorpromazine: dose mean 295 mg/day. N=12. 2. Placebo. N=12. 3. Chlorpromazine: dose mean 143.5 mg/day + Phenytoin ~ 155 mg/day. N=12. 4. Phenytoin: dose mean 327 mg/day. N=12.

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Xiong 1994 (*Continued*)

Outcomes	Leaving the study early. Unable to use - Mental state: BPRS, SANS (no data for placebo arm). Adverse effects (no data for the placebo arm).	
Notes	*Only data from groups 1 and 2 used.	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomly divided.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double blind.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Double blind.
Incomplete outcome data (attrition bias) All outcomes	High risk	Drop outs are unaccounted for in the final analysis.
Selective reporting (reporting bias)	Low risk	All measured outcomes were reported.
Other bias	Low risk	None obvious.

General Abbreviations
CPZ - Chlorpromazine
ECT - electroconvulsive therapy
EPS - extrapyramidal symptoms
HCL - hydrochloride
ITT - Intention-to-treat
IM - intra muscular injection
max - maximum
min - minimum
SD - standard deviation
SE - standard error
tds - three times daily
yrs - years
Rating scales
Behaviour -
OBRS - Oklahoma Behaviour Rating Scale

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PBRS - Parkside Behaviour Rating Scale
RRS - Rosenthal Rating Scale
Global impression -
CGI - Clinical Global Impression
Mental state -
BPRS - Brief Psychiatric Rating Scale
IMPS - Inpatient Multidimensional Psychiatric Rating Scale
MMPI - Minnesota Multiphasic Personality Inventory
MSRPP -Multidimensional Scale for Rating Psychiatric Patient
NOSIE - Nurses Observation Scale for Inpatient Evaluation
PRS - Psychiatric Rating Scale
Adverse effects -
SAS - Simpson-Angus Scale
TESS - Treatment Emergent Symptoms Scale

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

Study	Reason for exclusion
Abse 1960	Study 1 Allocation: randomised. Participants: people with schizophrenia. Interventions: reserpine versus powdered opium versus placebo Study 2 Allocation: randomised. Participants: people with schizophrenia. Interventions: chlorpromazine versus powdered opium versus placebo Results of two studies are added and placebo groups are reported as one
Acker 1965	Allocation: unclear, not described. Participants: people with schizophrenia. Interventions: chlorpromazine or thioridazine versus placebo. Outcomes: not reported for individual drugs.
Affleck 1966	Allocation: 'balanced order' - unclear if randomised, cross-over. Participants: any patient with anxiety as a major symptom - unclear if schizophrenia. Interventions: chlorpromazine + high expectations of effect versus chlorpromazine + low expectations of effect versus placebo + high expectations of effect versus placebo + low expectations of effect. Outcomes: no usable data before the first cross-over.
Agarwal 1985	Allocation: randomised. Participants: people with schizophrenia. Interventions; modified ECT versus simulated ECT, used chlorpromazine in the early stages of the study
Akimoto 1966	Allocation: unclear, "double-blind placebo method". Participants: people with schizophrenia. Interventions: chlorpromazine, placebo, levomepromazine, prochlorperazine.

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	Outcomes: behaviour, mental state - no outcomes for the chlorpromazine versus placebo comparison
Alpert 1966	Allocation: randomised. Participants: people with schizophrenia. Interventions: chlorpromazine versus placebo. Outcomes: no data presented by group of allocation, report focused on use of taped recordings to measure outcomes
Alpert 1978	Allocation: randomised. Participants: people with schizophrenia. Interventions: chlorpromazine versus L-dopa, no placebo.
Alson 1964	Allocation: not randomised, hospitalised patients switched from chlorpromazine to placebo
Aman 1985	Allocation: randomised. Participants: severely and profoundly retarded adolescents and adults
Amin 1977	Allocation: randomised. Participants: people with schizophrenia. Interventions: chlorpromazine versus benzquinamide versus benzquinamide and group therapy, no placebo group
Ananth 1972	Allocation: randomised. Participants: people with schizophrenia. Interventions: nicotinic acid, nicotinamide and placebo.
Andrews 1976	Allocation: randomised. Participants: people with schizophrenia, stabilised on chlorpromazine. Interventions: continuing chlorpromazine versus chlorpromazine withdrawal
Ashcroft 1961	Allocation: not randomised. Participants: people with schizophrenia. Interventions: chlorpromazine, tetrabenazine and placebo.
Ayers 1984	Allocation: not randomised, case series.
Azima 1954	Allocation: not randomised, case series.
Bagadia 1981	Allocation: randomised. Participants: people with schizophrenia. Interventions: chlorpromazine and simulated ECT versus placebo and ECT
Ban 1977	Allocation: unclear, 'double-blind study'. Participants: people with chronic schizophrenia. Interventions: chlorpromazine and placebo versus chlorpromazine and megavitamins
Beech 1990	Allocation: unclear, 'double-blind, cross-over study'. Participants: healthy volunteers.

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Benaim 1960	Allocation: not described. Participants: people with schizophrenia. Interventions: insulin versus insulin with chlorpromazine versus insulin with chlorpromazine and phenytoin
Bennett 1956	Allocation: alternate allocation. Participants: people with schizophrenia and other diagnoses. Interventions: chlorpromazine versus reserpine.
Blumberg 1964	Allocation: 'random assignment'. Participants: people with non chronic mental disorder, majority with schizophrenia. Interventions: chlorpromazine with procyclidine, imipramine and placebo. Outcomes: blood pressure data were not supported with SD's.
Blumberg 1969	Allocation: randomised. Participants: voluntary co-operative psychiatric patients on an open ward, not schizophrenia
Boullin 1975	Allocation: not randomised, case control study.
Bowes 1956	Allocation: quasi-randomised. Participants: people with schizophrenia. Interventions: frenkel versus placebo, not chlorpromazine.
Bressler 1971	Allocation: randomised. Participants: people with schizophrenia. Interventions: chlorpromazine versus thiothixene.
Brizer 1985	Allocation: randomised. Participants: people with treatment-resistant schizophrenia. Interventions: placebo versus methadone, chlorpromazine equivalents calculated
Burnett 1975	Allocation: randomised, cross-over design. Participants: people with schizophrenia. Interventions: chlorpromazine versus thiothixene, placebo used for washout only
Cabrera Gomez 1994	Allocation: randomised. Participants: people with schizophrenia. Interventions: recombinant alpha-interferon versus placebo, chlorpromazine used as needed but not randomised
Caffey 1963	Allocation: randomised. Participants: people with chronic schizophrenia. Interventions: chlorpromazine or thioridazine (maintenance dose) versus chlorpromazine or thioridazine (3/7 of dose) versus placebo, withdrawal study. Outcomes: data not reported for individual drug.
Caffey 1975	Allocation: not randomised, non-systematic review of other studies (confirmed by Russian translator)

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Campbell 1972	Allocation: non-randomised double-blind, cross-over trial.
Cardone 1969	Allocation: unclear, 'one group was given ...'. Participants: people with chronic schizophrenia. Interventions: chlorpromazine versus placebo versus nothing. Outcomes: psychological tests of body image, no clinical data
Carrillo 1971	Allocation: randomised. Participants: 'emotionally unstable character disorder', not schizophrenia
Casey 1960	Allocation: randomised. Participants: people with schizophrenia. Interventions: chlorpromazine versus promazine versus phenobarbital versus placebo. Outcomes: numbers allocated to each group not reported. US veterans association contacted for archived data - none available
Casey 1961	Allocation: randomised. Participants: people with chronic schizophrenia. Interventions: d-amphetamine versus isocarboxazid versus imipramine versus trifluoperazine versus placebo, chlorpromazine given to everyone
Chacon 1972	Allocation: 'randomly selected'. Participants: people with schizophrenia. Interventions: chlorpromazine, fluphenazine decanoate and placebo for 'washout'
Childers 1961	Allocation: not randomised - 'assigned sequentially as they were admitted'. Participants: people with schizophrenia. Interventions: chlorpromazine versus trifluoperazine versus placebo versus nothing
Chouinard 1977	Allocation: randomised. Participants: people with schizophrenia. Interventions: chlorpromazine and penfluridol -placebo used for washout period
Chouinard-G 1983	Allocation: 'randomly assigned'. Participants: people with schizophrenia. Interventions: chlorpromazine, fluspirilene and placebo. Outcomes: data not related to placebo.
Claghorn 1983	Allocation: randomised. Participants: people with schizophrenia. Interventions: chlorpromazine versus clozapine, placebo used for washout period only
Clark 1970c	Allocation: unclear. Participants: unclear. Interventions: chlorpromazine versus placebo versus a 'thioxanthene and a butyrophenone'. Outcomes: no data reported.

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Clark 1970d	Allocation: randomised. Participants: people with schizophrenia. Interventions: chlorpromazine versus placebo. Outcomes: body weight, serum cholesterol - no usable data (study 5 in cited report.)
Clark 1975	Allocation: randomised. Participants: people with schizophrenia. Interventions: chlorpromazine versus placebo. Outcomes: numbers allocated to each group not reported.
Cobb 1956	Allocation: not randomised.
Cole 1967	Allocation: 'randomly assigned to one of the three drug treatments' Participants: people with schizophrenia. Interventions: chlorpromazine, fluphenazine and acetophenazine
Coons 1962	Allocation: 'randomly assigned'. Participants: "long term mental hospital patients". Interventions: chlorpromazine, trifluoperazine and placebo. Outcomes: no SD's used.
Cowden 1956	Allocation: participants assigned on basis of behavioural rating scale and average hospitalisation of different groups - not random
Crane 1970	Allocation: randomised. Participants: people with chronic mental illness and tardive dyskinesia. Interventions: trifluoperazine and placebo.
Crane 1971	Allocation: not randomised, review.
Crow 1986	Allocation: randomised. Participants: people with non-affective psychosis. Interventions: continuing drug (chlorpromazine or fluphenazine or haloperidol or pimozide or trifluoperazine) versus placebo (drug withdrawal). Results not broken down by individual drug, and withdrawal study
Curry 1972	Allocation: randomised. Participants: people with schizophrenia. Interventions: chlorpromazine versus fluphenazine decanoate; placebo used for blinding purposes only ('double-dummy')
Cutler 1957	Allocation: 'divided into three groups' Participants: people with schizophrenia. Interventions: reserpine and placebo.
Dally 1966	Allocation: not described. Participants: people with anorexia nervosa.

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Danion 1992	Allocation: randomised. Participants: healthy volunteers.
Daston 1958	Allocation: not randomised, 'stylus maze performance test'.
Daston 1959	Allocation: unclear, 'double blind, cross-over trial'. Participants: people with schizophrenia. Interventions: chlorpromazine versus promazine versus phenobarbital versus placebo. Outcomes: psychological tests, no clinical outcomes, no dropout data
Davies 1973	Allocation: unclear, 'patients were divided into groups' - likely non-random. Participants: people with schizophrenia. Interventions: chlorpromazine versus placebo. Outcomes: no data presented.
Dean 1967	Allocation: randomised. Participants: 50 people with prophyria variegata, not schizophrenia
Den Boer 2000	Allocation: randomly assigned. Participants: people with schizophrenia. Interventions: ritanserin and placebo.
Denber 1955	Allocation: "selected at random". Participants: people with schizophrenia. Interventions: mescaline sulphate and chlorpromazine hydrochloride
Denber 1956	Allocation: not randomised, case study.
Denber 1957	Allocation: quasi-random, 'assigned in rotation' during consecutive admissions
Desager 1988	Allocation: double blind Latin-square design. Participants: healthy volunteers, not people with schizophrenia
Douglas 1969	Allocation: 'double blind'. Participants: 64 people with functional psychiatric disability. Interventions: chlorpromazine versus mesoridazine, not placebo
Downing 1963	Allocation: 'randomly assigned'. Participants: people with schizophrenia. Interventions: chlorpromazine, fluphenazine and thioridazine. Outcomes: no SD's used.
Dube 1981	Allocation: 'randomly administered'. Participants: people with schizophrenia. Interventions: lithium, chlorpromazine and placebo washout.

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Eitan 1991	Allocation: 'were assigned' - no further description. Participants: people with schizophrenia. Interventions: chlorpromazine versus thioridazine versus trifluoperazine versus placebo. Outcomes: cognitive function not reported for individual arms of cross-over
Ekdawi 1966	Allocation: randomised. Participants: people with chronic schizophrenia. Interventions: methixene hydrochloride versus orphenadrine versus procyclidine, all on antipsychotics including chlorpromazine
Elkes 1954	Allocation: unclear if randomised - 'double blind, cross-over trial'. Participants: chronically over-active psychotic people. Interventions: chlorpromazine versus placebo. Outcomes: first arm of cross-over not reported.
Feldman 1956	Allocation: 'a staff psychiatrist (not involved in the project) who cross-matched the patients into two similar groups' - not randomised
Fink 1958	Allocation: randomised. Participants: people with schizophrenia. Interventions: chlorpromazine versus insulin coma therapy, no placebo group
Fink 1965	Allocation: "randomly assigned". Participants: "classified as affective disorder". Interventions: chlorpromazine with procyclidine, imipramine and placebo. Outcomes: no usable data.
Fleischhacker 1995	Allocation: not randomised. Participants: not described. Interventions: seroquel, chlorpromazine and placebo. Outcomes: no usable data.
Fleming 1958	Allocation: randomised, cross-over design. Participants: people with schizophrenia and manic-depressive illness. Interventions: chlorpromazine versus B.W.203 versus placebo. Outcomes: data not reported for individual arms of cross-over
Foote 1958	Allocation: randomised. Participants: people with schizophrenia. Interventions: chlorpromazine-reserpine combination versus placebo
Forrest 1967	Allocation: randomised. Participants: healthy volunteers.
Freed 1956	Allocation: not randomised. Participants: "primary behaviour disorders, psychoneurotic, schizophrenic, reactive behaviour disorders". Interventions: chlorpromazine.

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(*Continued*)

Freedman 1965	Allocation: randomised. Participants: people with schizophrenia. Interventions: chlorpromazine, promazine and placebo. Outcomes: no usable data.
Freeman 1956	Allocation: 'divided into two groups matched primarily on the basis of their rating scores and, secondarily, on the basis of age, duration of hospitalisation, and years since lobotomy' - not randomised
Freeman 1973	Allocation: "randomly assigned". Participants: people with schizophrenia. Interventions: mesoridazine, chlorpromazine and placebo. Outcomes: chlorpromazine data not evaluated against placebo.
Friedhoff 1960	Allocation: '"divided into two sub-groups by alternation of patients"
Fromm 1956	Allocation: 'Dr Forsberg matched the patients and decided whether they were to receive chlorpromazine or placebo' - not randomised
Gaitz 1955	Allocation: "assigned randomly to 3 groups". Participants: "actively psychotic having a schizophrenic reaction". Interventions: group A was an artificial hibernation group, group B received chlorpromazine and group C receiving their usual treatment without chlorpromazine
Galbrecht 1968	Allocation: randomised. Participants: people with schizophrenia. Interventions: chlorpromazine versus fluphenazine versus thioridazine, no placebo
Galdi 1988	Allocation: randomised. Participants: people with schizophrenia. Interventions: chlorpromazine versus fluphenazine versus perphenazine, no placebo
Gallant 1963	Allocation: randomised - "divided at random" - no further details. Participants: people with chronic schizophrenia. Interventions: chlorpromazine versus methysergide (UML-491) versus placebo. Outcomes: no usable data as number in each group unspecified
Gallant 1967	Allocation: randomised. Participants: people with schizophrenia. Interventions: chlorpromazine + placebo versus chlorpromazine + BL-KR140
Gardner 1955	Allocation: no evidence of randomisation.
Gardos 1968	Allocation: divided into two groups- 'withdrawn' and 'agitated'. Participants: "psychotic". Interventions: trifluoperazine, chlorpromazine, (placebo used for 'wash out')
Gardos 1976	Allocation: not randomised, review article of other trials performing withdrawal studies

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Garfield 1962	Allocation: random assignment. Participants: "adjustment reaction of childhood (n=6), psychoneurotic disorder (n=5), schizophrenic reaction childhood type (n=5), personality trait disturbance (n=2), chronic brain disturbance with psychosis (n=1). Interventions: chlorpromazine versus placebo. Outcomes: no usable data.
Garmezy 1969	Allocation: "randomly assigned". Participants: people with schizophrenia. Interventions: chlorpromazine and placebo. Outcomes: no usable data (no SD).
Gauthier 1967	Allocation: random numbers table used. Participants: not described from french translation. Interventions: trifluperidol versus trifluoperazine.
Gendron 1973	Allocation: "randomly assigned". Participants: people with schizophrenia. Interventions: chlorpromazine and Al-1021
Gibbs 1956	Allocation: 'assigned by an unbiased, alternating method' and 'assigned to one of the three treatment groups on an alternating basis as they entered the study' - not randomised. Participants: heterogeneous diagnoses, "27 were diagnosed psychoneurotic and the remaining 12 psychotic"
Gilgash 1957	Allocation: unclear, 'two groups .... matched on the basis of admission diagnosis, age, sex and IQ'. Participants: patients with catatonic schizophrenia. Interventions: chlorpromazine versus placebo. Outcomes: cognitive function; no clinical measures.
Goldberg 1968	Allocation: "random assignment". Participants: people with schizophrenia, based on two separate hospital studies. Interventions: Acetophenazine, chlorpromazine, thioridazine fluphenazine and placebo. Outcomes: data based on prediction equations and are unusable
Goldberg 1970	Allocation: "allocated at random to a group". Participants: people with schizophrenia. Interventions: oxypertine and chlorpromazine with 3-week washout with placebo
Goldberg 1972	Allocation: randomised. Participants: people with schizophrenia. Interventions: chlorpromazine versus acetophenazine versus placebo. Outcomes: no usable data - unclear how many allocated to each group
Goldman 1955	Allocation: not randomised, review.
Good 1958	Allocation: randomised. Participants: people with schizophrenia stabilised on chlorpromazine.

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(*Continued*)

	Interventions: continued chlorpromazine versus placebo, withdrawal study
Goodwin-Austin 1971	Allocation: randomised. Participants: people with dementia and movement disorders, not schizophrenia
Goyne 1958	Allocation: not described. Participants: people with schizophrenia. Interventions: vesperin versus chlorpromazine.
Graupner 1972	Allocation: randomised. Participants: healthy volunteers.
Green 1996	Allocation: balanced Latin-square randomisation. Participants: healthy volunteers.
Green 1998	Allocation: not described. Participants: healthy volunteers.
Greenberg 1966	Allocation: unclear if randomised. Participants: people with schizophrenia. Interventions: chlorpromazine versus withdrawal of chlorpromazine to placebo
Griffiths 1979	Allocation: 'double blind'. Participants: people with a history of sedative drug abuse, not people with schizophrenia
Guy 1978	Allocation: not randomised, review.
Hammond 1978	Allocation: A-B-A design, not randomised.
Hamner 1996	Allocation: randomised. Participants: people with schizophrenia. Interventions: chlorpromazine and ICI 204 636.
Hankoff 1960	Allocation: randomised. Participants: people with schizophrenia. Interventions: chlorpromazine versus promazine versus placebo. Outcomes: chlorpromazine and promazine data combined - no usable outcomes
Hanlon 1958	Allocation: not described- cross over study. Participants: people with psychosis.
Hanlon 1960	Allocation: not randomised, survey.
Harper 1976	Allocation: unclear, 'double-blind, cross-over'. Participants: people with schizophrenia. Interventions: chlorpromazine versus fluphenazine decanoate.

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Hartley 1978	Allocation: 'Latin square counterbalanced design' Participants: healthy volunteers, not people with schizophrenia
Hartley 1987	Allocation: randomised. Participants: 'normals'. Interventions: chlorpromazine versus placebo. Outcomes: physiological tests.
Hartley 1989	Allocation: implied randomisation. Participants: healthy volunteers.
Hartley 1991	Allocation: 'double blind'. Participants: healthy volunteers, not people with schizophrenia
Hartmann 1973	Allocation: "balanced cross-over design". Participants: healthy volunteers.
Haskell 1974	Allocation: randomised. Participants: anxious and depressed people, not schizophrenia
Heilizer 1959	Allocation: randomised. Participants: people with schizophrenia. Interventions: chlorpromazine versus placebo. Outcomes: no usable data - unclear how many people allocated to each group
Hekimian 1967	Allocation: 'assigned in rotation' - quasi-randomised.
Herrera 1988	Allocation: not randomised. Participants: people with schizophrenia. Interventions: haloperidol with benztropine versus chlorpromazine with benztropine (placebo used for 'wash out')
Herrmann 1991a	Allocation: randomised, cross-over design. Participants: healthy men. Interventions: chlorpromazine versus savoxepine versus placebo
Herrmann 1991b	Allocation: randomised, cross-over design. Participants: healthy men. Interventions: chlorpromazine versus imipramine versus placebo
Herz 1991	Allocation: randomised. Participants: people with schizophrenia. Interventions: maintenance phenothiazines, including chlorpromazine versus intermittent drug treatment
Hoffer 1975	Allocation: randomised. Participants: people with schizophrenia. Interventions: niacin versus placebo.

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Hogarty 1976	Allocation: not randomised, discontinuation study.
Hollis 1968	Allocation: not randomised, case report.
Hollister 1955	Allocation: no evidence of randomisation (five studies). Participants: people with chronic schizophrenia. Interventions: chlorpromazine versus placebo.
Holt 1984	Allocation: 'matched', no further description - likely not randomised. Participants: 'male psychiatric inpatients'. Interventions: chlorpromazine versus haloperidol versus fluphenazine decanoate versus no drug therapy. Outcomes: platelet levels.
Hong 1996a	Allocation: randomised , four parallel groups. Participants: people with schizophrenia. Interventions: ICI 204, 636, chlorpromazine. Outcomes: no data provided for chlorpromazine and placebo.
Hong 1996b	Allocation: not described. Participants: people with schizophrenia. Interventions: ICI 204, 636 and placebo.
Hopkin 1954	Allocation: not randomised, case series. Participants: people in need of analgesia.
Hrushka 1966	Allocation: "random basis". Participants: people with psychosis. Interventions: chlorpromazine combined with placebo.
Huang 1967	Allocation: A-B design, not randomised.
Hughes 1967	Allocation: not randomised, before and after design.
Hurst 1960	Allocation: 'assigned to 3 groups ... alternately, in order of their admission to hospital' - quasi-random. double-blind, cross-over design. Participants: people with schizophrenia. Interventions: chlorpromazine versus pecazine versus placebo. Outcome: no usable data.
Hurst 1996	Allocation: not randomised, review .
Hussar 1969	Allocation: not described. Participants: people with schizophrenia and psychiatric patients without schizophrenia. Interventions: chlorpromazine and no treatment.

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IRCT138811022935N3 2010	Allocation: randomised. Participants: people with schizophrenia. Interventions: Chlorpromazine plus placebo versus chlorpromazine plus omega-3
Itil 1968	Allocation: 'random order', cross-over design. Participants: 'normals', people with psychoneurotic disorders and those with schizophrenia. Interventions: chlorpromazine versus imipramine versus chlordiazepoxide versus placebo. Outcomes: physiological tests; not reported for first arm of cross-over
Itil 1971	Allocation: not randomised, review.
Jia 2004	Allocation: randomised. Participants: people with schizophrenia. Interventions: chlorpromazine plus TCM drugs versus chlorpromazine plus placebo
Johnstone 1978	Allocation: randomly allocated. Participants: people with schizophrenia. Interventions: alpha-flupenthixol, 3-flupenthixol and placebo. chlorpromazine added to the active drugs
Jones 1969	Allocation: not randomised, A-B design.
Jones 1971	Allocation: unclear. Participants: people with schizophrenia. Interventions: chlorpromazine versus trifluoperazine; placebo for 'washout' only
Joseph 1979	Allocation: randomised. Participants: people with schizophrenia. Interventions: alpha-flupenthixol, beta-flupenthixol and placebo
Joshi 1980	Allocation: randomised. Participants: people with acute schizophrenia. Interventions: each of four groups received chlorpromazine (different doses) with either placebo or adjunctive B vitamins
Kabes 1982	Allocation: 'randomly distributed'. Participants: people with schizophrenia. Interventions: chlorpromazine, haloperidol, clorothepine and placebo. Outcomes: no data provided for chlorpromazine.
Kammerer 1968	Allocation: unclear. Participants: people mainly with affective disorders. Interventions: possibly Pertofran (Geigy) but not chlorpromazine versus placebo
Kaplan 1974	Allocation: A-B-A design, not randomised.
Keskiner 1970	Allocation: not randomised, placed into groups according to pre-study medication

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Kim 1960	Allocation: likely not randomised, 'divided into two matching groups'. Participants: people with treatment-refractory, chronic schizophrenia. Interventions: chlorpromazine + placebo versus chlorpromazine + prednisolone
Kimbell 1971	Allocation: not randomised, allocated by 'doctor's choice'.
King 1959	Allocation: randomised. Participants: people with schizophrenia. Interventions: prochlorperazine, chlorpromazine and placebo. Outcomes: no usable data.
King 1994	Allocation: randomised, cross-over design. Participants: healthy volunteers. Interventions: chlorpromazine versus remoxipride (immediate release) versus remoxipride (controlled release) versus lorazepam versus placebo
Klein 1974	Allocation: randomised. Participants: "some form of psychotic disturbance". Interventions: imipramine or chlorpromazine, self administered with or without instruction versus imipramine or chlorpromazine, nurse administered with or without instruction
Kopell 1968	Allocation: cross-over design, no mention of randomisation. Participants: people with schizophrenia and other psychotic disorders. Interventions: chlorpromazine versus methamphetamine versus placebo. Outcomes: signal detection, no clinically meaningful outcomes
Kordas 1968	Allocation: not randomised, 'allocated to three groups', and 'double-blind controlled trial' - no further information. Participants: people with chronic schizophrenia. Interventions: clopenthixol versus chlorpromazine versus placebo. Outcomes: no usable data (individual participant data, or means and SD)
Kornetsky 1957	Allocation: unclear, 'Latin square', cross-over design. Participants: normal volunteers. Interventions: chlorpromazine versus secobarbital versus meperidine hydrochloride versus lysergic acid diethylamide, placebo used between arms of cross-over
Kornetsky 1958	Allocation: unclear. Participants: normal volunteers. Interventions: chlorpromazine versus secobarbital, placebo for 'washout' only
Kornetsky 1959	Allocation: unclear, 'modified Latin square', cross-over design. Participants: people with schizophrenia. Interventions: chlorpromazine versus secobarbital versus placebo. Outcomes: various psychological tests, results not reported for individual arms of cross-over

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Korol 1965	Allocation: randomised. Participants: people with schizophrenia, stabilised on chlorpromazine. Interventions: continuing chlorpromazine versus chlorpromazine withdrawal
Kovitz 1955	Allocation: no evidence of randomisation, cross-over design. Participants: people with chronic schizophrenia, and other psychoses. Interventions: chlorpromazine versus reserpine versus placebo
Kramer 1975	Allocation: randomised. Participants: people with acute schizophrenia. Interventions: chlorpromazine versus metiapine versus placebo. Outcomes: various relevant outcomes, but study rejected because placebo group was withdrawn after the first 13 were randomised - no data for chlorpromazine at this point in the study
Kugler 1980	Allocation: unclear, double-blind, Latin-square design. Participants: healthy volunteers. Interventions: chlorpromazine versus amylobarbitone versus placebo
Kupfer 1971	Allocation: not randomised, A-B cross-over design.
Kurland 1981	Allocation: randomised. Participants: people with schizophrenia. Interventions: chlorpromazine or haloperidol supplemented with either viloxazine or placebo. Outcomes: no usable data.
Lampe 1969	Allocation: randomised. Participants: people with schizophrenia. Interventions: clomacran versus placebo.
Latz 1965	Allocation: no evidence of randomisation, Latin-square cross-over design. Participants: people with schizophrenia. Interventions: chlorpromazine versus secobarbital versus placebo. Outcomes: tests of cognitive function; no usable data (no N or SD, and results not reported for individual arms of cross-over)
Laurian 1981	Allocation: randomised. Participants: healthy volunteers, not people with schizophrenia
Leff 1971	Allocation: randomised (to drug group vs placebo), but allocation to different drugs not randomised (based on pre-study medication). Interventions: trifluoperazine or chlorpromazine versus placebo. Outcomes: not broken down by drug group.
Leszek 1991	Allocation: not described. Participants: people with schizophrenia. Interventions: interferon and placebo, chlorpromazine used to control symptoms

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Levin 1959	Allocation: not randomised, 'assigned to groups in sequence', and 'not possible to assign subjects in a purely random fashion'. Participants: people with schizophrenia. Interventions: chlorpromazine versus phenobarbital versus promethazine versus placebo
Levine 1997	Allocation: randomised. Participants: people with schizophrenia. Interventions: chlorpromazine, perphenazine and placebo. Outcomes: no usable data (no SD)
Levita 1961	Allocation: 'randomly assigned'. Participants: people with schizophrenia. Interventions: chlorpromazine, promazine and placebo. Outcomes: no usable data (no SD) .
Lewis 1973	Allocation: unclear, 'double-blind cross-over trial. Participants: children and adolescents with 'a psychiatric syndrome of sufficient severity to warrant the use of a major tranquillising drug'. Interventions: haloperidol versus chlorpromazine versus placebo. Outcomes: no usable data; information from each arm not separated
Li 2006	Allocation: randomised. Participants: people with schizophrenia. Interventions: chlorpromazine versus ziprasidone.
Liberman 1973	Allocation: not randomised, A-B cross-over design.
Little 1958	Allocation: randomised, cross-over design. Participants: people with chronic mental illness. Interventions: chlorpromazine versus amylobarbitone versus placebo. Outcomes: results not reported for individual arms of cross-over
Loranger 1968	Allocation: randomised. Participants: people with schizophrenia (n=30), psychoneurotic reaction (n=13), manic-depressive reaction (n=11), sociopathic personality disturbance (n=3), other psychoses (n=3). Interventions: chlorpromazine versus neurosterone versus placebo. Outcomes: this abstract reports P values only; no means or SD. Author contacted for further data, but none available.
Lorr 1961	Allocation: 'randomly assigned', to one of five treatment groups (no further description). Participants: '16% of patients were psychotic, 57% psychoneurotic, 27% psychophysiologic'
Lyberi 1956	Allocation: not randomised. Participants: not schizophrenia.
Maculans 1964	Allocation: randomised, cross-over design. Participants: people with chronic schizophrenia. Interventions: chlorpromazine versus chlorprothixene versus diazepam (placebo used for washout

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	period between arms of cross-over)
Mahal 1976	Allocation: randomised. Participants: people with schizophrenia. Interventions: tagara, brahmyadi yoga, chlorpromazine and placebo. Outcomes: no usable data (no SD).
Majewski 1968	Allocation: no evidence of randomisation (translation by Polish speaker)
Marjerrison 1969	Allocation: randomised, cross-over design. Participants: people newly admitted with acute schizophrenia. Interventions: chlorpromazine versus haloperidol versus chlorprothixene versus placebo. Placebo only compared with haloperidol and chlorprothixene.
Marrazzi 1972	Allocation: unclear if randomised, A-B-C design. Participants: people with schizophrenia. Interventions: chlorpromazine versus placebo with LSD challenge
Mason-Browne 1957	Allocation: no evidence of randomisation. Participants: 'chronic patients'; no indication of diagnosis. Interventions: chlorpromazine versus perphenazine versus placebo
Mathur 1981	Allocation: randomised. Participants: people with chronic schizophrenia stabilized on chlorpromazine. Interventions: continuing chlorpromazine versus placebo (withdrawal study)
Mattila 1994	Allocation: Latin-square cross-over. Participants: healthy volunteers, not people with schizophrenia
McClelland 1990	Allocation: randomised, cross-over design. Participants: healthy volunteers. Interventions: chlorpromazine versus haloperidol versus sulpiride versus placebo
Melnyk 1966	Allocation: randomised. Participants: people with schizophrenia. Interventions: thioridazine, chlorpromazine and placebo. Outcomes: no usable data (no SD).
Merry 1957	Allocation: unclear. Participants: people with chronic neurotic tension (no schizophrenia or psychoses). Interventions: chlorpromazine versus placebo.
Michaux 1966	Allocation: randomised. Participants: 181 people with schizophrenia. Interventions: chlorpromazine and placebo versus chlorpromazine and chlordiazepoxide versus chlorpromazine and imipramine

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Millar 1963	Allocation: "divided into random groups". Participants: people with schizophrenia. Interventions: fluphenazine and placebo.
Milne 1960	Allocation: quasi-randomised, 'divided arbitrarily into four groups'. Participants: people with chronic schizophrenia. Interventions: chlorpromazine versus prochlorperazine versus methotrimeprazine versus placebo. Outcomes: improvement, behaviour; no usable data (no mean, N or SD)
Milstein 1994	Allocation: randomised. Participants: people with schizophrenia. Interventions: Iloperidone versus chlorpromazine versus placebo Outcomes: EEG - no clinical outcomes.
Milton 1978	Allocation: randomised. Participants: people with delusions. Interventions: confrontation versus belief modification, also on chlorpromazine or clozapine but not randomised to these drugs
Mitchell 1956	Allocation: quasi-randomised (used surnames beginning A-L for first group). Participants: people with schizophrenia. Interventions: chlorpromazine versus placebo. Outcomes: no usable data (no means, N, or SD).
Mitchell 1960	Allocation: assigned by matching variables. Participants: "psychiatric patients" Interventions: chlorpromazine.
Monteleone 1999	Allocation: randomised. Participants: people with schizophrenia and healthy particpants. Interventions: D-fenfluramine and placebo.
Morgenstern 1960	Allocation: not described. Participants: "acutely disturbed patients". Interventions: triflupromazine, chlorpromazine, placebo with ECT being administered concurrently with the drug interventions
Morton 1968	Allocation: randomised. Participants: people with schizophrenia. Interventions: continued maintenance therapy (chlorpromazine or trifluoperazine) versus placebo (withdrawal study)
Moss 1958	Allocation: not randomised - appears to be A-B-A design. Participants: people with schizophrenia. Interventions: chlorpromazine versus placebo.

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Neal 1969	Allocation: randomised. Participants: people with chronic schizophrenia. Interventions: chlorpromazine versus oxypertine; placebo given during first 4 weeks of trial (for washout)
Newbold 1956	Allocation: not described. Participants: "patients undergoing thorazine treatment - 3 with a form of schizophrenia" Interventions: chlorpromazine and placebo. Outcomes: no usable data.
Okuma 1979	Allocation: randomised. Participants: 63 people with mania, not schizophrenia.
Orzack 1969	Allocation: 'randomly determined treatment"'. Participants: people with schizophrenia and normal volunteers. Interventions: chlorpromazine, and placebo used 'at two appropriate intervals'. Outcomes: no usable data.
Osmakova 1972	Allocation: not randomised, review article (translated by native Russian speaker)
Pai 2001	Allocation: randomised. Participants: people with schizophrenia. Interventions: risperidone and placebo.
Paredes 1966	Allocation: randomised. Participants: people with schizophrenia. Interventions: chlorpromazine and placebo. Outcomes: no usable data (no SD).
Park 1981	Allocation: randomised. Participants: people with acute schizophrenia. Interventions: chlorpromazine + triiodothyronine versus chlorpromazine + placebo
Pasamanick 1967	Allocation: randomised. Participants: people with schizophrenia. Interventions: home (drugs) versus home (placebo) versus hospital treatment; data not split by drug (chlorpromazine or trifluoperazine or thioridazine)
Patterson 1981	Allocation: unclear, Latin-square design. Participants: healthy male volunteers, not schizophrenia.
Peet 1980	Allocation: randomised, cross-over design. Participants: people with schizophrenia. Interventions: chlorpromazine versus chlorpromazine + propranolol
Pennington 1957	Allocation: not randomised, case series.
Pietzcker 1978	Allocation: not randomised, review.

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Pigache 1973	Allocation: randomised, cross-over design. Participants: people with schizophrenia, maintained on chlorpromazine. Interventions: chlorpromazine versus placebo; withdrawal study
Pigache 1993	Allocation: randomised, cross-over design. Participants: people with schizophrenia. Interventions: chlorpromazine (300-600 mg/day) versus chlorpromazine (600-1200 mg/day) versus chlorpromazine (900-1800 mg/day); no placebo period or placebo group (identical placebo tablets used for maintaining double-blind procedure)
Platz 1967	Allocation: randomised. Participants: people with schizophrenia. Interventions: chlorpromazine versus carphenazine versus trifluoperazine; placebo given during first 3 weeks of trial (for washout)
Pleasure 1956	Allocation: not randomised, alternately allocated.
Pollack 1956	Allocation: not randomised, case series.
Pollard 1959	Allocation: not described. Participants: people with schizophrenia. Interventions: chlorpromazine with meprobamate and placebo. Outcomes no usable data.
Quigley 1996	Allocation: unclear if randomised, Latin-square design. Participants: healthy volunteers, not schizophrenia.
Quinn 1960	Allocation: no evidence of randomisation - "the pharmacist ... allocated the treatment to the three groups". Participants: people with schizophrenia. Interventions: chlorpromazine versus placebo versus methotrimeprazine
Raaska 2000	Allocation: randomised. Participants: people with schizophrenia. Interventions: ciprofloxacin and placebo.
Ragland 1968	Allocation: randomised. Participants: people with chronic schizophrenia. Interventions: chlorpromazine versus placebo. Outcomes: no usable data (no individual patient outcomes, or means reported for continuous outcomes)
Raja 2000	Allocation: non-randomised study.
Rappaport 1967	Allocation: randomised. Participants: people with schizophrenia. Interventions: chlorpromazine versus perphenazine versus sodium pentobarbital versus placebo. Outcomes: auditory attention tasks, no clinical data.

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Rappaport 1968	Allocation: randomised. Participants: people with schizophrenia. Interventions: chlorpromazine versus perphenazine versus dextroamphetamine versus methylphenidate versus placebo. Outcomes: auditory attention tests, no clinical data.
Rathod 1958	Allocation: randomised, cross-over design. Participants: 'disturbed psychotic patients'. Interventions: chlorpromazine versus placebo. Outcomes: results not reported for individual arms of cross-over
Raymond 1957	Allocation: randomised, cross-over design. Participants: a 'heterogeneous group of psychoneurotic disorders' all with a 'tension component' - no mention of schizophrenia or psychosis
Remr 1970	Allocation: no evidence of randomisation, 'single-blind, placebo-controlled, cross-over design'. Participants: people with schizophrenia. Interventions: chlorpromazine versus placebo. Outcomes: various psychomotor tasks; results not reported for individual arms of cross-over
Rifkin 1978	Allocation: 'randomised unequally'. Participants: 'patients receiving a maintenance dose of antipsychotic medication'. Interventions: procyclidine and placebo.
Rinaldi 1956	Allocation: 'double blind crosover'. Participants: people with schizophrenia. Interventions: chlorpromazine versus placebo versus azacyclonol versus reserpine. Outcomes: no data reported for the chlorpromazine versus placebo comparison
Rivera-Calimlim 1973	Allocation: not randomised, case series.
Rojo-Sierra 1971	Allocation: not randomised, review.
Rosen 1972	Allocation: randomised. Participants: people with schizophrenia. Interventions: chlorpromazine versus placebo versus promazine. Outcomes: no usable data.
Rosenheck 2000	Allocation: randomised. Participants: people with schizophrenia. Interventions: clozapine and haloperidol.
Rosner 1955	Allocation: quasi-randomised; 'placed on one of the drugs or a placebo in strict order of admission'. Participants: people with various psychotic, neurotic or character disorders. Interventions: chlorpromazine versus reserpine versus phenobarbital versus placebo
Rudy 1957	Allocation: not randomised, A-B design.

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Rudy 1958	Allocation: 'double blind cross-over'. Participants: people with chronic psychotic illnesses. Interventions: trifluoperazine versus placebo, not chlorpromazine
Sainz 1955	Allocation: not described. Participants: people with schizophrenia, alcoholism, birth trauma, anxiety reactions, obsessive compulsive reactions
Saletu 1972	Allocation: randomised. Participants: healthy volunteers.
Salisbury 1957	Allocation: unclear, Latin-square design. Participants: people with chronic schizophrenia. Interventions: chlorpromazine versus 'control' (placebo) versus ritalin (at two dose levels). Outcomes: behaviour and mental state outcomes not reported for individual arms of cross-over
Schiele 1959	Allocation: divided into 2 matched groups of 19, not randomised
Schmidt 1957	Allocation: no evidence of randomisation. Participants: people with chronic schizophrenia. Interventions: combination of chlorpromazine + reserpine versus placebo
Schooler 1976	Allocation: randomised. Participants: people with schizophrenia. Interventions: chlorpromazine versus placebo. Outcomes: preliminary report of larger study.
Seager 1955	Allocation: no evidence of randomisation, cross-over design. Participants: people with schizophrenia (thirteen), depression (six), or dementia (twenty-nine). Interventions: chlorpromazine versus inert control.
Serafetinides 1973	Allocation: not randomised, review.
Shaskan 1975	Allocation: randomised. Participants: people with schizophrenia. Interventions: chlorpromazine + imipramine versus placebo + thiothixine
Shawver 1959	Allocation: randomised. Participants: people with schizophrenia. Interventions: continuing chlorpromazine versus reserpine versus placebo; a withdrawal study
Shopsin 1978	Allocation: unclear, 'double-blind controlled comparison'. Participants: people with schizophrenia. Interventions: chlorpromazine versus clozapine versus placebo. Outcomes: no usable data reported. NB: some evidence in this report suggests that this trial is the same as Shopsin 1979.

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Shopsin 1979	Allocation: randomised. Participants: patients with schizophrenia. Interventions: chlorpromazine versus clozapine versus placebo. However, 'all of the placebo-treated patients were prematurely terminated from study because of continued aggravation of psychopathology ... and it was mutually agreed that this study group be dissolved'. Outcomes: no comparison with placebo group possible, data from chlorpromazine group was never compared with placebo group at the point where allocation to placebo was terminated
Silver 2000	Allocation: randomised. Participants: people with schizophrenia. Interventions: fluvoxamine and placebo.
Simopoulos 1971	Allocation: randomised. Participants: people with schizophrenia. Interventions: dilantin versus placebo, no chlorpromazine group
Simpson 1974	Allocation: no evidence of randomisation; double-blind cross-over trial. Participants: people with schizophrenia. Interventions: chlorpromazine (generic) versus chlorpromazine (Thorazine branded); placebo administered during washout period
Simpson 1980	Allocation: no evidence of randomisation; 'double-blind split cross-over trial'. Participants: people with schizophrenia. Interventions: chlorpromazine + trihexyphenidyl hydrochloride versus chlorpromazine + placebo
Singh 1974	Allocation: no evidence of randomisation, cross-over design. Participants: people with schizophrenia. Interventions: chlorpromazine versus haloperidol versus benzotropine versus placebo, results not reported for placebo arms of cross-over (placebo used for baseline and washout periods)
Singh 1990	Allocation: randomised. Participants: people with schizophrenia, meeting criteria for supersensitivity psychosis. Interventions: neuroleptic medication versus placebo (withdrawal of usual medication) - neuroleptic drugs (haloperidol, fluphenazine, chlorpromazine, thioridazine, thiothixene or loxapine) not analysed separately
Small 1987	Allocation: no evidence of randomisation. Participants: people with treatment resistant schizophrenia. Interventions: chlorpromazine + benzotropine versus clozapine + placebo; placebo used in washout periods and as double-dummy to maintain blinding. Outcomes: EEG - no clinical outcomes.
Smith 1958	Allocation: no evidence of randomisation, cross-over design. Participants: people with chronic schizophrenia. Interventions: chlorpromazine versus trifluprom azine versus placebo. Outcomes: results not reported for individual arms of cross-over

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Smith 1960	Allocation: no evidence of randomisation, matched groups. Participants: people with chronic schizophrenia or manic-depression. Interventions: chlorpromazine versus chlordiazepoxide versus placebo
Smith 1967	Allocation: randomisation implied but not mentioned. Participants: people with schizophrenia. Interventions: chlorpromazine versus chlorpromazine and ECT, no placebo
Sommerness 1957	Allocation: no evidence of randomisation. Participants: people with schizophrenia, manic-depression, and various other psychoses. Interventions: chlorpromazine versus placebo. Outcomes: no usable data reported (no means, N or SD).
South-East 1961	Allocation: 'allocation to groups A and B'. Participants: people with schizophrenia. Interventions: chlorpromazine, prochlorperazine and placebo. Outcomes: no usable data (no SD).
Soyka 1968	Allocation: not described. Participants: people with psychosis, depression and neurosis
Spiegel 1967	Allocation: randomised. Participants: people with chronic schizophrenia. Interventions: chlorpromazine versus trifluoperazine versus carphenazine, placebo for 'washout' only
Spohn 1974	Allocation: randomised, cross-over. Participants: healthy volunteers.
Sugerman 1964	Allocation: no evidence of randomisation, cross-over design. Participants: people with schizophrenia. Interventions: chlorpromazine versus placebo versus perphenazine versus deanol. Outcomes: EEG; no data for clinical outcomes; no data given per arm of cross-over
Sun 2006	Allocation: randomised. Participants: people with chronic schizophrenia. Interventions: Chlopromazine plus placebo versus chlorpromazine plus venlafaxine
Syvalahti 1997	Allocation: randomised. Participants: people with schizophrenia. Interventions: citalopram or placebo given as an adjuvant to neuroleptic medication
Talbot 1964	Allocation: randomised. Participants: people with schizophrenia. Interventions: chlorpromazine versus trifluoperazine versus chlorpromazine + trifluoperazine; placebo used to maintain double-blind conditions

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Tang 2005	Allocation: randomised. Participants: people with schizophrenia. Interventions: chlorpromazine plus placebo versus chlorpromazine plus herb mixture
Tang 2005a	Allocation: randomised. Participants: people with schizophrenia. Interventions: chlorpromazine plus placebo versus chlorpromazine plus Chinese medicine
Tang 2006	Allocation: randomised. Participants: people with schizophrenia. Interventions: chlorpromazine plus placebo versus chlorpromazine plus TCM herbs
Tassis 1959	Allocation: not described. Participants: people with schizophrenia. Interventions: insulin, ECT and chlorpromazine.
Teja 1975	Allocation: randomised. Participants: people with schizophrenia. Interventions: chlorpromazine versus trifluoperazine versus thiothixine versus haloperidol versus placebo. Outcomes: no usable data.
Tenenblatt 1956	Allocation: no evidence of randomisation.
Terminska 1989	Allocation: unclear. Participants: people with paranoid schizophrenia. Interventions: chlorpromazine versus perazine versus fluphenazine versus trifluoperazine versus haloperidol; no placebo group (confirmed by Polish speaker)
Tetreault 1969a	Allocation: randomised. Participants: people with schizophrenia. Intervention: fluphenazine in enanthate, fluphenazine bichlorhydrate and placebo
Thorpe 1956	Allocation: randomised. Participants: people with schizophrenia. Interventions: chlorpromazine versus pacatal versus no treatment versus placebo. Outcomes: no usable data.
Tourlentes 1958	Allocation: “randomly assigned”. Participants: people with schizophrenia. Interventions: chlorpromazine versus placebo. Outcomes: no usable data.
Troshinsky 1962	Allocation: randomised. Participants: people with schizophrenia. Interventions: placebo versus ’active medication’ (phenothiazine); phenothiazines were chlorpromazine, trifluoperazine, triflupromazine, thioridazine Outcomes: results not reported for individual drugs - withdrawal study

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Turner 1956	Allocation: not described. Participants: "people neurosis, psychosis and epilepsy". Interventions: chlorpromazine.
Turner 1966	Allocation: random order Latin-square design. Participants: healthy volunteers, not people with schizophrenia
Urquhart 1959	Allocation: randomised. Participants: people with schizophrenia. Interventions: stage 1: placebo versus acetyl promazine versus promazine hydrochloride, cross-over design; stage 2: chlorpromazine versus reserpine, cross-over design; no arm comparing chlorpromazine versus placebo
van Praag 1975	Allocation: randomised. Participants: people with acute psychotic disorders. Interventions: chlorpromazine versus oxypertine, placebo used to maintain blinding during dose changes
Vestre 1961	Allocation: not described. Participants: people with schizophrenia. Interventions: chlorpromazine and placebo. Outcomes: no usable data.
Vinar 1973	Allocation: randomised, a 'continuous controlled trial'. Participants: people with functional psychoses. Interventions: chlorpromazine versus 'control'. Outcomes: no usable data, multivariate analysis of Brief Psychiatric Rating Scale and 1-year outcomes of total group, no comparisons between chlorpromazine and control
Vinar 1976	Allocation: not randomised.
Volavka 1983	Allocation: randomised, cross-over design. Participants: people with schizophrenia. Interventions: (Des-tyr)-gamma-endorphin versus placebo.
Warner 1996	Allocation: unclear. Participants: people with schizophrenia and other diagnoses. Interventions: unspecified neuroleptic medications versus unmedicated controls
Weir 1968	Allocation: randomised. Participants: disturbed, 'mentally subnormal' people, not people with schizophrenia
Welbel 1980	Allocation: unclear. Participants: people with schizophrenia. Interventions: chlorpromazine versus clozapine versus levopromazine versus triflupromazine versus pimozide versus sulpiride, no placebo group (confirmed by Polish-speaker)

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Whitehead 1958	Allocation: randomised. Participants: people with chronic psychoses. Interventions:chlorpromazine versus placebo, unclear how many people assigned to each group
Wilcott 1962	Allocation: not described. Participants: emotionally disturbed children.
Wilson 1961	Allocation: unclear, 'Latin square', cross-over design. Participants: people with paranoid schizophrenia. Interventions: chlorpromazine versus prochlorperazine versus trifluoperazine versus placebo
Winkelman 1957	Allocation: not described- case report series.
Winter 1956	Allocation: randomised. Participants: people with a 'variety of diagnostic categories', and 'acutely disturbed'. Interventions: chlorpromazine versus placebo. Outcomes: chlorpromazine and placebo groups not reported separately
Wode-Helgodt 1977	Allocation: randomised. Participants: those with psychoses, and 'schizophrenic symptomology'. Interventions: chlorpromazine 200 mg/day versus chlorpromazine 400 mg/day versus chlorpromazine 600 mg/day, placebo used for washout only
Wold 1959	Allocation: not described. Participants: people with schizophrenia. Interventions: chlorpromazine and placebo. Outcomes: no usable data.
Wolpert 1969	Allocation: 'assigned at random'. Participants: people with schizophrenia. Interventions: chlorpromazine, triiodothyronine and placebo. Outcomes: no usable data.
Wyatt 1997	Allocation: randomised. Participants: people with schizophrenia. Interventions: milieu therapy versus psychotherapy versus ECT versus antipsychotic medications (including chlorpromazine amongst others) versus antipsychotic medication + psychotherapy Outcomes: not possible to separate chlorpromazine data from totals
Wykes 1994	Allocation: randomised. Participants: people with schizophrenia and cognitive difficulties. Interventions: cognitive remediation versus treatment as usual
Yan 2004	Allocation: randomised. Participants: people with schizophrenia. Interventions: chlorpromazine plus placebo versus chlorpromazine plus ferrous sulphate

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(*Continued*)

Yang 2005	Allocation: randomised. Participants: people with schizophrenia. Interventions: psychological rehabilitation therapy versus general rehabilitation
Yorkston 1977	Allocation: randomised. Participants: people with schizophrenia. Interventions: propranolol versus placebo, all on antipsychotics, doses expressed as chlorpromazine equivalents
Yuan-guang 1994	Allocation: randomised. Participants: 41 people with schizophrenia. Interventions: three different doses of chlorpromazine, no placebo
Zeller 1956	Allocation: possibly randomised, 'selected at random'. Participants: mainly people with schizophrenia. Interventions: continuing chlorpromazine or reserpine versus placebo, withdrawal study
王强, 1995	Allocation: randomised. Participants: people with schizophrenia. Interventions: cross-over trial, chlorpromazine plus lithium versus chlorpromazine plus placebo
金建烽, 2008	Allocation: randomised. Participants: people with schizophrenia. Interventions: chlorpromazine plus placebo versus chlorpromazine plus aripiprazole

CPZ - chlorpromazine
ECT - electroconvulsive therapy
EEG - electroencephalogram
SD - standard deviation
TCM - traditional Chinese medicine

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DATA AND ANALYSES

Comparison 1. CHLORPROMAZINE versus PLACEBO

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death	1	14	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Relapse	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 short term (0-8 weeks)	2	74	Risk Ratio (M-H, Random, 95% CI)	0.24 [0.01, 5.49]
2.2 medium term (9 weeks - 6 months)	4	809	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.21, 1.72]
2.3 long term (6 months - 2 years)	3	512	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.47, 0.90]
2.4 2 - 5 years	2	394	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.51, 1.09]
3 Global state: 1a. No overall improvement (psychiatrist-rated)	27		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 short term (0-8 weeks)	13	728	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.46, 0.82]
3.2 medium term (9 weeks - 6 months)	14	1164	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.58, 0.86]
4 Global state: 1b. No overall improvement (nurse-rated)	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 short term (0-8 weeks)	1	29	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.65, 1.27]
4.2 medium term (9 weeks-6 months)	3	84	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.35, 0.66]
5 Global state: 2. Average endpoint score - short term (CGI, high score=worse)	1	19	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.35, 0.55]
6 Global state: 3a. Severity of illness, severely ill or worse (CGI 5+ points, psychiatrist-rated)	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 short term (0-8 weeks)	1	44	Risk Ratio (M-H, Fixed, 95% CI)	0.46 [0.16, 1.30]
6.2 medium term (9 weeks - 6 months)	3	694	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.74, 0.86]
7 Global state: 3b. Severity of illness, severely ill or worse - medium term (CGI 5+ points, nurse-rated)	2	66	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.45, 0.90]
8 Leaving the study early	45		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1 short term (0-8 weeks)	17	1065	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.63, 0.92]
8.2 medium term (9 weeks - 6 months)	27	1831	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.53, 0.78]
8.3 long term (>6 months - 2 years)	2	492	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.71, 1.59]
8.4 >2 - 5 years	1	374	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.35, 1.36]
9 Mental state: 1. Improved - short term (BPRS, 50% change)	1	106	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [0.36, 4.40]

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10 Mental state: 2. Average endpoint scores (BPRS, high score=worse)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
10.1 short term (0-8 weeks)	2	49	Mean Difference (IV, Fixed, 95% CI)	-4.82 [-8.48, -1.15]
10.2 medium term (9 weeks - 6 months)	1	30	Mean Difference (IV, Fixed, 95% CI)	-7.70 [-14.77, -0.63]
11 Behaviour: 1. Deteriorated/ disturbed/un-cooperative	10		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
11.1 short term - (0-8 weeks)	2	87	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.34, 1.35]
11.2 medium term (9 weeks - 6 months)	8	1040	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.24, 1.00]
12 Behaviour: 2. Unchanged	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
12.1 short term (0-8 weeks)	1	40	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.25, 1.58]
12.2 medium term (9 weeks - 6 months)	2	68	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.64, 2.07]
13 Behaviour: 3. Average endpoint scores (RRS, high score=worse)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
13.1 short term (0-8 weeks)	1	30	Mean Difference (IV, Fixed, 95% CI)	-2.90 [-6.74, 0.94]
13.2 medium term (9 weeks - 6 months)	1	30	Mean Difference (IV, Fixed, 95% CI)	-4.60 [-9.47, 0.27]
14 Behaviour: 4. Average endpoint score - short term (PBRS, high score=good)	1	14	Mean Difference (IV, Fixed, 95% CI)	6.0 [1.97, 10.03]
15 Behaviour: 5. Average endpoint scores - medium term (Fergus Falls Behavioural rating scale)	1	42	Mean Difference (IV, Fixed, 95% CI)	-2.36 [-6.11, 1.39]
16 Adverse effects: 1. Movement disorders	25		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
16.1 acute movement disorders (dystonia)	5	942	Risk Ratio (M-H, Fixed, 95% CI)	3.47 [1.50, 8.03]
16.2 parkinsonism (includes EPS)	15	1468	Risk Ratio (M-H, Fixed, 95% CI)	2.11 [1.59, 2.80]
16.3 tremor	7	392	Risk Ratio (M-H, Fixed, 95% CI)	1.66 [1.01, 2.73]
16.4 rigidity	7	412	Risk Ratio (M-H, Fixed, 95% CI)	2.24 [1.42, 3.54]
16.5 akathisia	9	1164	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.54, 1.11]
16.6 chronic movement disorders (tardive dyskinesia)	1	18	Risk Ratio (M-H, Fixed, 95% CI)	1.5 [0.32, 6.94]
16.7 ataxia	1	97	Risk Ratio (M-H, Fixed, 95% CI)	8.64 [0.94, 79.31]
17 Adverse effects: 2. Movement disorders: Average endpoint scores (Extrapyramidal Bilan, high score=worse)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
17.1 short term (0-8 weeks)	1	30	Mean Difference (IV, Fixed, 95% CI)	-1.40 [-3.22, 0.42]
17.2 medium term (9 weeks - 6 months)	1	30	Mean Difference (IV, Fixed, 95% CI)	-1.80 [-4.19, 0.59]
18 Adverse effects: 1. Central nervous system	25		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
18.1 sleepiness	23	1627	Risk Ratio (M-H, Fixed, 95% CI)	2.79 [2.25, 3.45]
18.2 fits / loss of consciousness	3	695	Risk Ratio (M-H, Fixed, 95% CI)	3.11 [1.05, 9.18]
18.3 weakness	3	92	Risk Ratio (M-H, Fixed, 95% CI)	3.33 [1.02, 10.88]
18.4 convulsions	1	52	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.82]

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19 Adverse effects: 3. Blood, skin, liver, eyes	20		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
19.1 blood problems (agranulocytosis, leukopenia)	7	394	Risk Ratio (M-H, Fixed, 95% CI)	2.08 [0.74, 5.83]
19.2 rashes/itching/skin disorders	13	1313	Risk Ratio (M-H, Fixed, 95% CI)	1.45 [0.92, 2.29]
19.3 liver problems	4	249	Risk Ratio (M-H, Fixed, 95% CI)	4.31 [0.98, 18.95]
19.4 photosensitivity	6	799	Risk Ratio (M-H, Fixed, 95% CI)	6.04 [3.22, 11.32]
19.5 eye opacity / eye pigment problems	2	657	Risk Ratio (M-H, Fixed, 95% CI)	3.09 [1.87, 5.11]
20 Adverse effects: 4. Other	21		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
20.1 blood pressure - low +/- dizziness/syncope	18	1488	Risk Ratio (M-H, Fixed, 95% CI)	2.38 [1.74, 3.25]
20.2 constipation	10	1117	Risk Ratio (M-H, Fixed, 95% CI)	2.05 [1.33, 3.15]
20.3 urinary problems	5	926	Risk Ratio (M-H, Fixed, 95% CI)	1.73 [0.70, 4.30]
20.4 blurred vision	7	962	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.51, 2.65]
20.5 dry mouth	7	1015	Risk Ratio (M-H, Fixed, 95% CI)	4.56 [2.35, 8.85]
20.6 weight increase	5	165	Risk Ratio (M-H, Fixed, 95% CI)	4.92 [2.32, 10.43]
20.7 weight decrease	5	165	Risk Ratio (M-H, Fixed, 95% CI)	0.38 [0.22, 0.66]
20.8 nausea/vomiting	5	1024	Risk Ratio (M-H, Fixed, 95% CI)	2.07 [1.14, 3.73]
20.9 salivation	3	830	Risk Ratio (M-H, Fixed, 95% CI)	3.37 [1.07, 10.57]
20.10 menorrhagia / abnormal menstruation	2	46	Risk Ratio (M-H, Fixed, 95% CI)	1.39 [0.62, 3.13]
20.11 amenorrhea	1	161	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.17, 3.99]
20.12 lactation	2	192	Risk Ratio (M-H, Fixed, 95% CI)	1.48 [0.57, 3.81]
21 SUBGROUP ANALYSIS: 1. MEN vs WOMEN: Behaviour: Deteriorated/disturbed/un-cooperative	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
21.1 only men	1	40	Risk Ratio (M-H, Fixed, 95% CI)	0.04 [0.00, 0.63]
21.2 only women	3	158	Risk Ratio (M-H, Fixed, 95% CI)	0.46 [0.29, 0.73]
22 SUBGROUP ANALYSIS: 2. ACUTE vs CHRONIC	31		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
22.1 acute - Relapse (9 wks - 6 months)	1	127	Risk Ratio (M-H, Random, 95% CI)	1.21 [0.94, 1.55]
22.2 chronic - Relapse (9 wks - 6 months)	3	682	Risk Ratio (M-H, Random, 95% CI)	0.46 [0.18, 1.15]
22.3 acute - Global state 1. No overall improvement (0-8 wks)	2	149	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.44, 1.05]
22.4 chronic - Global state 1. No overall improvement (0-8 wks)	9	459	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.39, 0.84]
22.5 acute - Global state 2. No overall improvement (9 wks-6 months)	1	23	Risk Ratio (M-H, Random, 95% CI)	0.18 [0.03, 1.28]
22.6 chronic - Global state 2. No overall improvement (9 wks-6 months)	12	1121	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.64, 0.86]
22.7 acute - Behaviour deteriorated/disturbed/unco-operative	1	42	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.60, 1.29]

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22.8 chronic - Behaviour deteriorated/disturbed/unco-operative	9	1085	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.26, 0.92]
23 SUBGROUP ANALYSIS: 3. HIGH vs LOW DOSE	22		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
23.1 high - Relapse (9 wks-6 Months)	1	420	Risk Ratio (M-H, Random, 95% CI)	0.14 [0.08, 0.26]
23.2 low - Relapse (9 wks-6 Months)	3	474	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.26, 0.98]
23.3 high - Global state 1. No overall improvement (0-8 wks)	2	201	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.18, 1.25]
23.4 low - Global state 1. No overall improvement (0-8 wks)	9	425	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.52, 1.01]
23.5 high - Global state 1. No overall improvement (9 wks-6 months)	6	576	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.51, 0.94]
23.6 low - Global state 1. No overall improvement (9 wks-6 months)	3	493	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.60, 1.16]
23.7 high - Behaviour 1. Deteriorated/disturbed/unco-operative	2	447	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.04, 6.21]
23.8 low - Behaviour 1. Deteriorated/disturbed/unco-operative	2	462	Risk Ratio (M-H, Random, 95% CI)	0.39 [0.27, 0.56]
24 SUBGROUP ANALYSIS: 4. DIAGNOSTIC CRITERIA vs NO DIAGNOSTIC CRITERIA	36		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
24.1 diagnostic criteria - Relapse (0-8 wks)	1	34	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.26, 2.19]
24.2 no diagnostic criteria - Relapse (0-8 wks)	1	40	Risk Ratio (M-H, Random, 95% CI)	0.05 [0.00, 0.76]
24.3 diagnostic criteria - Relapse (9 wks-6 months)	2	662	Risk Ratio (M-H, Random, 95% CI)	0.34 [0.13, 0.90]
24.4 no diagnostic criteria - Relapse (9 wks-6 months)	2	147	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.66, 1.60]
24.5 diagnostic criteria - Global state 1. No overall improvement (0-8 wks)	3	192	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.40, 0.99]
24.6 no diagnostic criteria - Global state 1. No overall improvement (0-8 wks)	11	565	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.46, 0.90]
24.7 diagnostic criteria - Global state 1. No overall improvement (9 wks-6 months)	3	689	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.57, 1.05]
24.8 no diagnostic criteria - Global state 1. No overall improvement (9 wks-6 months)	11	475	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.59, 0.85]

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24.9 diagnostic criteria - Global state 3. Severity of illness (9 wks-6 months)	1	628	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.75, 0.88]
24.10 no diagnostic criteria - Global state 3. Severity of illness (9 wks-6 months)	2	66	Risk Ratio (M-H, Random, 95% CI)	0.58 [0.36, 0.95]
24.11 diagnostic criteria - Behaviour 1. deteriorated/ disturbed/unco-operative	2	670	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.14, 1.72]
24.12 no diagnostic criteria - Behaviour 1. deteriorated/ disturbed/unco-operative	8	457	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.33, 0.97]
25 SUBGROUP ANALYSIS: 5. STUDIES PRE-1990 vs STUDIES 1990-2007	32		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
25.1 Pre-1990 - Global state 1. No overall improvement (0-8 wks)	11	555	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.46, 0.91]
25.2 1990 to 2002 - Global state 1. No overall improvement (0-8 wks)	3	202	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.40, 0.94]
25.3 Pre-1990 - Global state 1. No overall improvement (9 wks-6 months)	13	1121	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.67, 0.88]
25.4 1990 to 2002 - Global state 1. No overall improvement (9 wks-6 months)	1	43	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.30, 0.79]
25.5 Pre-1990 - Behaviour 1. deteriorated/disturbed/unco-operative	9	1085	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.26, 0.92]
25.6 1990 to 2002 - Behaviour 1. deteriorated/ disturbed/unco-operative	1	42	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.60, 1.29]
26 SENSITIVITY ANALYSIS: 1. RANDOMISATION	14		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
26.1 not stated - Global state: 1. No overall improvement (9 weeks - 6 months)	1	43	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.30, 0.79]
26.2 stated - Global state: 1. No overall improvement (9 weeks - 6 months)	13	1121	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.75, 0.85]
27 SENSITIVITY ANALYSIS: 2. ASSUMPTIONS FOR LOST BINARY DATA	14		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
27.1 LOCF - Global state: 1. No overall improvement (0-8 weeks)	2	86	Risk Ratio (M-H, Random, 95% CI)	0.46 [0.17, 1.29]
27.2 not LOCF - Global state: 1. No overall improvement (0-8 weeks)	12	671	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.49, 0.88]

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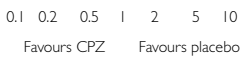
Analysis 1.1. Comparison 1 CHLORPROMAZINE versus PLACEBO, Outcome 1 Death.

Review: Chlorpromazine versus placebo for schizophrenia

Comparison: 1 CHLORPROMAZINE versus PLACEBO

Outcome: 1 Death

Study or subgroup	Chlorpromazine n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Baker 1959	0/7	0/7			Not estimable
Total (95% CI)	7	7			**Not estimable**
Total events: 0 (Chlorpromazine), 0 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Test for subgroup differences: Not applicable					



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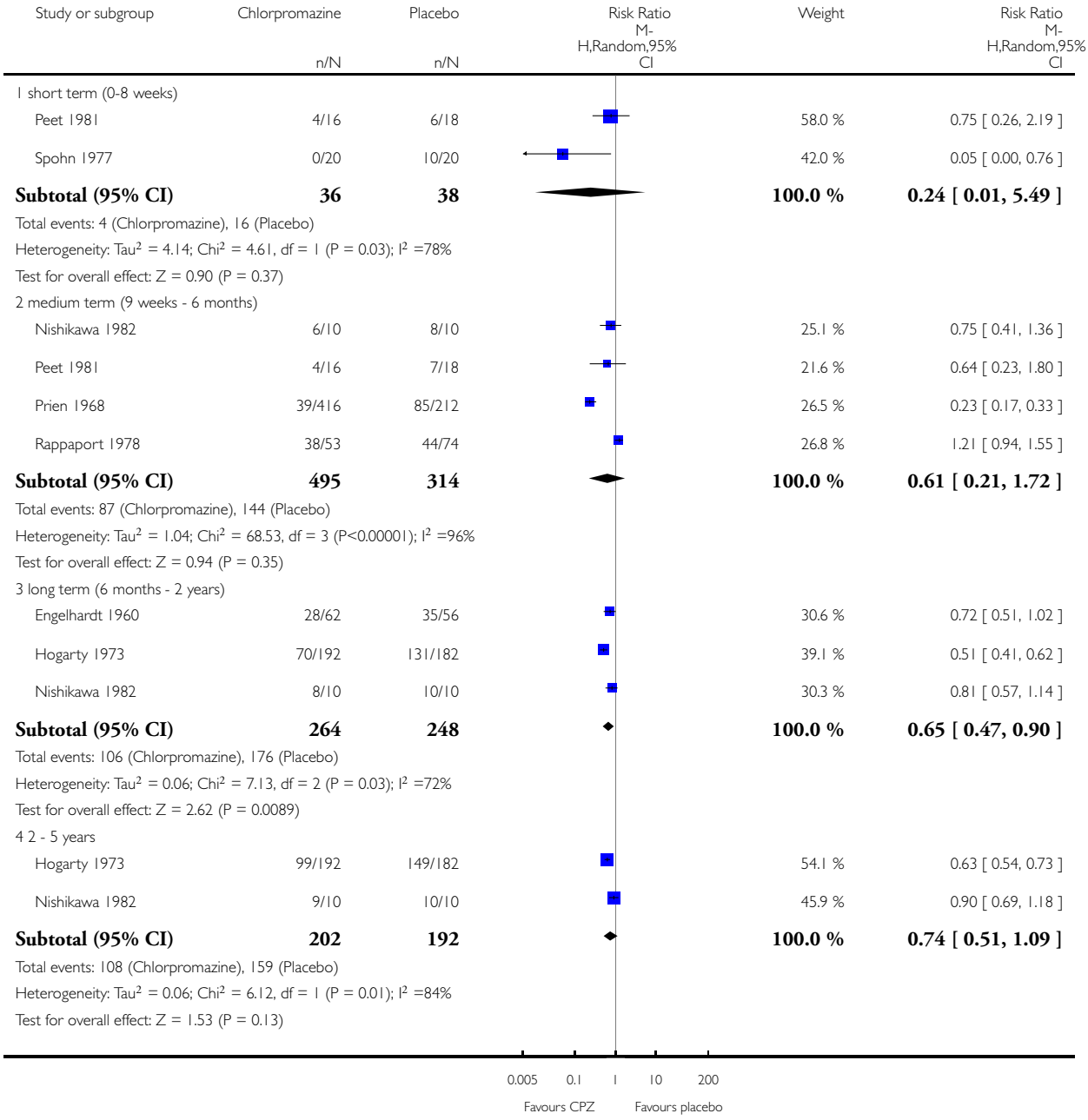
Analysis 1.2. Comparison 1 CHLORPROMAZINE versus PLACEBO, Outcome 2 Relapse.

Review: Chlorpromazine versus placebo for schizophrenia

Comparison: 1 CHLORPROMAZINE versus PLACEBO

Outcome: 2 Relapse



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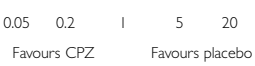
Analysis 1.3. Comparison 1 CHLORPROMAZINE versus PLACEBO, Outcome 3 Global state: 1a. No overall improvement (psychiatrist-rated).

Review: Chlorpromazine versus placebo for schizophrenia

Comparison: 1 CHLORPROMAZINE versus PLACEBO

Outcome: 3 Global state: 1a. No overall improvement (psychiatrist-rated)

Study or subgroup	Chlorpromazine n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 short term (0-8 weeks)					
Baker 1959	7/7	6/7		10.5 %	1.15 [0.79, 1.68]
Chouinard 1990 (1)	9/21	13/21		8.3 %	0.69 [0.38, 1.26]
Clark 1971 (2)	3/23	11/21		4.4 %	0.25 [0.08, 0.77]
Cooper 2000	26/53	35/53		11.0 %	0.74 [0.53, 1.04]
Fink 1963	10/51	30/44		8.4 %	0.29 [0.16, 0.52]
Hankoff 1962	12/16	65/68		11.4 %	0.78 [0.59, 1.05]
Kurland 1961	9/33	30/74		8.1 %	0.67 [0.36, 1.25]
Ramu 1999	6/27	18/27		6.9 %	0.33 [0.16, 0.71]
Reschke 1974	7/10	4/11		5.9 %	1.93 [0.80, 4.64]
Shepherd 1956	3/8	10/16		5.3 %	0.60 [0.23, 1.59]
Somerville 1960	7/15	23/30		8.5 %	0.61 [0.34, 1.08]
Vaughan 1955	8/24	19/24		8.3 %	0.42 [0.23, 0.77]
Walsh 1959	2/22	8/22		3.1 %	0.25 [0.06, 1.05]
Subtotal (95% CI)	**310**	**418**		**100.0 %**	**0.61 [0.46, 0.82]**
Total events: 109 (Chlorpromazine), 272 (Placebo)					
Heterogeneity: $Tau^2 = 0.17$; $Chi^2 = 38.79$, df = 12 (P = 0.00011); $I^2 = 69\%$					
Test for overall effect: Z = 3.33 (P = 0.00087)					
2 medium term (9 weeks - 6 months)					
Ban 1975	6/10	8/10		5.9 %	0.75 [0.41, 1.36]
Bishop 1963	2/10	10/10		2.6 %	0.24 [0.08, 0.71]
Clark 1961	13/19	19/19		9.4 %	0.69 [0.51, 0.95]
Clark 1968a	10/18	30/36		7.7 %	0.67 [0.43, 1.03]
Clark 1970a	8/15	9/14		5.7 %	0.83 [0.45, 1.53]
Clark 1972	10/19	14/18		7.0 %	0.68 [0.41, 1.11]



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Study or subgroup	Chlorpromazine n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Clark 1977	3/9	9/9		3.7 %	0.37 [0.16, 0.87]
Grygier 1958	13/15	13/15		9.9 %	1.00 [0.76, 1.32]
Hall 1955	56/87	72/88		11.1 %	0.79 [0.65, 0.95]
Hine 1958	6/11	11/11		6.5 %	0.57 [0.33, 0.96]
Prien 1968 (3)	380/416	205/212		12.2 %	0.94 [0.91, 0.98]
Ramu 1999a	10/23	18/20		7.1 %	0.48 [0.30, 0.79]
Reardon 1966	1/11	6/12		1.0 %	0.18 [0.03, 1.28]
Serafetinides 1972	12/14	13/13		10.3 %	0.86 [0.67, 1.11]
Subtotal (95% CI)	**677**	**487**		**100.0 %**	**0.71 [0.58, 0.86]**
Total events: 530 (Chlorpromazine), 437 (Placebo)					
Heterogeneity: $Tau^2 = 0.08$; $Chi^2 = 68.82$, df = 13 (P<0.00001); $I^2 = 81\%$					
Test for overall effect: Z = 3.44 (P = 0.00059)					

(1) LOCF

(2) LOCF

(3) Trial has a high dose arm and a low dose arm, data for the two arms has been combined.

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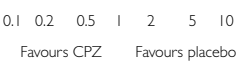
Analysis 1.4. Comparison 1 CHLORPROMAZINE versus PLACEBO, Outcome 4 Global state: 1b. No overall improvement (nurse-rated).

Review: Chlorpromazine versus placebo for schizophrenia

Comparison: 1 CHLORPROMAZINE versus PLACEBO

Outcome: 4 Global state: 1b. No overall improvement (nurse-rated)

Study or subgroup	Chlorpromazine n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 short term (0-8 weeks)					
Weckowicz 1960	11/14	13/15		100.0 %	0.91 [0.65, 1.27]
Subtotal (95% CI)	**14**	**15**		**100.0 %**	**0.91 [0.65, 1.27]**
Total events: 11 (Chlorpromazine), 13 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.57 (P = 0.57)					
2 medium term (9 weeks-6 months)					
Clark 1970a	7/15	14/14		34.5 %	0.48 [0.29, 0.82]
Clark 1972	9/19	18/18		43.7 %	0.49 [0.31, 0.78]
Clark 1977	4/9	9/9		21.9 %	0.47 [0.24, 0.95]
Subtotal (95% CI)	**43**	**41**		**100.0 %**	**0.48 [0.35, 0.66]**
Total events: 20 (Chlorpromazine), 41 (Placebo)					
Heterogeneity: Chi^2 = 0.00, df = 2 (P = 1.00); I^2 =0.0%					
Test for overall effect: Z = 4.54 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 7.13, df = 1 (P = 0.01), I^2 =86%					



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Analysis 1.5. Comparison 1 CHLORPROMAZINE versus PLACEBO, Outcome 5 Global state: 2. Average endpoint score - short term (CGI, high score=worse).

Review: Chlorpromazine versus placebo for schizophrenia

Comparison: 1 CHLORPROMAZINE versus PLACEBO

Outcome: 5 Global state: 2. Average endpoint score - short term (CGI, high score=worse)

Study or subgroup	Chlorpromazine N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Borison 1991	9	4.4 (0.5)	10	4.3 (0.5)		100.0 %	0.10 [-0.35, 0.55]
Total (95% CI)	**9**		**10**			**100.0 %**	**0.10 [-0.35, 0.55]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.44 (P = 0.66)

Test for subgroup differences: Not applicable

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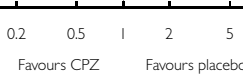
Analysis 1.6. Comparison 1 CHLORPROMAZINE versus PLACEBO, Outcome 6 Global state: 3a. Severity of illness, severely ill or worse (CGI 5+ points, psychiatrist-rated).

Review: Chlorpromazine versus placebo for schizophrenia

Comparison: 1 CHLORPROMAZINE versus PLACEBO

Outcome: 6 Global state: 3a. Severity of illness, severely ill or worse (CGI 5+ points, psychiatrist-rated)

Study or subgroup	Chlorpromazine n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 short term (0-8 weeks)					
Clark 1971	4/23	8/21		100.0 %	0.46 [0.16, 1.30]
Subtotal (95% CI)	**23**	**21**		**100.0 %**	**0.46 [0.16, 1.30]**
Total events: 4 (Chlorpromazine), 8 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.47 (P = 0.14)					
2 medium term (9 weeks - 6 months)					
Clark 1970a	3/15	6/14		2.3 %	0.47 [0.14, 1.52]
Clark 1972	9/19	14/18		5.4 %	0.61 [0.36, 1.04]
Prien 1968	298/416	186/212		92.3 %	0.82 [0.75, 0.88]
Subtotal (95% CI)	**450**	**244**		**100.0 %**	**0.80 [0.74, 0.86]**
Total events: 310 (Chlorpromazine), 206 (Placebo)					
Heterogeneity: Chi^2 = 2.12, df = 2 (P = 0.35); I^2 =6%					
Test for overall effect: Z = 5.52 (P < 0.00001)					



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Analysis 1.7. Comparison 1 CHLORPROMAZINE versus PLACEBO, Outcome 7 Global state: 3b. Severity of illness, severely ill or worse - medium term (CGI 5+ points, nurse-rated).

Review: Chlorpromazine versus placebo for schizophrenia

Comparison: 1 CHLORPROMAZINE versus PLACEBO

Outcome: 7 Global state: 3b. Severity of illness, severely ill or worse - medium term (CGI 5+ points, nurse-rated)

Study or subgroup	Chlorpromazine n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Clark 1970a	8/15	14/14		52.9 %	0.55 [0.34, 0.88]
Clark 1972	10/19	13/18		47.1 %	0.73 [0.44, 1.22]
Total (95% CI)	**34**	**32**		**100.0 %**	**0.63 [0.45, 0.90]**
Total events: 18 (Chlorpromazine), 27 (Placebo)					
Heterogeneity: Chi^2 = 0.64, df = 1 (P = 0.42); I^2 =0.0%					
Test for overall effect: Z = 2.57 (P = 0.010)					
Test for subgroup differences: Not applicable					

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Analysis 1.8. Comparison 1 CHLORPROMAZINE versus PLACEBO, Outcome 8 Leaving the study early.

Review: Chlorpromazine versus placebo for schizophrenia

Comparison: 1 CHLORPROMAZINE versus PLACEBO

Outcome: 8 Leaving the study early

Study or subgroup	Chlorpromazine n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 short term (0-8 weeks)					
Baker 1959	0/7	0/7			Not estimable
Chouinard 1990	4/21	7/21		5.3 %	0.57 [0.20, 1.66]
Clark 1971	3/23	4/21		3.2 %	0.68 [0.17, 2.71]
Cole 1964	10/112	37/125		26.5 %	0.30 [0.16, 0.58]
Cooper 2000	25/53	25/53		18.9 %	1.00 [0.67, 1.50]
Fink 1963	0/12	0/7			Not estimable
Hamill 1975	6/22	5/22		3.8 %	1.20 [0.43, 3.36]
Hamilton 1960	0/18	0/18			Not estimable
Hankoff 1962	8/25	23/95		7.3 %	1.32 [0.67, 2.59]
Klein 1973	0/46	0/42			Not estimable
Kurland 1961	24/33	63/74		29.4 %	0.85 [0.68, 1.07]
Peet 1981	6/16	8/18		5.7 %	0.84 [0.37, 1.91]
Reschke 1974	0/10	0/11			Not estimable
Shepherd 1956	0/8	0/16			Not estimable
Simon 1958	0/20	0/20			Not estimable
Somerville 1960	0/15	0/30			Not estimable
Walsh 1959	0/22	0/22			Not estimable
Subtotal (95% CI)	**463**	**602**		**100.0 %**	**0.76 [0.63, 0.92]**
Total events: 86 (Chlorpromazine), 172 (Placebo)					
Heterogeneity: Chi^2 = 14.19, df = 7 (P = 0.05); I^2 =51%					
Test for overall effect: Z = 2.76 (P = 0.0059)					
2 medium term (9 weeks - 6 months)					
Abrams 1958	2/20	4/20		2.2 %	0.50 [0.10, 2.43]
Ban 1975	0/10	0/10			Not estimable
Bishop 1963	0/10	0/10			Not estimable
Clark 1967	11/51	0/21		0.4 %	9.73 [0.60, 157.98]

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Study or subgroup	Chlorpromazine n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Clark 1968a	3/18	3/36		1.1 %	2.00 [0.45, 8.94]
Clark 1968b	1/23	0/23		0.3 %	3.00 [0.13, 70.02]
Clark 1970a	2/15	1/14		0.6 %	1.87 [0.19, 18.38]
Clark 1970b	5/53	1/18		0.8 %	1.70 [0.21, 13.58]
Clark 1972	2/19	2/18		1.1 %	0.95 [0.15, 6.03]
Clark 1977	0/9	2/9		1.4 %	0.20 [0.01, 3.66]
Cohen 1968	0/42	0/42			Not estimable
Dean 1958	0/9	0/9			Not estimable
Fleming 1959	4/21	4/21		2.2 %	1.00 [0.29, 3.48]
Gwynne 1962	0/26	3/26		1.9 %	0.14 [0.01, 2.63]
Hall 1955	3/87	0/88		0.3 %	7.08 [0.37, 135.06]
Hine 1958	1/11	0/11		0.3 %	3.00 [0.14, 66.53]
Letemendia 1967	0/14	0/14			Not estimable
Peet 1981	6/16	9/18		4.6 %	0.75 [0.34, 1.64]
Prien 1968	83/416	81/212		58.2 %	0.52 [0.40, 0.68]
Rappaport 1978	14/53	33/74		14.9 %	0.59 [0.35, 0.99]
Reardon 1966	2/11	4/12		2.1 %	0.55 [0.12, 2.41]
Saretsky 1966	0/20	0/20			Not estimable
Schiele 1961	0/20	1/20		0.8 %	0.33 [0.01, 7.72]
Serafetinides 1972	3/14	1/13		0.6 %	2.79 [0.33, 23.52]
Smith 1961	2/15	0/15		0.3 %	5.00 [0.26, 96.13]
Tetreault 1969	0/15	0/15			Not estimable
Xiong 1994	0/12	11/12		6.2 %	0.04 [0.00, 0.66]
Subtotal (95% CI)	**1030**	**801**		**100.0 %**	**0.64 [0.53, 0.78]**
Total events: 144 (Chlorpromazine), 160 (Placebo)					
Heterogeneity: Chi^2 = 24.66, df = 19 (P = 0.17); I^2 =23%					
Test for overall effect: Z = 4.46 (P < 0.00001)					
3 long term (>6 months - 2 years)					
Engelhardt 1960	25/62	19/56		58.1 %	1.19 [0.74, 1.91]
Hogarty 1973	13/192	14/182		41.9 %	0.88 [0.43, 1.82]
Subtotal (95% CI)	**254**	**238**		**100.0 %**	**1.06 [0.71, 1.59]**
Total events: 38 (Chlorpromazine), 33 (Placebo)					
Heterogeneity: Chi^2 = 0.47, df = 1 (P = 0.49); I^2 =0.0%					
Test for overall effect: Z = 0.28 (P = 0.78)					

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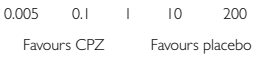
Study or subgroup	Chlorpromazine n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
4 >2 - 5 years					
Hogarty 1973	13/192	18/182		100.0 %	0.68 [0.35, 1.36]
Subtotal (95% CI)	**192**	**182**		**100.0 %**	**0.68 [0.35, 1.36]**
Total events: 13 (Chlorpromazine), 18 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.09 (P = 0.28)					



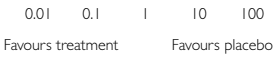
Analysis 1.9. Comparison 1 CHLORPROMAZINE versus PLACEBO, Outcome 9 Mental state: 1. Improved - short term (BPRS, 50% change).

Review: Chlorpromazine versus placebo for schizophrenia

Comparison: 1 CHLORPROMAZINE versus PLACEBO

Outcome: 9 Mental state: 1. Improved - short term (BPRS, 50% change)

Study or subgroup	Chlorpromazine n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Cooper 2000	5/53	4/53		100.0 %	1.25 [0.36, 4.40]
Total (95% CI)	**53**	**53**		**100.0 %**	**1.25 [0.36, 4.40]**
Total events: 5 (Chlorpromazine), 4 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.35 (P = 0.73)					
Test for subgroup differences: Not applicable					



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Analysis 1.10. Comparison 1 CHLORPROMAZINE versus PLACEBO, Outcome 10 Mental state: 2. Average endpoint scores (BPRS, high score=worse).

Review: Chlorpromazine versus placebo for schizophrenia

Comparison: 1 CHLORPROMAZINE versus PLACEBO

Outcome: 10 Mental state: 2. Average endpoint scores (BPRS, high score=worse)

Study or subgroup	Chlorpromazine N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 short term (0-8 weeks)							
Tetreault 1969	15	42.5 (7.64)	15	48.2 (7.64)		44.9 %	-5.70 [-11.17, -0.23]
Borison 1991	9	46.4 (4.5)	10	50.5 (6.4)		55.1 %	-4.10 [-9.04, 0.84]
Subtotal (95% CI)	**24**		**25**			**100.0 %**	**-4.82 [-8.48, -1.15]**
Heterogeneity: Chi^2 = 0.18, df = 1 (P = 0.67); I^2 =0.0%							
Test for overall effect: Z = 2.58 (P = 0.010)							
2 medium term (9 weeks - 6 months)							
Tetreault 1969	15	41.2 (9.88)	15	48.9 (9.88)		100.0 %	-7.70 [-14.77, -0.63]
Subtotal (95% CI)	**15**		**15**			**100.0 %**	**-7.70 [-14.77, -0.63]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.13 (P = 0.033)							
Test for subgroup differences: Chi^2 = 0.50, df = 1 (P = 0.48), I^2 =0.0%							

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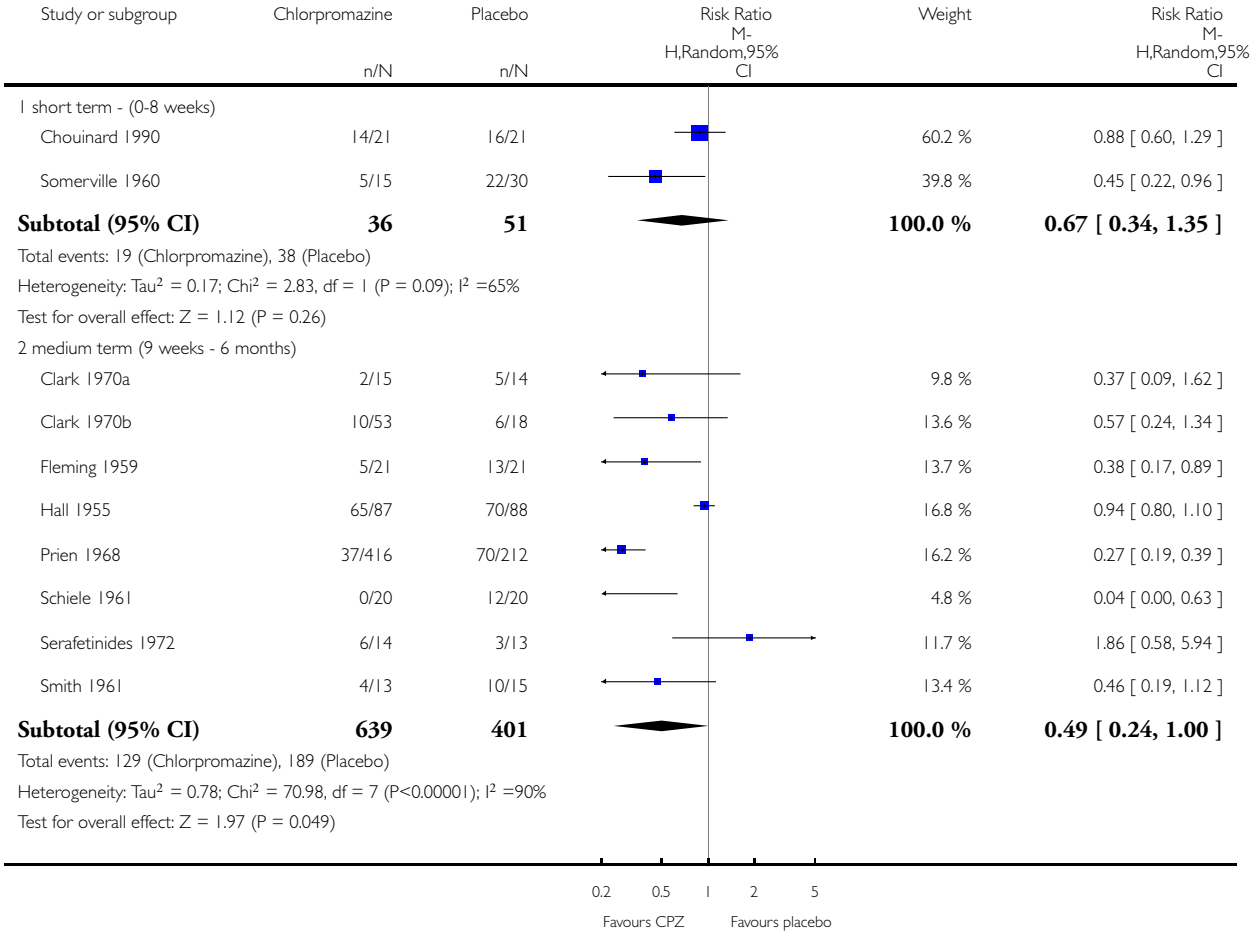
Analysis 1.11. Comparison 1 CHLORPROMAZINE versus PLACEBO, Outcome 11 Behaviour: 1. Deteriorated/ disturbed/un-cooperative.

Review: Chlorpromazine versus placebo for schizophrenia

Comparison: 1 CHLORPROMAZINE versus PLACEBO

Outcome: 11 Behaviour: 1. Deteriorated/ disturbed/un-cooperative



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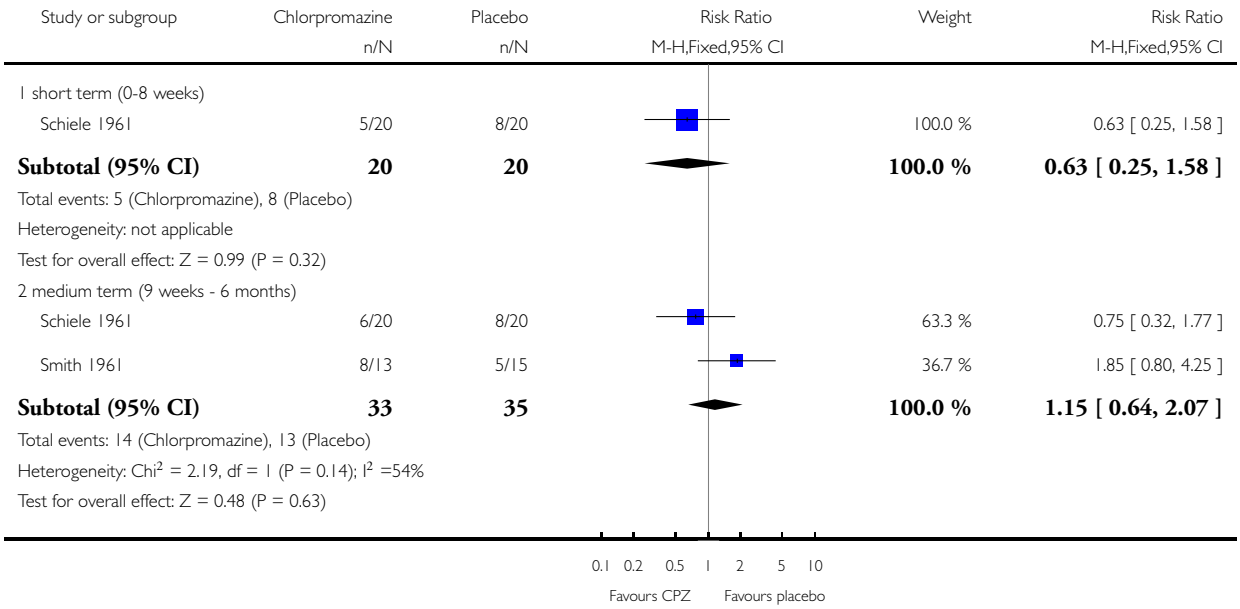
Analysis 1.12. Comparison 1 CHLORPROMAZINE versus PLACEBO, Outcome 12 Behaviour: 2. Unchanged.

Review: Chlorpromazine versus placebo for schizophrenia

Comparison: 1 CHLORPROMAZINE versus PLACEBO

Outcome: 12 Behaviour: 2. Unchanged



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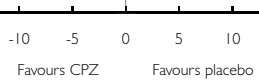
Analysis 1.13. Comparison 1 CHLORPROMAZINE versus PLACEBO, Outcome 13 Behaviour: 3. Average endpoint scores (RRS, high score=worse).

Review: Chlorpromazine versus placebo for schizophrenia

Comparison: 1 CHLORPROMAZINE versus PLACEBO

Outcome: 13 Behaviour: 3. Average endpoint scores (RRS, high score=worse)

Study or subgroup	Chlorpromazine N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 short term (0-8 weeks)							
Tetreault 1969	15	14.5 (5.36)	15	17.4 (5.36)		100.0 %	-2.90 [-6.74, 0.94]
Subtotal (95% CI)	**15**		**15**			**100.0 %**	**-2.90 [-6.74, 0.94]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.48 (P = 0.14)							
2 medium term (9 weeks - 6 months)							
Tetreault 1969	15	16.8 (6.8)	15	21.4 (6.8)		100.0 %	-4.60 [-9.47, 0.27]
Subtotal (95% CI)	**15**		**15**			**100.0 %**	**-4.60 [-9.47, 0.27]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.85 (P = 0.064)							
Test for subgroup differences: Chi^2 = 0.29, df = 1 (P = 0.59), I^2 =0.0%							



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Analysis 1.14. Comparison 1 CHLORPROMAZINE versus PLACEBO, Outcome 14 Behaviour: 4. Average endpoint score - short term (PBRS, high score=good).

Review: Chlorpromazine versus placebo for schizophrenia

Comparison: 1 CHLORPROMAZINE versus PLACEBO

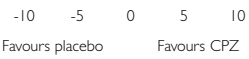
Outcome: 14 Behaviour: 4. Average endpoint score - short term (PBRS, high score=good)

Study or subgroup	Chlorpromazine N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Baker 1959	7	22.6 (3.2)	7	16.6 (4.4)		100.0 %	6.00 [1.97, 10.03]
Total (95% CI)	**7**		**7**			**100.0 %**	**6.00 [1.97, 10.03]**

Heterogeneity: not applicable

Test for overall effect: Z = 2.92 (P = 0.0035)

Test for subgroup differences: Not applicable



Analysis 1.15. Comparison 1 CHLORPROMAZINE versus PLACEBO, Outcome 15 Behaviour: 5. Average endpoint scores - medium term (Fergus Falls Behavioural rating scale).

Review: Chlorpromazine versus placebo for schizophrenia

Comparison: 1 CHLORPROMAZINE versus PLACEBO

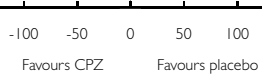
Outcome: 15 Behaviour: 5. Average endpoint scores - medium term (Fergus Falls Behavioural rating scale)

Study or subgroup	Chlorpromazine N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Ramu 1999a (1)	22	22.59 (7.56)	20	24.95 (4.63)		100.0 %	-2.36 [-6.11, 1.39]
Total (95% CI)	**22**		**20**			**100.0 %**	**-2.36 [-6.11, 1.39]**

Heterogeneity: not applicable

Test for overall effect: Z = 1.23 (P = 0.22)

Test for subgroup differences: Not applicable



(1) N not reported, assumed to be the number reported in each group after losses to follow-up.

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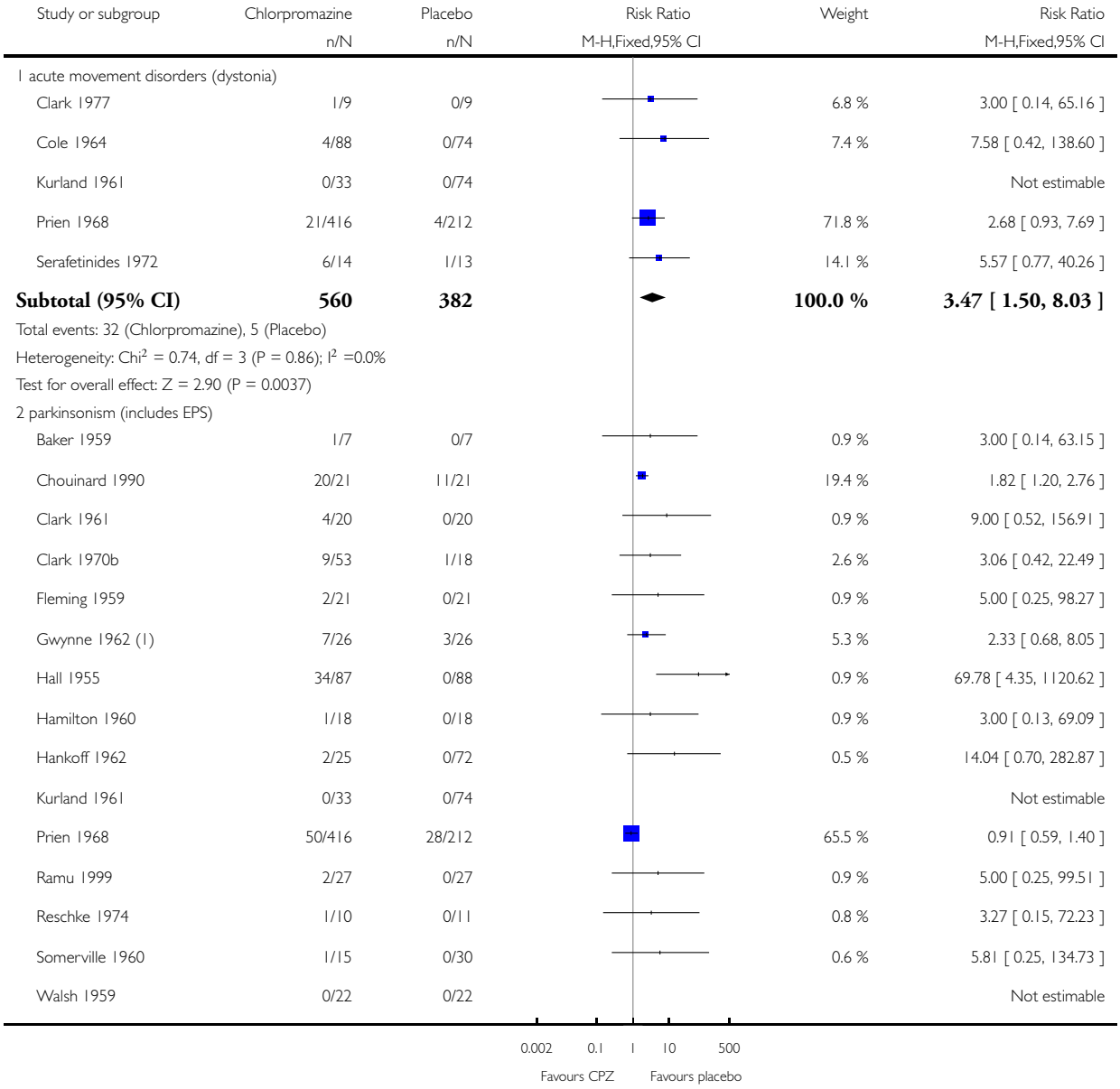
Analysis 1.16. Comparison 1 CHLORPROMAZINE versus PLACEBO, Outcome 16 Adverse effects: 1. Movement disorders.

Review: Chlorpromazine versus placebo for schizophrenia

Comparison: 1 CHLORPROMAZINE versus PLACEBO

Outcome: 16 Adverse effects: 1. Movement disorders



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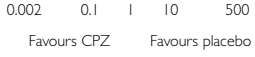
Study or subgroup	Chlorpromazine n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Subtotal (95% CI)	**801**	**667**	◆	**100.0 %**	**2.11 [1.59, 2.80]**
Total events: 134 (Chlorpromazine), 43 (Placebo)					
Heterogeneity: Chi^2 = 25.08, df = 12 (P = 0.01); I^2 =52%					
Test for overall effect: Z = 5.19 (P < 0.00001)					
3 tremor					
Clark 1968b	3/23	0/23		2.8 %	7.00 [0.38, 128.33]
Clark 1970a	0/15	0/14			Not estimable
Clark 1971	6/23	2/21		11.6 %	2.74 [0.62, 12.12]
Clark 1972	4/19	2/18		11.4 %	1.89 [0.39, 9.11]
Cole 1964	5/88	4/74		24.1 %	1.05 [0.29, 3.77]
Peet 1981	11/16	8/18		41.8 %	1.55 [0.84, 2.86]
Schiele 1961	0/20	1/20		8.3 %	0.33 [0.01, 7.72]
Subtotal (95% CI)	**204**	**188**	◆	**100.0 %**	**1.66 [1.01, 2.73]**
Total events: 29 (Chlorpromazine), 17 (Placebo)					
Heterogeneity: Chi^2 = 2.94, df = 5 (P = 0.71); I^2 =0.0%					
Test for overall effect: Z = 1.98 (P = 0.048)					
4 rigidity					
Clark 1968a	7/18	6/36		18.6 %	2.33 [0.92, 5.93]
Clark 1968b	2/23	0/23		2.3 %	5.00 [0.25, 98.75]
Clark 1970a	0/15	0/14			Not estimable
Clark 1971	10/23	3/21		14.6 %	3.04 [0.97, 9.58]
Clark 1972	5/19	2/18		9.5 %	2.37 [0.52, 10.70]
Cole 1964	22/88	10/74		50.4 %	1.85 [0.94, 3.65]
Schiele 1961	2/20	1/20		4.6 %	2.00 [0.20, 20.33]
Subtotal (95% CI)	**206**	**206**	◆	**100.0 %**	**2.24 [1.42, 3.54]**
Total events: 48 (Chlorpromazine), 22 (Placebo)					
Heterogeneity: Chi^2 = 0.88, df = 5 (P = 0.97); I^2 =0.0%					
Test for overall effect: Z = 3.46 (P = 0.00053)					
5 akathisia					
Clark 1968b	1/23	0/23		0.9 %	3.00 [0.13, 70.02]
Clark 1970a	0/15	0/14			Not estimable
Clark 1970b	4/53	2/18		5.3 %	0.68 [0.14, 3.40]
Clark 1971	6/23	2/21		3.7 %	2.74 [0.62, 12.12]
Clark 1972	2/19	2/18		3.6 %	0.95 [0.15, 6.03]
Cole 1964	5/88	3/74		5.8 %	1.40 [0.35, 5.67]
Kurland 1961	0/33	0/74			Not estimable



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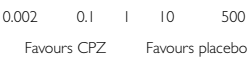
Study or subgroup	Chlorpromazine n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Prien 1968	38/416	34/212		79.8 %	0.57 [0.37, 0.88]
Schiele 1961	2/20	0/20		0.9 %	5.00 [0.26, 98.00]
Subtotal (95% CI)	**690**	**474**		**100.0 %**	**0.78 [0.54, 1.11]**
Total events: 58 (Chlorpromazine), 43 (Placebo)					
Heterogeneity: Chi^2 = 7.71, df = 6 (P = 0.26); I^2 =22%					
Test for overall effect: Z = 1.37 (P = 0.17)					
6 chronic movement disorders (tardive dyskinesia)					
Clark 1977	3/9	2/9		100.0 %	1.50 [0.32, 6.94]
Subtotal (95% CI)	**9**	**9**		**100.0 %**	**1.50 [0.32, 6.94]**
Total events: 3 (Chlorpromazine), 2 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.52 (P = 0.60)					
7 ataxia					
Hankoff 1962	3/25	1/72		100.0 %	8.64 [0.94, 79.31]
Subtotal (95% CI)	**25**	**72**		**100.0 %**	**8.64 [0.94, 79.31]**
Total events: 3 (Chlorpromazine), 1 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.91 (P = 0.057)					



(1) N not reported, assumed to be N randomised.

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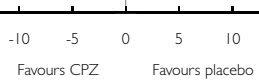
Analysis 1.17. Comparison 1 CHLORPROMAZINE versus PLACEBO, Outcome 17 Adverse effects: 2. Movement disorders: Average endpoint scores (Extrapyramidal Bilan, high score=worse).

Review: Chlorpromazine versus placebo for schizophrenia

Comparison: 1 CHLORPROMAZINE versus PLACEBO

Outcome: 17 Adverse effects: 2. Movement disorders: Average endpoint scores (Extrapyramidal Bilan, high score=worse)

Study or subgroup	Chlorpromazine N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 short term (0-8 weeks)							
Tetreault 1969	15	7.1 (2.55)	15	8.5 (2.55)		100.0 %	-1.40 [-3.22, 0.42]
Subtotal (95% CI)	**15**		**15**			**100.0 %**	**-1.40 [-3.22, 0.42]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.50 (P = 0.13)							
2 medium term (9 weeks - 6 months)							
Tetreault 1969	15	6.1 (3.34)	15	7.9 (3.34)		100.0 %	-1.80 [-4.19, 0.59]
Subtotal (95% CI)	**15**		**15**			**100.0 %**	**-1.80 [-4.19, 0.59]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.48 (P = 0.14)							
Test for subgroup differences: Chi^2 = 0.07, df = 1 (P = 0.79), I^2 =0.0%							



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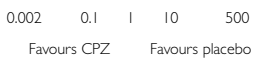
Analysis 1.18. Comparison 1 CHLORPROMAZINE versus PLACEBO, Outcome 18 Adverse effects: 1. Central nervous system.

Review: Chlorpromazine versus placebo for schizophrenia

Comparison: 1 CHLORPROMAZINE versus PLACEBO

Outcome: 18 Adverse effects: 1. Central nervous system

Study or subgroup	Chlorpromazine n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 sleepiness					
Baker 1959	1/7	0/7		0.5 %	3.00 [0.14, 63.15]
Clark 1961	4/20	6/20		6.4 %	0.67 [0.22, 2.01]
Clark 1968a	7/18	3/36		2.1 %	4.67 [1.37, 15.94]
Clark 1968b	9/23	3/23		3.2 %	3.00 [0.93, 9.68]
Clark 1970a	8/15	1/14		1.1 %	7.47 [1.07, 52.33]
Clark 1970b	15/53	1/18		1.6 %	5.09 [0.72, 35.89]
Clark 1971	17/23	6/21		6.7 %	2.59 [1.26, 5.31]
Clark 1972	9/19	3/18		3.3 %	2.84 [0.91, 8.86]
Clark 1977	3/9	0/9		0.5 %	7.00 [0.41, 118.69]
Cole 1964	47/88	7/74		8.1 %	5.65 [2.72, 11.73]
Gwynne 1962 (1)	12/26	1/26		1.1 %	12.00 [1.68, 85.72]
Hamilton 1960	0/18	0/18			Not estimable
Hankoff 1962	10/25	9/72		4.9 %	3.20 [1.47, 6.96]
Payne 1960	2/7	0/7		0.5 %	5.00 [0.28, 88.53]
Peet 1981	11/16	9/18		9.0 %	1.38 [0.78, 2.43]
Prien 1968	110/416	30/212		42.2 %	1.87 [1.29, 2.70]
Ramu 1999a	3/22	0/20		0.6 %	6.39 [0.35, 116.57]
Reschke 1974	6/10	0/11		0.5 %	14.18 [0.90, 223.54]
Schiele 1961	4/20	3/20		3.2 %	1.33 [0.34, 5.21]
Serafetinides 1972	11/14	3/13		3.3 %	3.40 [1.22, 9.53]
Somerville 1960	5/15	0/30		0.4 %	21.31 [1.26, 361.69]
Walsh 1959	2/22	0/22		0.5 %	5.00 [0.25, 98.52]
Weckowicz 1960	2/16	0/16		0.5 %	5.00 [0.26, 96.59]
Subtotal (95% CI)	**902**	**725**		**100.0 %**	**2.79 [2.25, 3.45]**



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Study or subgroup	Chlorpromazine n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Total events: 298 (Chlorpromazine), 85 (Placebo)					
Heterogeneity: Chi^2 = 30.61, df = 21 (P = 0.08); I^2 =31%					
Test for overall effect: Z = 9.45 (P < 0.00001)					
2 fits / loss of consciousness					
Clark 1972	2/19	3/18		65.0 %	0.63 [0.12, 3.35]
Prien 1968	14/416	0/212		14.0 %	14.81 [0.89, 247.12]
Tetreault 1969	3/15	1/15		21.1 %	3.00 [0.35, 25.68]
Subtotal (95% CI)	**450**	**245**		**100.0 %**	**3.11 [1.05, 9.18]**
Total events: 19 (Chlorpromazine), 4 (Placebo)					
Heterogeneity: Chi^2 = 4.69, df = 2 (P = 0.10); I^2 =57%					
Test for overall effect: Z = 2.05 (P = 0.040)					
3 weakness					
Hine 1958	1/11	0/11		16.7 %	3.00 [0.14, 66.53]
Schiele 1961	1/20	0/20		16.7 %	3.00 [0.13, 69.52]
Tetreault 1969	7/15	2/15		66.7 %	3.50 [0.86, 14.18]
Subtotal (95% CI)	**46**	**46**		**100.0 %**	**3.33 [1.02, 10.88]**
Total events: 9 (Chlorpromazine), 2 (Placebo)					
Heterogeneity: Chi^2 = 0.01, df = 2 (P = 0.99); I^2 =0.0%					
Test for overall effect: Z = 1.99 (P = 0.046)					
4 convulsions					
Gwynne 1962 (2)	0/26	1/26		100.0 %	0.33 [0.01, 7.82]
Subtotal (95% CI)	**26**	**26**		**100.0 %**	**0.33 [0.01, 7.82]**
Total events: 0 (Chlorpromazine), 1 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.68 (P = 0.50)					

(1) N not reported, assumed to be N randomised.

(2) N not reported, assumed to be N randomised.

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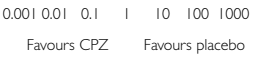
Analysis 1.19. Comparison 1 CHLORPROMAZINE versus PLACEBO, Outcome 19 Adverse effects: 3. Blood, skin, liver, eyes.

Review: Chlorpromazine versus placebo for schizophrenia

Comparison: 1 CHLORPROMAZINE versus PLACEBO

Outcome: 19 Adverse effects: 3. Blood, skin, liver, eyes

Study or subgroup	Chlorpromazine n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 blood problems (agranulocytosis, leukopenia)					
Clark 1961	1/20	0/20		10.0 %	3.00 [0.13, 69.52]
Clark 1968b	1/23	0/23		10.0 %	3.00 [0.13, 70.02]
Clark 1970b	4/53	1/18		29.7 %	1.36 [0.16, 11.38]
Fleming 1959	1/21	0/21		10.0 %	3.00 [0.13, 69.70]
Kurland 1961	1/33	0/74		6.2 %	6.62 [0.28, 158.32]
Prien 1968	1/42	0/16		14.3 %	1.19 [0.05, 27.70]
Tetreault 1969	1/15	1/15		19.9 %	1.00 [0.07, 14.55]
Subtotal (95% CI)	**207**	**187**		**100.0 %**	**2.08 [0.74, 5.83]**
Total events: 10 (Chlorpromazine), 2 (Placebo)					
Heterogeneity: Chi^2 = 1.23, df = 6 (P = 0.98); I^2 =0.0%					
Test for overall effect: Z = 1.39 (P = 0.16)					
2 rashes/itching/skin disorders					
Clark 1961	2/20	0/20		1.8 %	5.00 [0.26, 98.00]
Clark 1968a	4/18	3/36		7.1 %	2.67 [0.67, 10.66]
Clark 1968b	1/23	0/23		1.8 %	3.00 [0.13, 70.02]
Clark 1970b	5/53	1/18		5.3 %	1.70 [0.21, 13.58]
Clark 1971	4/23	2/21		7.5 %	1.83 [0.37, 8.96]
Clark 1972	4/19	2/18		7.3 %	1.89 [0.39, 9.11]
Cole 1964	3/88	2/74		7.8 %	1.26 [0.22, 7.35]
Dean 1958	0/9	0/9			Not estimable
Hine 1958	1/11	0/11		1.8 %	3.00 [0.14, 66.53]
Kurland 1961	2/33	1/74		2.2 %	4.48 [0.42, 47.74]
Prien 1968	17/416	11/212		52.0 %	0.79 [0.38, 1.65]
Schiele 1961	1/20	1/20		3.6 %	1.00 [0.07, 14.90]
Walsh 1959	1/22	0/22		1.8 %	3.00 [0.13, 69.87]
Subtotal (95% CI)	**755**	**558**		**100.0 %**	**1.45 [0.92, 2.29]**



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Study or subgroup	Chlorpromazine n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Total events: 45 (Chlorpromazine), 23 (Placebo)					
Heterogeneity: Chi² = 5.83, df = 11 (P = 0.88); I² =0.0%					
Test for overall effect: Z = 1.59 (P = 0.11)					
3 liver problems					
Clark 1970a	2/15	0/14		25.2 %	4.69 [0.24, 89.88]
Dean 1958	0/9	0/9			Not estimable
Hall 1955	3/87	0/88		24.2 %	7.08 [0.37, 135.06]
Serafetinides 1972	3/14	1/13		50.6 %	2.79 [0.33, 23.52]
Subtotal (95% CI)	**125**	**124**		**100.0 %**	**4.31 [0.98, 18.95]**
Total events: 8 (Chlorpromazine), 1 (Placebo)					
Heterogeneity: Chi² = 0.27, df = 2 (P = 0.87); I² =0.0%					
Test for overall effect: Z = 1.93 (P = 0.053)					
4 photosensitivity					
Clark 1971	7/23	2/21		18.5 %	3.20 [0.75, 13.70]
Clark 1972	8/19	2/18		18.1 %	3.79 [0.93, 15.51]
Clark 1977	1/9	0/9		4.4 %	3.00 [0.14, 65.16]
Prien 1968	50/416	4/212		46.8 %	6.37 [2.33, 17.40]
Serafetinides 1972	5/14	1/13		9.2 %	4.64 [0.62, 34.65]
Somerville 1960	10/15	0/30		3.0 %	40.69 [2.54, 650.71]
Subtotal (95% CI)	**496**	**303**		**100.0 %**	**6.04 [3.22, 11.32]**
Total events: 81 (Chlorpromazine), 9 (Placebo)					
Heterogeneity: Chi² = 3.25, df = 5 (P = 0.66); I² =0.0%					
Test for overall effect: Z = 5.61 (P < 0.00001)					
5 eye opacity / eye pigment problems					
Clark 1970a	0/15	0/14			Not estimable
Prien 1968	97/416	16/212		100.0 %	3.09 [1.87, 5.11]
Subtotal (95% CI)	**431**	**226**		**100.0 %**	**3.09 [1.87, 5.11]**
Total events: 97 (Chlorpromazine), 16 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 4.40 (P = 0.000011)					

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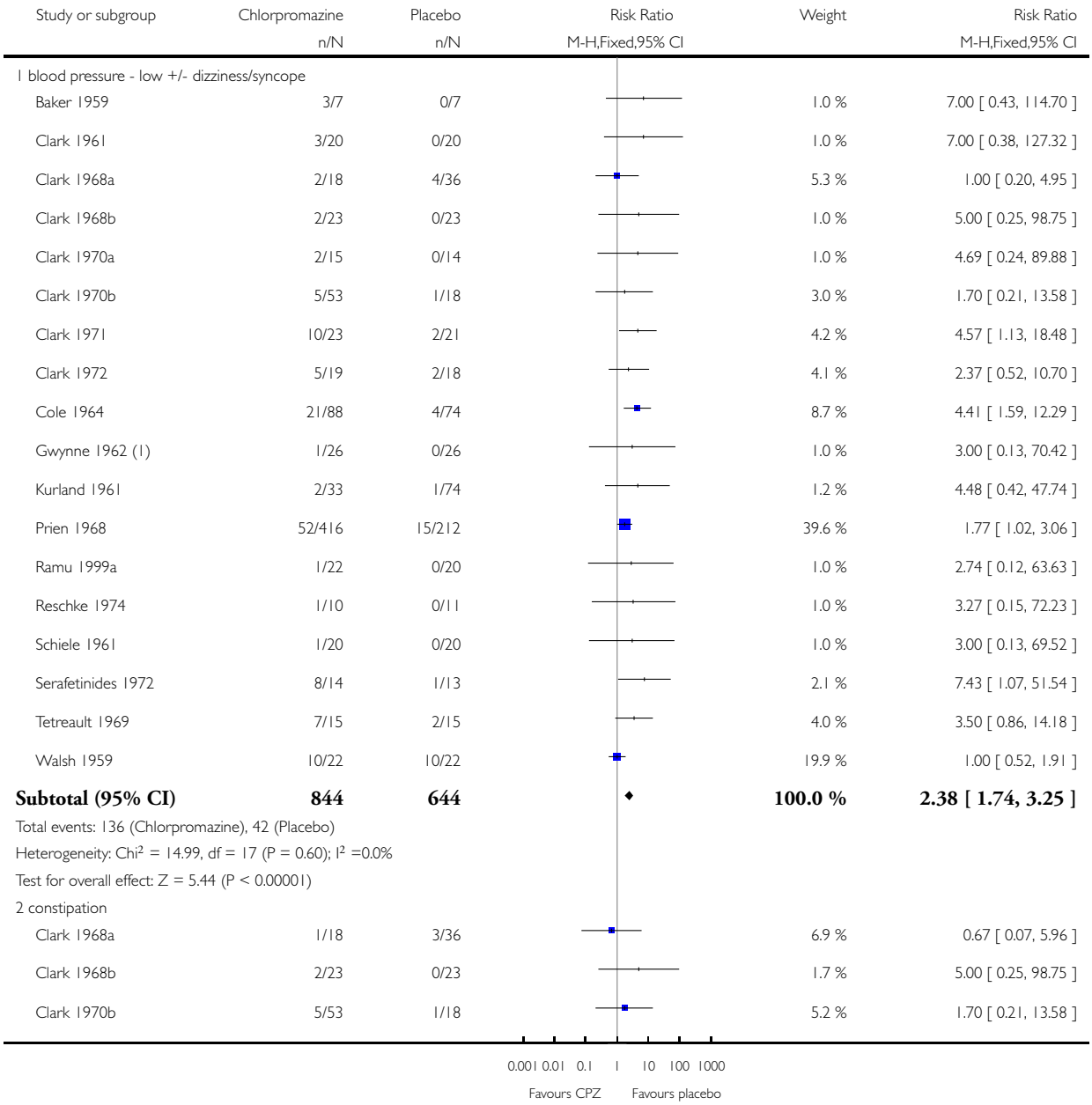
Analysis 1.20. Comparison 1 CHLORPROMAZINE versus PLACEBO, Outcome 20 Adverse effects: 4. Other.

Review: Chlorpromazine versus placebo for schizophrenia

Comparison: 1 CHLORPROMAZINE versus PLACEBO

Outcome: 20 Adverse effects: 4. Other



Study or subgroup	Chlorpromazine n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 blood pressure - low +/- dizziness/syncope					
Baker 1959	3/7	0/7		1.0 %	7.00 [0.43, 114.70]
Clark 1961	3/20	0/20		1.0 %	7.00 [0.38, 127.32]
Clark 1968a	2/18	4/36		5.3 %	1.00 [0.20, 4.95]
Clark 1968b	2/23	0/23		1.0 %	5.00 [0.25, 98.75]
Clark 1970a	2/15	0/14		1.0 %	4.69 [0.24, 89.88]
Clark 1970b	5/53	1/18		3.0 %	1.70 [0.21, 13.58]
Clark 1971	10/23	2/21		4.2 %	4.57 [1.13, 18.48]
Clark 1972	5/19	2/18		4.1 %	2.37 [0.52, 10.70]
Cole 1964	21/88	4/74		8.7 %	4.41 [1.59, 12.29]
Gwynne 1962 (1)	1/26	0/26		1.0 %	3.00 [0.13, 70.42]
Kurland 1961	2/33	1/74		1.2 %	4.48 [0.42, 47.74]
Prien 1968	52/416	15/212		39.6 %	1.77 [1.02, 3.06]
Ramu 1999a	1/22	0/20		1.0 %	2.74 [0.12, 63.63]
Reschke 1974	1/10	0/11		1.0 %	3.27 [0.15, 72.23]
Schiele 1961	1/20	0/20		1.0 %	3.00 [0.13, 69.52]
Serafetinides 1972	8/14	1/13		2.1 %	7.43 [1.07, 51.54]
Tetreault 1969	7/15	2/15		4.0 %	3.50 [0.86, 14.18]
Walsh 1959	10/22	10/22		19.9 %	1.00 [0.52, 1.91]
Subtotal (95% CI)	**844**	**644**		**100.0 %**	**2.38 [1.74, 3.25]**
Total events: 136 (Chlorpromazine), 42 (Placebo)					
Heterogeneity: Chi² = 14.99, df = 17 (P = 0.60); I² =0.0%					
Test for overall effect: Z = 5.44 (P < 0.00001)					
2 constipation					
Clark 1968a	1/18	3/36		6.9 %	0.67 [0.07, 5.96]
Clark 1968b	2/23	0/23		1.7 %	5.00 [0.25, 98.75]
Clark 1970b	5/53	1/18		5.2 %	1.70 [0.21, 13.58]

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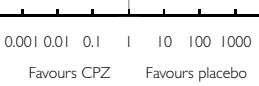
Study or subgroup	Chlorpromazine n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Clark 1971	4/23	2/21		7.2 %	1.83 [0.37, 8.96]
Clark 1972	3/19	2/18		7.1 %	1.42 [0.27, 7.54]
Clark 1977	0/9	1/9		5.2 %	0.33 [0.02, 7.24]
Cole 1964	29/88	9/74		33.8 %	2.71 [1.37, 5.35]
Prien 1968	19/416	6/212		27.5 %	1.61 [0.65, 3.98]
Serafetinides 1972	5/14	1/13		3.6 %	4.64 [0.62, 34.65]
Tetreault 1969	1/15	0/15		1.7 %	3.00 [0.13, 68.26]
Subtotal (95% CI)	**678**	**439**		**100.0 %**	**2.05 [1.33, 3.15]**
Total events: 69 (Chlorpromazine), 25 (Placebo)					
Heterogeneity: Chi^2 = 4.53, df = 9 (P = 0.87); I^2 =0.0%					
Test for overall effect: Z = 3.28 (P = 0.0010)					
3 urinary problems					
Clark 1971	4/23	2/21		28.5 %	1.83 [0.37, 8.96]
Cole 1964	4/88	1/74		14.8 %	3.36 [0.38, 29.44]
Gwynne 1962 (2)	0/26	0/26			Not estimable
Prien 1968	7/416	2/212		36.2 %	1.78 [0.37, 8.51]
Schiele 1961	0/20	1/20		20.5 %	0.33 [0.01, 7.72]
Subtotal (95% CI)	**573**	**353**		**100.0 %**	**1.73 [0.70, 4.30]**
Total events: 15 (Chlorpromazine), 6 (Placebo)					
Heterogeneity: Chi^2 = 1.42, df = 3 (P = 0.70); I^2 =0.0%					
Test for overall effect: Z = 1.19 (P = 0.24)					
4 blurred vision					
Clark 1968a	0/18	3/36		24.6 %	0.28 [0.02, 5.11]
Clark 1971	5/23	2/21		21.6 %	2.28 [0.49, 10.54]
Clark 1972	3/19	2/18		21.2 %	1.42 [0.27, 7.54]
Gwynne 1962 (3)	1/26	0/26		5.2 %	3.00 [0.13, 70.42]
Kurland 1961	0/33	0/74			Not estimable
Prien 1968	2/416	2/212		27.4 %	0.51 [0.07, 3.59]
Schiele 1961	0/20	0/20			Not estimable
Subtotal (95% CI)	**555**	**407**		**100.0 %**	**1.16 [0.51, 2.65]**
Total events: 11 (Chlorpromazine), 9 (Placebo)					
Heterogeneity: Chi^2 = 2.76, df = 4 (P = 0.60); I^2 =0.0%					
Test for overall effect: Z = 0.35 (P = 0.73)					
5 dry mouth					
Clark 1971	6/23	2/21		19.6 %	2.74 [0.62, 12.12]
Clark 1977	1/9	0/9		4.7 %	3.00 [0.14, 65.16]



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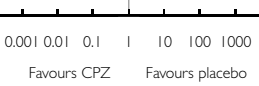
Study or subgroup	Chlorpromazine n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Cole 1964	22/88	4/74		40.7 %	4.63 [1.67, 12.82]
Hankoff 1962	1/25	0/72		2.5 %	8.42 [0.35, 200.36]
Prien 1968	23/416	2/212		24.8 %	5.86 [1.39, 24.62]
Reschke 1974	1/10	0/11		4.5 %	3.27 [0.15, 72.23]
Somerville 1960	1/15	0/30		3.2 %	5.81 [0.25, 134.73]
Subtotal (95% CI)	**586**	**429**		**100.0 %**	**4.56 [2.35, 8.85]**
Total events: 55 (Chlorpromazine), 8 (Placebo)					
Heterogeneity: Chi^2 = 0.85, df = 6 (P = 0.99); I^2 =0.0%					
Test for overall effect: Z = 4.48 (P < 0.00001)					
6 weight increase					
Clark 1968a	6/18	4/36		39.4 %	3.00 [0.97, 9.30]
Clark 1970a	4/15	0/14		7.6 %	8.44 [0.50, 143.77]
Clark 1972	10/19	2/18		30.3 %	4.74 [1.20, 18.73]
Clark 1977	4/9	0/9		7.4 %	9.00 [0.55, 146.11]
Serafetinides 1972	7/14	1/13		15.3 %	6.50 [0.92, 45.90]
Subtotal (95% CI)	**75**	**90**		**100.0 %**	**4.92 [2.32, 10.43]**
Total events: 31 (Chlorpromazine), 7 (Placebo)					
Heterogeneity: Chi^2 = 1.13, df = 4 (P = 0.89); I^2 =0.0%					
Test for overall effect: Z = 4.16 (P = 0.000032)					
7 weight decrease					
Clark 1968a	4/18	16/36		31.0 %	0.50 [0.20, 1.28]
Clark 1970a	0/15	5/14		16.5 %	0.09 [0.01, 1.41]
Clark 1972	2/19	8/18		23.9 %	0.24 [0.06, 0.97]
Clark 1977	0/9	1/9		4.4 %	0.33 [0.02, 7.24]
Serafetinides 1972	5/14	8/13		24.1 %	0.58 [0.25, 1.32]
Subtotal (95% CI)	**75**	**90**		**100.0 %**	**0.38 [0.22, 0.66]**
Total events: 11 (Chlorpromazine), 38 (Placebo)					
Heterogeneity: Chi^2 = 2.87, df = 4 (P = 0.58); I^2 =0.0%					
Test for overall effect: Z = 3.42 (P = 0.00063)					
8 nausea/vomiting					
Cole 1964	25/88	3/74		20.4 %	7.01 [2.20, 22.29]
Hankoff 1962	0/25	3/72		11.5 %	0.40 [0.02, 7.51]
Kurland 1961	0/33	1/74		5.9 %	0.74 [0.03, 17.59]
Prien 1968	10/416	6/212		49.7 %	0.85 [0.31, 2.31]
Tetreault 1969	2/15	2/15		12.5 %	1.00 [0.16, 6.20]
Subtotal (95% CI)	**577**	**447**		**100.0 %**	**2.07 [1.14, 3.73]**



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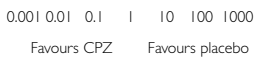
Study or subgroup	Chlorpromazine n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Total events: 37 (Chlorpromazine), 15 (Placebo)					
Heterogeneity: Chi² = 9.54, df = 4 (P = 0.05); I² =58%					
Test for overall effect: Z = 2.40 (P = 0.016)					
9 salivation					
Cole 1964	5/88	0/74		12.9 %	9.27 [0.52, 164.92]
Prien 1968	12/416	2/212		63.2 %	3.06 [0.69, 13.54]
Schiele 1961	1/20	1/20		23.9 %	1.00 [0.07, 14.90]
Subtotal (95% CI)	**524**	**306**		**100.0 %**	**3.37 [1.07, 10.57]**
Total events: 18 (Chlorpromazine), 3 (Placebo)					
Heterogeneity: Chi² = 1.27, df = 2 (P = 0.53); I² =0.0%					
Test for overall effect: Z = 2.08 (P = 0.037)					
10 menorrhagia / abnormal menstruation					
Clark 1968b	8/12	4/9		81.5 %	1.50 [0.65, 3.45]
Clark 1970a	1/13	1/12		18.5 %	0.92 [0.06, 13.18]
Subtotal (95% CI)	**25**	**21**		**100.0 %**	**1.39 [0.62, 3.13]**
Total events: 9 (Chlorpromazine), 5 (Placebo)					
Heterogeneity: Chi² = 0.12, df = 1 (P = 0.73); I² =0.0%					
Test for overall effect: Z = 0.80 (P = 0.42)					
11 amenorrhea					
Cole 1964	3/88	3/73		100.0 %	0.83 [0.17, 3.99]
Subtotal (95% CI)	**88**	**73**		**100.0 %**	**0.83 [0.17, 3.99]**
Total events: 3 (Chlorpromazine), 3 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.23 (P = 0.82)					
12 lactation					
Clark 1970a	5/15	5/15		90.2 %	1.00 [0.36, 2.75]
Cole 1964	3/88	0/74		9.8 %	5.90 [0.31, 112.39]
Subtotal (95% CI)	**103**	**89**		**100.0 %**	**1.48 [0.57, 3.81]**
Total events: 8 (Chlorpromazine), 5 (Placebo)					
Heterogeneity: Chi² = 1.42, df = 1 (P = 0.23); I² =30%					
Test for overall effect: Z = 0.81 (P = 0.42)					



(1) N not reported, assumed to be N randomised.

(2) N not reported, assumed to be N randomised.

(3) N not reported, assumed to be N randomised.

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Analysis 1.21. Comparison 1 CHLORPROMAZINE versus PLACEBO, Outcome 21 SUBGROUP ANALYSIS: 1. MEN vs WOMEN: Behaviour: Deteriorated/disturbed/un-cooperative.

Review: Chlorpromazine versus placebo for schizophrenia

Comparison: 1 CHLORPROMAZINE versus PLACEBO

Outcome: 21 SUBGROUP ANALYSIS: 1. MEN vs WOMEN: Behaviour: Deteriorated/disturbed/un-cooperative

Study or subgroup	Chlorpromazine n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 only men					
Schiele 1961	0/20	12/20		100.0 %	0.04 [0.00, 0.63]
Subtotal (95% CI)	**20**	**20**		**100.0 %**	**0.04 [0.00, 0.63]**
Total events: 0 (Chlorpromazine), 12 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.28 (P = 0.022)					
2 only women					
Clark 1970b	10/53	6/18		24.5 %	0.57 [0.24, 1.34]
Fleming 1959	5/21	13/21		35.5 %	0.38 [0.17, 0.89]
Somerville 1960	5/15	22/30		40.0 %	0.45 [0.22, 0.96]
Subtotal (95% CI)	**89**	**69**		**100.0 %**	**0.46 [0.29, 0.73]**
Total events: 20 (Chlorpromazine), 41 (Placebo)					
Heterogeneity: Chi^2 = 0.40, df = 2 (P = 0.82); I^2 =0.0%					
Test for overall effect: Z = 3.29 (P = 0.0010)					
Test for subgroup differences: Chi^2 = 2.91, df = 1 (P = 0.09), I^2 =66%					

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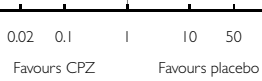
Analysis 1.22. Comparison 1 CHLORPROMAZINE versus PLACEBO, Outcome 22 SUBGROUP ANALYSIS: 2. ACUTE vs CHRONIC.

Review: Chlorpromazine versus placebo for schizophrenia

Comparison: 1 CHLORPROMAZINE versus PLACEBO

Outcome: 22 SUBGROUP ANALYSIS: 2. ACUTE vs CHRONIC

Study or subgroup	Chlorpromazine n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 acute - Relapse (9 wks - 6 months)					
Rappaport 1978	38/53	44/74		100.0 %	1.21 [0.94, 1.55]
Subtotal (95% CI)	**53**	**74**		**100.0 %**	**1.21 [0.94, 1.55]**
Total events: 38 (Chlorpromazine), 44 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.45 (P = 0.15)					
2 chronic - Relapse (9 wks - 6 months)					
Nishikawa 1982	6/10	8/10		34.7 %	0.75 [0.41, 1.36]
Peet 1981	4/16	7/18		26.9 %	0.64 [0.23, 1.80]
Prien 1968	39/416	85/212		38.4 %	0.23 [0.17, 0.33]
Subtotal (95% CI)	**442**	**240**		**100.0 %**	**0.46 [0.18, 1.15]**
Total events: 49 (Chlorpromazine), 100 (Placebo)					
Heterogeneity: Tau^2 = 0.54; Chi^2 = 13.80, df = 2 (P = 0.001); I^2 =86%					
Test for overall effect: Z = 1.66 (P = 0.097)					
3 acute - Global state 1. No overall improvement (0-8 wks)					
Chouinard 1990	9/21	13/21		52.0 %	0.69 [0.38, 1.26]
Kurland 1961	9/33	30/74		48.0 %	0.67 [0.36, 1.25]
Subtotal (95% CI)	**54**	**95**		**100.0 %**	**0.68 [0.44, 1.05]**
Total events: 18 (Chlorpromazine), 43 (Placebo)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.00, df = 1 (P = 0.95); I^2 =0.0%					
Test for overall effect: Z = 1.74 (P = 0.083)					
4 chronic - Global state 1. No overall improvement (0-8 wks)					
Baker 1959	7/7	6/7		13.9 %	1.15 [0.79, 1.68]
Cooper 2000	26/53	35/53		14.3 %	0.74 [0.53, 1.04]
Fink 1963	10/51	30/44		11.6 %	0.29 [0.16, 0.52]
Ramu 1999	6/27	18/27		9.9 %	0.33 [0.16, 0.71]
Shepherd 1956	3/8	10/16		7.9 %	0.60 [0.23, 1.59]
Somerville 1960	7/15	23/30		11.8 %	0.61 [0.34, 1.08]
Vaughan 1955	8/24	19/24		11.5 %	0.42 [0.23, 0.77]



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Study or subgroup	Chlorpromazine n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Walsh 1959	2/22	8/22		4.9 %	0.25 [0.06, 1.05]
Weckowicz 1960	11/14	13/15		14.3 %	0.91 [0.65, 1.27]
Subtotal (95% CI)	**221**	**238**		**100.0 %**	**0.57 [0.39, 0.84]**
Total events: 80 (Chlorpromazine), 162 (Placebo)					
Heterogeneity: Tau² = 0.24; Chi² = 35.30, df = 8 (P = 0.00002); I² =77%					
Test for overall effect: Z = 2.86 (P = 0.0043)					
5 acute - Global state 2. No overall improvement (9 wks-6 months)					
Reardon 1966	1/11	6/12		100.0 %	0.18 [0.03, 1.28]
Subtotal (95% CI)	**11**	**12**		**100.0 %**	**0.18 [0.03, 1.28]**
Total events: 1 (Chlorpromazine), 6 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.71 (P = 0.087)					
6 chronic - Global state 2. No overall improvement (9 wks-6 months)					
Bishop 1963	2/10	10/10		1.6 %	0.24 [0.08, 0.71]
Clark 1961	13/19	19/19		10.2 %	0.69 [0.51, 0.95]
Clark 1968a	10/18	30/36		6.9 %	0.67 [0.43, 1.03]
Clark 1970a	8/15	9/14		4.3 %	0.83 [0.45, 1.53]
Clark 1972	10/19	14/18		5.9 %	0.68 [0.41, 1.11]
Clark 1977	3/9	9/9		2.5 %	0.37 [0.16, 0.87]
Grygier 1958	13/15	13/15		11.2 %	1.00 [0.76, 1.32]
Hall 1955	56/87	72/88		14.8 %	0.79 [0.65, 0.95]
Hine 1958	6/11	11/11		5.3 %	0.57 [0.33, 0.96]
Prien 1968	330/416	192/212		18.9 %	0.88 [0.82, 0.94]
Ramu 1999a	10/23	18/20		6.0 %	0.48 [0.30, 0.79]
Serafetinides 1972	12/14	13/13		12.4 %	0.86 [0.67, 1.11]
Subtotal (95% CI)	**656**	**465**		**100.0 %**	**0.74 [0.64, 0.86]**
Total events: 473 (Chlorpromazine), 410 (Placebo)					
Heterogeneity: Tau² = 0.03; Chi² = 26.86, df = 11 (P = 0.005); I² =59%					
Test for overall effect: Z = 4.05 (P = 0.000052)					
7 acute - Behaviour deteriorated/disturbed/unco-operative					
Chouinard 1990	14/21	16/21		100.0 %	0.88 [0.60, 1.29]
Subtotal (95% CI)	**21**	**21**		**100.0 %**	**0.88 [0.60, 1.29]**
Total events: 14 (Chlorpromazine), 16 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.68 (P = 0.50)					
8 chronic - Behaviour deteriorated/disturbed/unco-operative					
Clark 1970a	2/15	5/14		8.4 %	0.37 [0.09, 1.62]

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Study or subgroup	Chlorpromazine n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Clark 1970b	10/53	6/18		11.9 %	0.57 [0.24, 1.34]
Fleming 1959	5/21	13/21		12.0 %	0.38 [0.17, 0.89]
Hall 1955	65/87	70/88		15.0 %	0.94 [0.80, 1.10]
Prien 1968	37/416	70/212		14.5 %	0.27 [0.19, 0.39]
Schiele 1961	0/20	12/20		3.9 %	0.04 [0.00, 0.63]
Serafetinides 1972	6/14	3/13		10.1 %	1.86 [0.58, 5.94]
Smith 1961	4/13	10/15		11.7 %	0.46 [0.19, 1.12]
Somerville 1960	5/15	22/30		12.5 %	0.45 [0.22, 0.96]
Subtotal (95% CI)	**654**	**431**		**100.0 %**	**0.49 [0.26, 0.92]**
Total events: 134 (Chlorpromazine), 211 (Placebo)					
Heterogeneity: $Tau^2 = 0.69$; $Chi^2 = 72.28$, df = 8 (P<0.00001); $I^2 = 89\%$					
Test for overall effect: Z = 2.21 (P = 0.027)					
Test for subgroup differences: $Chi^2 = 20.53$, df = 7 (P = 0.00), $I^2 = 66\%$					

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Analysis 1.23. Comparison 1 CHLORPROMAZINE versus PLACEBO, Outcome 23 SUBGROUP ANALYSIS: 3. HIGH vs LOW DOSE.

Review: Chlorpromazine versus placebo for schizophrenia

Comparison: 1 CHLORPROMAZINE versus PLACEBO

Outcome: 23 SUBGROUP ANALYSIS: 3. HIGH vs LOW DOSE

Study or subgroup	Chlorpromazine n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 high - Relapse (9 wks-6 Months)					
Prien 1968 (1)	12/208	85/212		100.0 %	0.14 [0.08, 0.26]
Subtotal (95% CI)	**208**	**212**		**100.0 %**	**0.14 [0.08, 0.26]**
Total events: 12 (Chlorpromazine), 85 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 6.63 (P < 0.00001)					
2 low - Relapse (9 wks-6 Months)					
Nishikawa 1982	6/10	8/10		35.3 %	0.75 [0.41, 1.36]
Peet 1981	4/16	7/18		22.5 %	0.64 [0.23, 1.80]
Prien 1968 (2)	27/208	85/212		42.2 %	0.32 [0.22, 0.48]
Subtotal (95% CI)	**234**	**240**		**100.0 %**	**0.51 [0.26, 0.98]**
Total events: 37 (Chlorpromazine), 100 (Placebo)					
Heterogeneity: Tau^2 = 0.23; Chi^2 = 6.71, df = 2 (P = 0.03); I^2 =70%					
Test for overall effect: Z = 2.01 (P = 0.045)					
3 high - Global state 1. No overall improvement (0-8 wks)					
Cooper 2000	26/53	35/53		53.2 %	0.74 [0.53, 1.04]
Fink 1963	10/51	30/44		46.8 %	0.29 [0.16, 0.52]
Subtotal (95% CI)	**104**	**97**		**100.0 %**	**0.48 [0.18, 1.25]**
Total events: 36 (Chlorpromazine), 65 (Placebo)					
Heterogeneity: Tau^2 = 0.43; Chi^2 = 8.10, df = 1 (P = 0.004); I^2 =88%					
Test for overall effect: Z = 1.51 (P = 0.13)					
4 low - Global state 1. No overall improvement (0-8 wks)					
Baker 1959	7/7	6/7		15.2 %	1.15 [0.79, 1.68]
Hankoff 1962	12/16	65/68		16.6 %	0.78 [0.59, 1.05]
Kurland 1961	9/33	30/74		11.4 %	0.67 [0.36, 1.25]
Ramu 1999	6/27	18/27		9.6 %	0.33 [0.16, 0.71]
Reschke 1974	7/10	4/11		8.2 %	1.93 [0.80, 4.64]
Shepherd 1956	3/8	10/16		7.3 %	0.60 [0.23, 1.59]
Vaughan 1955	8/24	19/24		11.7 %	0.42 [0.23, 0.77]

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Study or subgroup	Chlorpromazine n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Walsh 1959	2/22	8/22		4.2 %	0.25 [0.06, 1.05]
Weckowicz 1960	11/14	13/15		15.8 %	0.91 [0.65, 1.27]
Subtotal (95% CI)	**161**	**264**		**100.0 %**	**0.72 [0.52, 1.01]**
Total events: 65 (Chlorpromazine), 173 (Placebo)					
Heterogeneity: Tau² = 0.15; Chi² = 25.70, df = 8 (P = 0.001); I² =69%					
Test for overall effect: Z = 1.93 (P = 0.054)					
5 high - Global state 1. No overall improvement (9 wks-6 months)					
Bishop 1963	2/10	10/10		6.1 %	0.24 [0.08, 0.71]
Clark 1968a	10/18	30/36		17.8 %	0.67 [0.43, 1.03]
Clark 1972	10/19	14/18		16.2 %	0.68 [0.41, 1.11]
Clark 1977	3/9	9/9		8.8 %	0.37 [0.16, 0.87]
Prien 1968 (3)	187/208	205/212		27.5 %	0.93 [0.88, 0.98]
Serafetinides 1972	12/14	13/13		23.5 %	0.86 [0.67, 1.11]
Subtotal (95% CI)	**278**	**298**		**100.0 %**	**0.69 [0.51, 0.94]**
Total events: 224 (Chlorpromazine), 281 (Placebo)					
Heterogeneity: Tau² = 0.09; Chi² = 23.08, df = 5 (P = 0.00033); I² =78%					
Test for overall effect: Z = 2.33 (P = 0.020)					
6 low - Global state 1. No overall improvement (9 wks-6 months)					
Grygier 1958	13/15	13/15		33.5 %	1.00 [0.76, 1.32]
Prien 1968 (4)	193/208	205/212		44.1 %	0.96 [0.92, 1.00]
Ramu 1999a	10/23	18/20		22.4 %	0.48 [0.30, 0.79]
Subtotal (95% CI)	**246**	**247**		**100.0 %**	**0.83 [0.60, 1.16]**
Total events: 216 (Chlorpromazine), 236 (Placebo)					
Heterogeneity: Tau² = 0.06; Chi² = 9.92, df = 2 (P = 0.01); I² =80%					
Test for overall effect: Z = 1.08 (P = 0.28)					
7 high - Behaviour 1. Deteriorated/disturbed/unco-operative					
Prien 1968 (5)	10/208	70/212		51.9 %	0.15 [0.08, 0.27]
Serafetinides 1972	6/14	3/13		48.1 %	1.86 [0.58, 5.94]
Subtotal (95% CI)	**222**	**225**		**100.0 %**	**0.50 [0.04, 6.21]**
Total events: 16 (Chlorpromazine), 73 (Placebo)					
Heterogeneity: Tau² = 3.10; Chi² = 14.58, df = 1 (P = 0.00013); I² =93%					
Test for overall effect: Z = 0.54 (P = 0.59)					
8 low - Behaviour 1. Deteriorated/disturbed/unco-operative					
Fleming 1959	5/21	13/21		18.7 %	0.38 [0.17, 0.89]
Prien 1968 (6)	27/208	70/212		81.3 %	0.39 [0.26, 0.59]
Subtotal (95% CI)	**229**	**233**		**100.0 %**	**0.39 [0.27, 0.56]**
Total events: 32 (Chlorpromazine), 83 (Placebo)					
Heterogeneity: Tau² = 0.0; Chi² = 0.00, df = 1 (P = 0.96); I² =0.0%					

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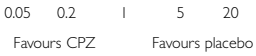
Study or subgroup	Chlorpromazine n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Test for overall effect: Z = 5.09 (P < 0.00001)					
Test for subgroup differences: Chi² = 35.21, df = 7 (P = 0.00), I² =80%					



(1) Trial had a high dose and low dose arm.

(2) Trial had a high dose and low dose arm.

(3) Trial had a high dose and low dose arm. Data provided as percentages and numbers are calculated based on all participants randomised.

(4) Trial had a high dose and low dose arm. Data provided as percentages and numbers are calculated based on all participants randomised.

(5) Trial had a high dose and low dose arm.

(6) Trial had a high dose and low dose arm.

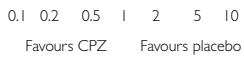
Analysis 1.24. Comparison 1 CHLORPROMAZINE versus PLACEBO, Outcome 24 SUBGROUP ANALYSIS: 4. DIAGNOSTIC CRITERIA vs NO DIAGNOSTIC CRITERIA.

Review: Chlorpromazine versus placebo for schizophrenia

Comparison: 1 CHLORPROMAZINE versus PLACEBO

Outcome: 24 SUBGROUP ANALYSIS: 4. DIAGNOSTIC CRITERIA vs NO DIAGNOSTIC CRITERIA

Study or subgroup	Chlorpromazine n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 diagnostic criteria - Relapse (0-8 wks)					
Peet 1981	4/16	6/18		100.0 %	0.75 [0.26, 2.19]
Subtotal (95% CI)	**16**	**18**		**100.0 %**	**0.75 [0.26, 2.19]**
Total events: 4 (Chlorpromazine), 6 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.53 (P = 0.60)					
2 no diagnostic criteria - Relapse (0-8 wks)					
Spohn 1977	0/20	10/20		100.0 %	0.05 [0.00, 0.76]
Subtotal (95% CI)	**20**	**20**		**100.0 %**	**0.05 [0.00, 0.76]**
Total events: 0 (Chlorpromazine), 10 (Placebo)					



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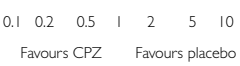
Study or subgroup	Chlorpromazine n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Heterogeneity: not applicable					
Test for overall effect: Z = 2.15 (P = 0.031)					
3 diagnostic criteria - Relapse (9 wks-6 months)					
Peet 1981	4/16	7/18		38.1 %	0.64 [0.23, 1.80]
Prien 1968	39/416	85/212		61.9 %	0.23 [0.17, 0.33]
Subtotal (95% CI)	**432**	**230**		**100.0 %**	**0.34 [0.13, 0.90]**
Total events: 43 (Chlorpromazine), 92 (Placebo)					
Heterogeneity: Tau^2 = 0.36; Chi^2 = 3.36, df = 1 (P = 0.07); I^2 =70%					
Test for overall effect: Z = 2.17 (P = 0.030)					
4 no diagnostic criteria - Relapse (9 wks-6 months)					
Nishikawa 1982	6/10	8/10		33.4 %	0.75 [0.41, 1.36]
Rappaport 1978	38/53	44/74		66.6 %	1.21 [0.94, 1.55]
Subtotal (95% CI)	**63**	**84**		**100.0 %**	**1.03 [0.66, 1.60]**
Total events: 44 (Chlorpromazine), 52 (Placebo)					
Heterogeneity: Tau^2 = 0.06; Chi^2 = 2.08, df = 1 (P = 0.15); I^2 =52%					
Test for overall effect: Z = 0.13 (P = 0.90)					
5 diagnostic criteria - Global state 1. No overall improvement (0-8 wks)					
Chouinard 1990	9/21	13/21		33.0 %	0.69 [0.38, 1.26]
Clark 1971	3/23	11/21		13.5 %	0.25 [0.08, 0.77]
Cooper 2000	26/53	35/53		53.5 %	0.74 [0.53, 1.04]
Subtotal (95% CI)	**97**	**95**		**100.0 %**	**0.63 [0.40, 0.99]**
Total events: 38 (Chlorpromazine), 59 (Placebo)					
Heterogeneity: Tau^2 = 0.07; Chi^2 = 3.54, df = 2 (P = 0.17); I^2 =43%					
Test for overall effect: Z = 2.00 (P = 0.046)					
6 no diagnostic criteria - Global state 1. No overall improvement (0-8 wks)					
Baker 1959	7/7	6/7		11.7 %	1.15 [0.79, 1.68]
Fink 1963	10/51	30/44		9.6 %	0.29 [0.16, 0.52]
Hankoff 1962	12/16	65/68		12.5 %	0.78 [0.59, 1.05]
Kurland 1961	9/33	30/74		9.3 %	0.67 [0.36, 1.25]
Ramu 1999	6/27	18/27		8.1 %	0.33 [0.16, 0.71]
Reschke 1974	7/10	4/11		7.1 %	1.93 [0.80, 4.64]
Shepherd 1956	3/8	10/16		6.4 %	0.60 [0.23, 1.59]
Somerville 1960	7/15	23/30		9.8 %	0.61 [0.34, 1.08]
Vaughan 1955	8/24	19/24		9.5 %	0.42 [0.23, 0.77]
Walsh 1959	2/22	8/22		3.9 %	0.25 [0.06, 1.05]
Weckowicz 1960	11/14	13/15		12.0 %	0.91 [0.65, 1.27]



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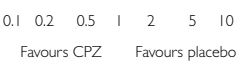
Study or subgroup	Chlorpromazine n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Subtotal (95% CI)	**227**	**338**		**100.0 %**	**0.64 [0.46, 0.90]**
Total events: 82 (Chlorpromazine), 226 (Placebo)					
Heterogeneity: Tau^2 = 0.22; Chi^2 = 40.32, df = 10 (P = 0.00001); I^2 =75%					
Test for overall effect: Z = 2.58 (P = 0.0099)					
7 diagnostic criteria - Global state 1. No overall improvement (9 wks-6 months)					
Clark 1961	13/19	19/19		37.2 %	0.69 [0.51, 0.95]
Prien 1968	330/416	192/212		60.5 %	0.88 [0.82, 0.94]
Reardon 1966	1/11	6/12		2.3 %	0.18 [0.03, 1.28]
Subtotal (95% CI)	**446**	**243**		**100.0 %**	**0.77 [0.57, 1.05]**
Total events: 344 (Chlorpromazine), 217 (Placebo)					
Heterogeneity: Tau^2 = 0.04; Chi^2 = 4.91, df = 2 (P = 0.09); I^2 =59%					
Test for overall effect: Z = 1.67 (P = 0.095)					
8 no diagnostic criteria - Global state 1. No overall improvement (9 wks-6 months)					
Ban 1975	6/10	8/10		6.5 %	0.75 [0.41, 1.36]
Bishop 1963	2/10	10/10		2.4 %	0.24 [0.08, 0.71]
Clark 1968a	10/18	30/36		9.5 %	0.67 [0.43, 1.03]
Clark 1970a	8/15	9/14		6.2 %	0.83 [0.45, 1.53]
Clark 1972	10/19	14/18		8.3 %	0.68 [0.41, 1.11]
Clark 1977	3/9	9/9		3.7 %	0.37 [0.16, 0.87]
Grygier 1958	13/15	13/15		14.3 %	1.00 [0.76, 1.32]
Hall 1955	56/87	72/88		17.7 %	0.79 [0.65, 0.95]
Hine 1958	6/11	11/11		7.5 %	0.57 [0.33, 0.96]
Ramu 1999a	10/23	18/20		8.4 %	0.48 [0.30, 0.79]
Serafetinides 1972	12/14	13/13		15.4 %	0.86 [0.67, 1.11]
Subtotal (95% CI)	**231**	**244**		**100.0 %**	**0.71 [0.59, 0.85]**
Total events: 136 (Chlorpromazine), 207 (Placebo)					
Heterogeneity: Tau^2 = 0.04; Chi^2 = 19.93, df = 10 (P = 0.03); I^2 =50%					
Test for overall effect: Z = 3.71 (P = 0.00021)					
9 diagnostic criteria - Global state 3. Severity of illness (9 wks-6 months)					
Prien 1968	298/416	186/212		100.0 %	0.82 [0.75, 0.88]
Subtotal (95% CI)	**416**	**212**		**100.0 %**	**0.82 [0.75, 0.88]**
Total events: 298 (Chlorpromazine), 186 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 5.05 (P < 0.00001)					
10 no diagnostic criteria - Global state 3. Severity of illness (9 wks-6 months)					
Clark 1970a	3/15	6/14		17.0 %	0.47 [0.14, 1.52]
Clark 1972	9/19	14/18		83.0 %	0.61 [0.36, 1.04]



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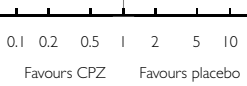
Study or subgroup	Chlorpromazine n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Subtotal (95% CI)	**34**	**32**		**100.0 %**	**0.58 [0.36, 0.95]**
Total events: 12 (Chlorpromazine), 20 (Placebo)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.17, df = 1 (P = 0.68); I^2 =0.0%					
Test for overall effect: Z = 2.18 (P = 0.029)					
11 diagnostic criteria - Behaviour 1. deteriorated/disturbed/unco-operative					
Chouinard 1990	14/21	16/21		49.9 %	0.88 [0.60, 1.29]
Prien 1968	37/416	70/212		50.1 %	0.27 [0.19, 0.39]
Subtotal (95% CI)	**437**	**233**		**100.0 %**	**0.48 [0.14, 1.72]**
Total events: 51 (Chlorpromazine), 86 (Placebo)					
Heterogeneity: Tau^2 = 0.80; Chi^2 = 22.97, df = 1 (P<0.00001); I^2 =96%					
Test for overall effect: Z = 1.12 (P = 0.26)					
12 no diagnostic criteria - Behaviour 1. deteriorated/disturbed/unco-operative					
Clark 1970a	2/15	5/14		8.3 %	0.37 [0.09, 1.62]
Clark 1970b	10/53	6/18		13.9 %	0.57 [0.24, 1.34]
Fleming 1959	5/21	13/21		14.2 %	0.38 [0.17, 0.89]
Hall 1955	65/87	70/88		20.8 %	0.94 [0.80, 1.10]
Schiele 1961	0/20	12/20		3.3 %	0.04 [0.00, 0.63]
Serafetinides 1972	6/14	3/13		10.8 %	1.86 [0.58, 5.94]
Smith 1961	4/13	10/15		13.5 %	0.46 [0.19, 1.12]
Somerville 1960	5/15	22/30		15.2 %	0.45 [0.22, 0.96]
Subtotal (95% CI)	**238**	**219**		**100.0 %**	**0.56 [0.33, 0.97]**
Total events: 97 (Chlorpromazine), 141 (Placebo)					
Heterogeneity: Tau^2 = 0.36; Chi^2 = 25.14, df = 7 (P = 0.00072); I^2 =72%					
Test for overall effect: Z = 2.06 (P = 0.039)					
Test for subgroup differences: Chi^2 = 16.01, df = 11 (P = 0.14), I^2 =31%					



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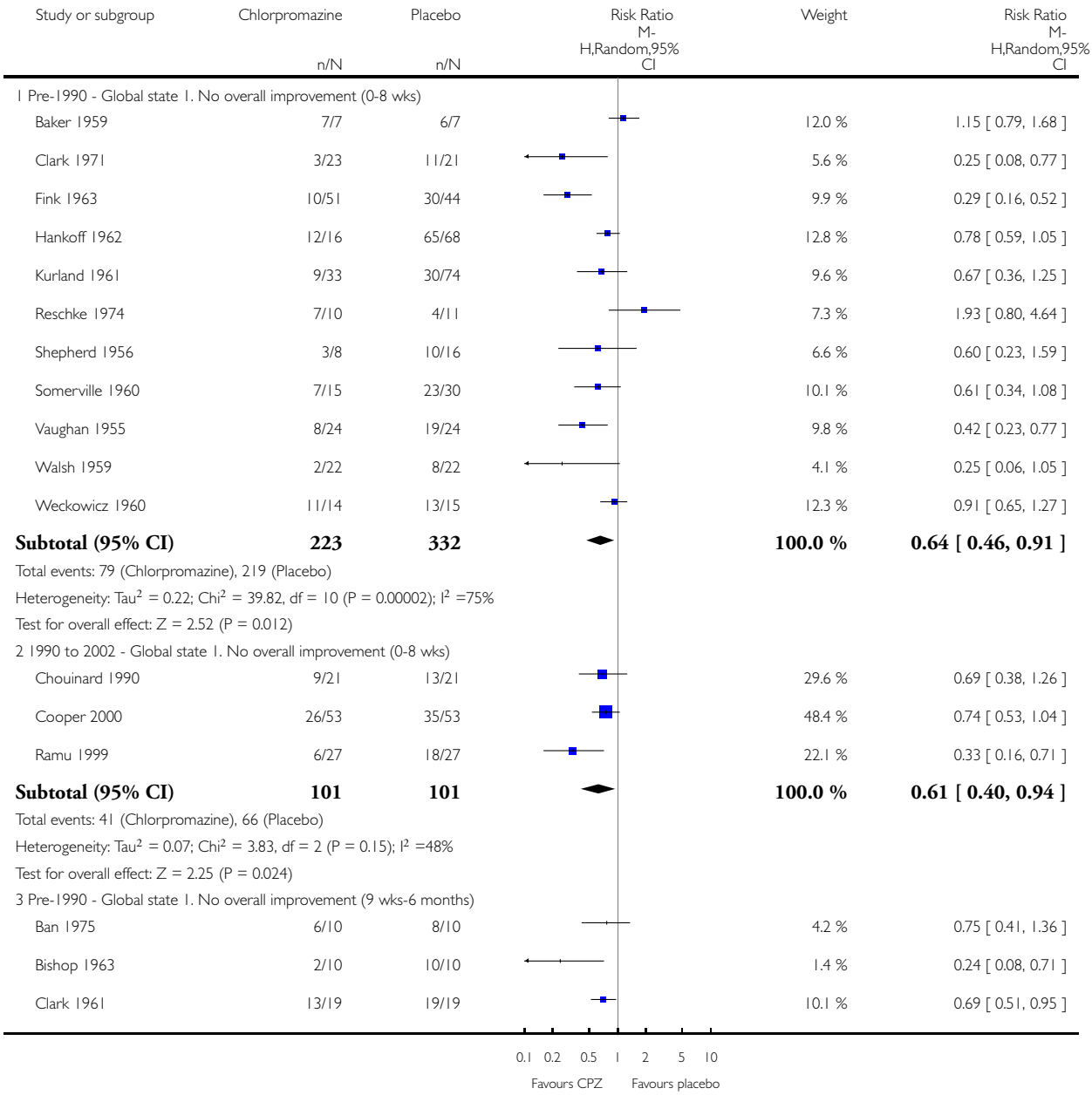
Analysis 1.25. Comparison 1 CHLORPROMAZINE versus PLACEBO, Outcome 25 SUBGROUP ANALYSIS: 5. STUDIES PRE-1990 vs STUDIES 1990-2007.

Review: Chlorpromazine versus placebo for schizophrenia

Comparison: 1 CHLORPROMAZINE versus PLACEBO

Outcome: 25 SUBGROUP ANALYSIS: 5. STUDIES PRE-1990 vs STUDIES 1990-2007



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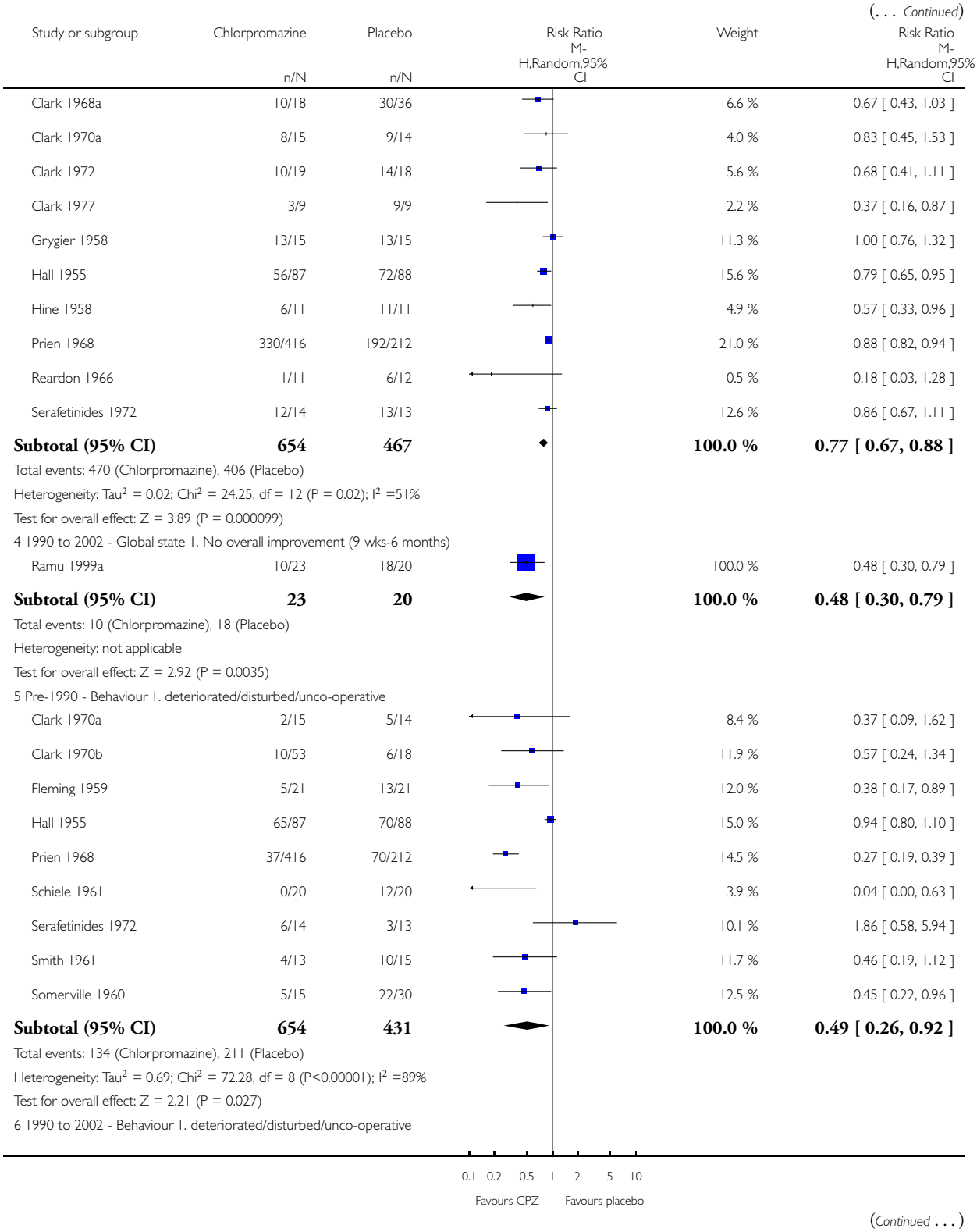

Study or subgroup	Chlorpromazine n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Clark 1968a	10/18	30/36		6.6 %	0.67 [0.43, 1.03]
Clark 1970a	8/15	9/14		4.0 %	0.83 [0.45, 1.53]
Clark 1972	10/19	14/18		5.6 %	0.68 [0.41, 1.11]
Clark 1977	3/9	9/9		2.2 %	0.37 [0.16, 0.87]
Grygier 1958	13/15	13/15		11.3 %	1.00 [0.76, 1.32]
Hall 1955	56/87	72/88		15.6 %	0.79 [0.65, 0.95]
Hine 1958	6/11	11/11		4.9 %	0.57 [0.33, 0.96]
Prien 1968	330/416	192/212		21.0 %	0.88 [0.82, 0.94]
Reardon 1966	1/11	6/12		0.5 %	0.18 [0.03, 1.28]
Serafetinides 1972	12/14	13/13		12.6 %	0.86 [0.67, 1.11]
Subtotal (95% CI)	**654**	**467**		**100.0 %**	**0.77 [0.67, 0.88]**
Total events: 470 (Chlorpromazine), 406 (Placebo)					
Heterogeneity: Tau² = 0.02; Chi² = 24.25, df = 12 (P = 0.02); I² =51%					
Test for overall effect: Z = 3.89 (P = 0.000099)					
4 1990 to 2002 - Global state 1. No overall improvement (9 wks-6 months)					
Ramu 1999a	10/23	18/20		100.0 %	0.48 [0.30, 0.79]
Subtotal (95% CI)	**23**	**20**		**100.0 %**	**0.48 [0.30, 0.79]**
Total events: 10 (Chlorpromazine), 18 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.92 (P = 0.0035)					
5 Pre-1990 - Behaviour 1. deteriorated/disturbed/unco-operative					
Clark 1970a	2/15	5/14		8.4 %	0.37 [0.09, 1.62]
Clark 1970b	10/53	6/18		11.9 %	0.57 [0.24, 1.34]
Fleming 1959	5/21	13/21		12.0 %	0.38 [0.17, 0.89]
Hall 1955	65/87	70/88		15.0 %	0.94 [0.80, 1.10]
Prien 1968	37/416	70/212		14.5 %	0.27 [0.19, 0.39]
Schiele 1961	0/20	12/20		3.9 %	0.04 [0.00, 0.63]
Serafetinides 1972	6/14	3/13		10.1 %	1.86 [0.58, 5.94]
Smith 1961	4/13	10/15		11.7 %	0.46 [0.19, 1.12]
Somerville 1960	5/15	22/30		12.5 %	0.45 [0.22, 0.96]
Subtotal (95% CI)	**654**	**431**		**100.0 %**	**0.49 [0.26, 0.92]**
Total events: 134 (Chlorpromazine), 211 (Placebo)					
Heterogeneity: Tau² = 0.69; Chi² = 72.28, df = 8 (P<0.00001); I² =89%					
Test for overall effect: Z = 2.21 (P = 0.027)					
6 1990 to 2002 - Behaviour 1. deteriorated/disturbed/unco-operative					

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Study or subgroup	Chlorpromazine n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Chouinard 1990	14/21	16/21		100.0 %	0.88 [0.60, 1.29]
Subtotal (95% CI)	**21**	**21**		**100.0 %**	**0.88 [0.60, 1.29]**
Total events: 14 (Chlorpromazine), 16 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.68 (P = 0.50)					
Test for subgroup differences: Chi² = 6.77, df = 5 (P = 0.24), I² =26%					

Analysis 1.26. Comparison 1 CHLORPROMAZINE versus PLACEBO, Outcome 26 SENSITIVITY ANALYSIS: 1. RANDOMISATION.

Review: Chlorpromazine versus placebo for schizophrenia

Comparison: 1 CHLORPROMAZINE versus PLACEBO

Outcome: 26 SENSITIVITY ANALYSIS: 1. RANDOMISATION

Study or subgroup	Chlorpromazine n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 not stated - Global state: 1. No overall improvement (9 weeks - 6 months)					
Ramu 1999a	10/23	18/20		100.0 %	0.48 [0.30, 0.79]
Subtotal (95% CI)	**23**	**20**		**100.0 %**	**0.48 [0.30, 0.79]**
Total events: 10 (Chlorpromazine), 18 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.92 (P = 0.0035)					
2 stated - Global state: 1. No overall improvement (9 weeks - 6 months)					
Ban 1975	6/10	8/10		1.7 %	0.75 [0.41, 1.36]
Bishop 1963	2/10	10/10		2.3 %	0.24 [0.08, 0.71]
Clark 1961	13/19	19/19		4.2 %	0.69 [0.51, 0.95]
Clark 1968a	10/18	30/36		4.3 %	0.67 [0.43, 1.03]
Clark 1970a	8/15	9/14		2.0 %	0.83 [0.45, 1.53]

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Study or subgroup	Chlorpromazine n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Clark 1972	10/19	14/18		3.1 %	0.68 [0.41, 1.11]
Clark 1977	3/9	9/9		2.1 %	0.37 [0.16, 0.87]
Grygier 1958	13/15	13/15		2.8 %	1.00 [0.76, 1.32]
Hall 1955	56/87	72/88		15.5 %	0.79 [0.65, 0.95]
Hine 1958	6/11	11/11		2.5 %	0.57 [0.33, 0.96]
Prien 1968	330/416	192/212		55.1 %	0.88 [0.82, 0.94]
Reardon 1966	1/11	6/12		1.2 %	0.18 [0.03, 1.28]
Serafetinides 1972	12/14	13/13		3.0 %	0.86 [0.67, 1.11]
Subtotal (95% CI)	**654**	**467**		**100.0 %**	**0.80 [0.75, 0.85]**
Total events: 470 (Chlorpromazine), 406 (Placebo)					
Heterogeneity: Chi^2 = 24.25, df = 12 (P = 0.02); I^2 =51%					
Test for overall effect: Z = 7.11 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 3.99, df = 1 (P = 0.05), I^2 =75%					

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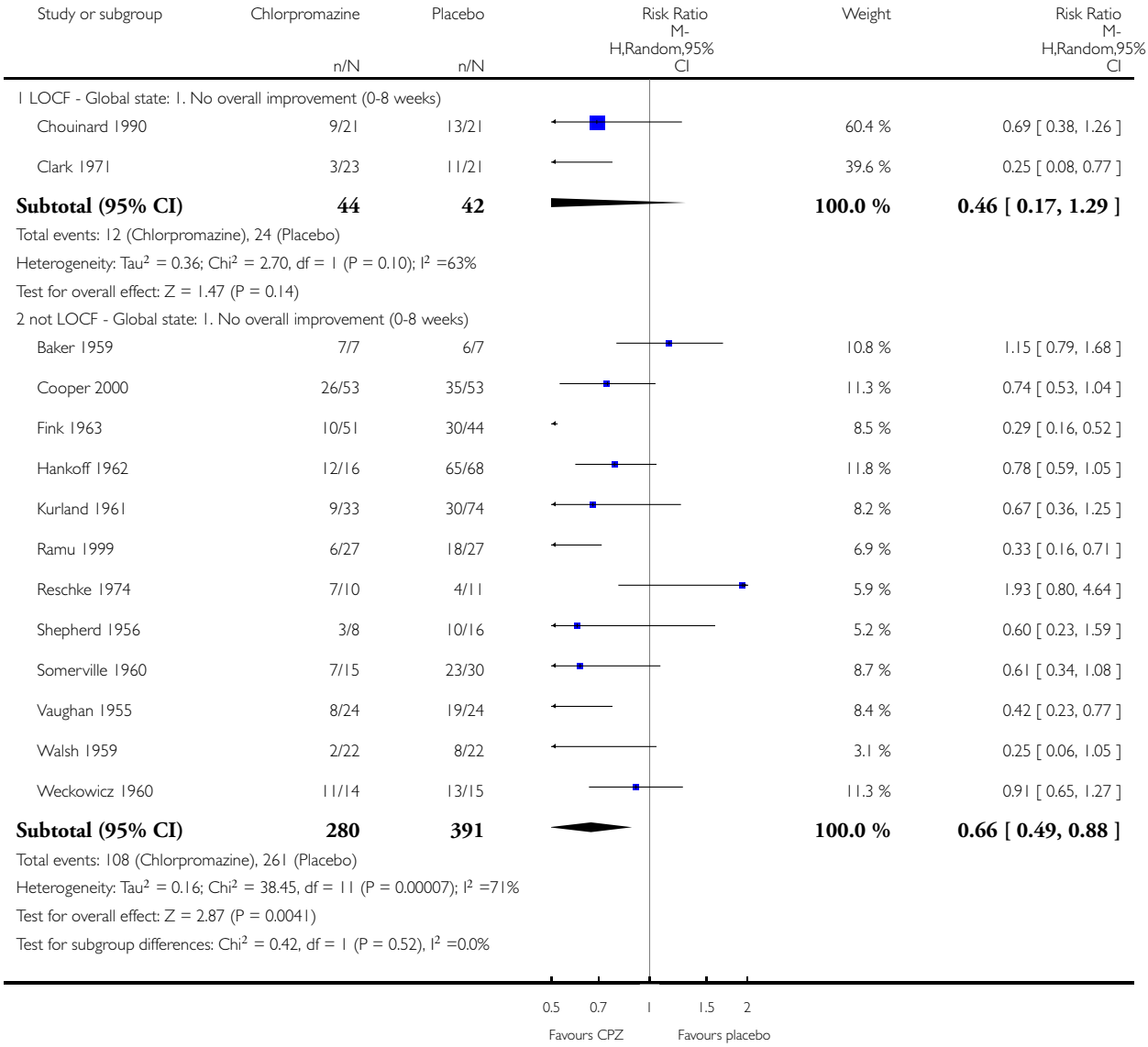
Analysis 1.27. Comparison 1 CHLORPROMAZINE versus PLACEBO, Outcome 27 SENSITIVITY ANALYSIS: 2. ASSUMPTIONS FOR LOST BINARY DATA.

Review: Chlorpromazine versus placebo for schizophrenia

Comparison: 1 CHLORPROMAZINE versus PLACEBO

Outcome: 27 SENSITIVITY ANALYSIS: 2. ASSUMPTIONS FOR LOST BINARY DATA



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ADDITIONAL TABLES

Table 1. Mental state: 3. Average BPRS change score (large decline=best)

Study	Chlorpromazine mean	Chlorpromazine SD	Chlorpromazine N	Placebo mean	Placebo SD	Placebo N
Cooper 2000	-4.3	19.1	53 (LOCF)	-2.9	16.3	53 (LOCF)

LOCF - last observation carried forward

APPENDICES

Appendix 1. Previous plain language summary

Chlorpromazine versus placebo for schizophrenia

Schizophrenia is a long-term illness with a worldwide lifetime prevalence of about one per cent. Many people who suffer from schizophrenia live with considerable disability. Chlorpromazine was one of the first drugs discovered to be effective in its treatment back in the 1950s - and is still used extensively today.This review updates the information available from trials in which chlorpromazine was compared with placebo. In addition it attempts to look at outcomes in smaller sub-groups of people, by sex, by age, by length of illness, by dose of chlorpromazine, by criteria of diagnosis or by whether they were diagnosed before or after 1990. This update adds five studies giving a total of 55 studies and the included data have been divided as to whether they refer to short, medium or long-term treatment. When looking at chlorpromazine versus placebo for schizophrenia since the first review in 1995, 370 trials have been considered but 315 have been excluded, many because of flaws in the research methods or the reporting of the data. This is a shame and much opportunity has been lost to report outcomes of interest to the reviewers and others.Chlorpromazine has been shown to improve both a person's symptoms and functioning in 14 trials containing 1164 people. Chlorpromazine reduces relapse in the short, medium and long term. Many trials, however, have demonstrated that chlorpromazine has a number of adverse effects when compared with placebo important ones being movement disorders, sleepiness, skin sensitivity to sunlight, low blood pressure and constipation. The main weakness of these trials is that the majority are conducted on people who are in hospital. The results, therefore, may, at best, be only partially applicable to people in the community.(Plain language summary prepared for this review by Janey Antoniou of RETHINK, UK www.rethink.org).

Appendix 2. Previous search strategies

1.2 Details of previous electronic search:
1.2.1 We searched The Cochrane Schizophrenia Group Trials Register (June 2002) using the phrase:

{[(*anadep* or *chloractil* or *chlorazin* or *chlorpromados* or *chlorpromazine* or *chlorprom-ez-ets* or *(chlor p-z)* or *chromedazine* or *cpz* or *elmarine* or *esmind* or *fenactil* or *hibanil* or *hibernal* or *klorazin* or *klorproman* or *klorpromez* or *largactil* or *megaphen* or *neurazine* or *plegomazine* or *procalm* or *promachel* or *promacid* or *promapar* or *promexin* or *promosol* or *prozil* or *psychozine* or *psylactil* or *serazone* or *sonazine* or *thoradex* or *thorazine* or *tranzine*) in title, abstract, index terms of REFERENCE] or [chlorpromazine* in interventions of STUDY]}
Chlorpromazine is known by many names and we constructed the following search phrase in order to try to aid identification:
(chlorpromazine-phrase)=(anadep or chloractil or chlorazin or chlorpromados or chlorpromazine or chlorprom-ez-ets or (chlor p-z) or chromedazine or cpz or elmarine or esmind or fenactil or hibanil or hibernal or klorazin or klorproman or klorpromez or largactil

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or megaphen or neurazine or plegomazine or procalm or promachel or promacid or promapar or promexin or promosol or prozil or psychozine or psylactil or (RP near1 4560) or serazone or sonazine or thoradex or thorazine or tranzine).
1.2.2 We searched The Cochrane Schizophrenia Group Trials Register (October 1999) using the phrase:
(((chlorpromazine-phrase) or (#42=5)) and (placebo* or (#42=4)))
#42 is the 'Intervention' field and 5 is the code for chlorpromazine; 4 is the code for placebo
1.2.3 We searched Biological Abstracts (January 1982 to May 1995) using The Cochrane Schizophrenia Group's phrase for both randomised controlled trials and schizophrenia (see: Group search strategy) combined with the phrase:
((chlorpromazine-phrase) and placebo*)
1.2.4 We searched The Cochrane Library (1999, Issue 2) using the phrase:
((chlorpromazine-phrase) and placebo)
1.2.5 We searched EMBASE (January 1980 to May 1995) using The Cochrane Schizophrenia Group's phrase for both randomised controlled trials and schizophrenia (see Group search strategy) combined with the phrase:
(and (chlorpromazine-phrase) and placebo*)
1.2.6 We searched MEDLINE (January 1966 to May 1995) using The Cochrane Schizophrenia Group's phrase for both randomised controlled trials and schizophrenia (see Group search strategy) combined with the phrase:
(and (chlorpromazine-phrase) and placebo*)
1.2.7 We searched PsycLIT (January 1974 to May 1995) using The Cochrane Schizophrenia Group's phrase for both randomised controlled trials and schizophrenia (see Group search strategy) combined with the phrase:
(and (chlorpromazine-phrase) and placebo*)
1.2.8 We searched local library listings of books/university series/dissertations relating to chlorpromazine using the phrase:
(and (chlorpromazine-phrase) and placebo*)
1.2.9 We searched Scisearch Citation Index database using each citation from the included studies. We inspected reports of articles that had cited these studies in order to identify further trials.

1. Cochrane Schizophrenia Group Trials Register (January 2007)

We searched The Cochrane Schizophrenia Group Trials Register (January 2007) using the phrase:
{[((*anadep* or *chlora* or *chlorprom* or *(chlor p-z)* or *chromeda* or *cpz* or *elmarine* or *esmind* or *fenactil* or *hibanil* or *hibernal* or *klorazin* or *klorpro* or *largactil* or *megaphen* or *neurazin* or *plegomaz* or *procalm* or *proma* or *promexin* or *promosol* or *prozil* or *psychozin* or *psylactil* or *serazon* or *sonazin* or *thoradex* or *tranzine*) and placebo*) in title, abstract, index terms of REFERENCE] or [)chlorpromazine* and placebo*) in interventions of STUDY]}

Appendix 3. Previous data collection

1. Study selection
We (BT, CEA and JR) independently inspected citations from the searches and identified relevant abstracts. GA independently re-inspected a random 10% sample to ensure reliability. Where disputes arose, we acquired the full report for more detailed scrutiny. We (BT and JR) obtained and inspected full reports of the abstracts meeting the review criteria. Again, a random 10% of reports were re-inspected by CEA and GA in order to ensure reliable selection. Where it was not possible to resolve disagreement by discussion, an attempt was made to contact the authors of the study for clarification. For the 2007 update, we independently inspected and selected citations from the search results.
2. Assessment of methodological quality
We (BT, JR) assessed the methodological quality of included trials in this review using the criteria described in The Cochrane Handbook (Higgins 2005). It is based on the evidence of a strong relationship between allocation concealment and direction of effect (Schulz 1995). When disputes arose as to which category a trial should be allocated, again we attempted resolution by discussion. When this was not possible, we did not enter the data and added the trial to the list of those awaiting assessment until further information could be obtained. The categories are defined below:
A. Low risk of bias (adequate allocation concealment)
B. Moderate risk of bias (some doubt about the results)
C. High risk of bias (inadequate allocation concealment).
In addition, for the first version of this review, we rated studies using the Jadad Scale (Jadad 1996) but this was not applied for the updates, as it was found to add little to the initial version. The reliability of quality-rating was checked by CEA and GA who re-rated a 10% sample of the selected studies.

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3. Data management

3.1. Data extraction

We (BT and JR) independently extracted data and, where further clarification was needed we contacted the authors of trials to provide missing data. CEA and GA independently checked a 10% sample for reliability. Any disagreements were discussed and decisions documented. For the 2007 update, JR independently extracted data and contacted authors of trials for missing data.

4. Data synthesis

4.1 Data types: We assessed outcomes using continuous (e.g. average changes on a behaviour scale), categorical (e.g. one of three categories on a behaviour scale, such as 'little change', 'moderate change' or 'much change') or dichotomous measures, e.g. either 'no important change' or 'important change' in a person's behaviour. RevMan software does not currently support categorical data, so we only presented these in the text of the review.

4.2 Binary data

For binary outcomes we calculated the relative risk (RR) and its 95% confidence interval (CI) based on the fixed-effect model. Relative Risk is more intuitive (Boissel 1999) than odds ratios and odds ratios tend to be interpreted as RR by clinicians (Deeks 2000). This misinterpretation then leads to an overestimate of the impression of the effect. When the overall results were significant we calculated the number needed to treat (NNT) and the number needed to harm (NNH). Where people were lost to follow-up at the end of the study, we assumed that they had had a poor outcome and once they were randomised we included them in the analysis (intention-to-treat /ITT analysis).

Where possible, we attempted to convert outcome measures to binary 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 was generally assumed that if there had been a 50% reduction in a scale-derived score such as the Brief Psychiatric Rating Scale (BPRS, Overall 1962) or the Positive and Negative Syndrome Scale (PANSS, Kay 1986), this could be considered as a clinically significant response (Leucht 2005a; Leucht 2005b). It was recognised that for many people, especially those with chronic or severe illness, a less rigorous definition of important improvement (e.g. 25% on the BPRS) would be equally valid. If individual patient data were available, we used the 50% cut-off for the definition in the case of non-chronically ill people and 25% for those with chronic illness. If data based on these thresholds were not available, we used the primary cut-off presented by the original authors.

4.3 Continuous data

4.3.1 Normal distribution

Continuous data on outcomes in trials relevant to mental health issues are often not normally distributed. To avoid the pitfall of applying parametric tests to non-parametric data we applied the following standards to continuous final value endpoint data before inclusion: (a) standard deviations and means were reported in the paper or were obtainable from the authors; (b) when a scale started from zero, the standard deviation, when multiplied by two, should be less than the mean (otherwise the mean is unlikely to be an appropriate measure of the centre of the distribution, Altman 1996); In cases with data that are greater than the mean we entered these into 'Other data' table as skewed data. If a scale starts from a positive value (such as PANSS, which can have values from 30 to 210) the calculation described above in (b) should be modified to take the scale starting point into account. In these cases skewness is present if 2SD>(S-Smin), where S is the mean score and Smin is the minimum score.

For change data (mean change from baseline on a rating scale) it is impossible to tell whether or not data are non-normally distributed (skewed) unless individual patient data are available. After consulting the ALLSTAT electronic statistics mailing list, we presented change data in RevMan graphs to summarise available information. In doing this, we assumed either that data were not skewed or that the analysis could cope with the unknown degree of skew.

4.3.2 Final endpoint value versus change data

Where both final endpoint data and change data were available for the same outcome category, we only presented endpoint data. We acknowledge that by doing this much of the published change data may be excluded, but argue that endpoint data is more clinically relevant and that if change data were to be presented along with endpoint data, it would be given undeserved equal prominence.

4.4 Rating scales: A wide range of instruments are available to measure mental health outcomes. These instruments vary in quality and many are not valid, and are known to be subject to bias in trials of treatments for schizophrenia (Marshall 2000). Therefore we only included continuous data from rating scales if the measuring instrument had been described in a peer-reviewed journal.

4.5 Cross-over design

We expected that some trials would use a cross-over design. In order to exclude the potential additive effect in the second or later stages in these trials we only analysed data from the first stage.

4.6 Cluster trials

Studies increasingly employ "cluster randomisation" (such as randomisation by clinician or practice) but analysis and pooling of clustered data poses problems. Firstly, authors often fail to account for intra class correlation in clustered studies, leading to a "unit of analysis"

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error (Divine 1992) whereby P values are spuriously low, confidence intervals unduly narrow and statistical significance overestimated. This causes type 1 errors (Bland 1997; Gulliford 1999).
Where clustering was not accounted for in primary studies, we presented the data in a table, with a (*) symbol to indicate the presence of a probable unit of analysis error. in subsequent versions of this review we will seek to contact first authors of studies to obtain intra-class correlation co-efficients of their clustered data and to adjust for this using accepted methods (Gulliford 1999). Where clustering has been incorporated into the analysis of primary studies, we will also present 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 intraclass correlation co-efficient (ICC) [Design effect=1+ (m-1)*ICC] (Donner 2002). If the ICC was not reported it was assumed to be 0.1 (Ukoumunne 1999).

If cluster studies had been appropriately analysed taking into account intra-class correlation coefficients and relevant data documented in the report, synthesis with other studies would have been possible using the generic inverse variance technique.
5. Investigation for heterogeneity
Firstly, we considered all the included studies within any comparison to judge for clinical heterogeneity then we visually inspected the graphs to investigate the possibility of statistical heterogeneity. This was supplemented using, primarily, the I-squared statistic. This provides an estimate of the percentage of variability due to heterogeneity rather than chance alone. Where the I-squared estimate was greater than or equal to 75%, we interpreted this as indicating the presence of high levels of heterogeneity (Higgins 2003). If heterogeneity was found, we re-analysed the data using a random-effects model to see if this made a substantial difference. If it did, we did not add the studies responsible for heterogeneity to the main body of homogeneous trials, but summated and presented them separately and investigated reasons for heterogeneity.
6. Addressing publication bias
We undertook funnel plots (trial affect versus trial size) for outcomes where more than five trials reported usable data and no clear asymmetry was apparent.
7. Sensitivity analysis
We anticipated that this would be a large review in comparison to many within the field of mental health. As a result this gave an opportunity for several sensitivity analyses to be undertaken. These sensitivity analyses are listed (see: in Objectives). BT, CEA and JR selected relevant trials at the data extraction stage of the review. The synthesised results of the groups of trials were inspected for overlap of the 95% confidence intervals.
8. General
Where possible we presented data so that results shown to the left of the line of no effect favoured chlorpromazine.

F E E D B A C K

Methods and results

Summary

Methods - summary statistic
I think it would be helpful if you were to include in your review additional measures of effect size. While you report the relative risk and number needed to treat, many of us not in medical or epidemiological fields tend to use effect size analysis (Cohen 1983), in standard deviation, units to evaluate strength of effect. For binary outcomes, we also tend to use the difference in the percentage of those having the desired outcome in the experimental treatment minus the percentage having the desired effect in the control treatment. Using your study to illustrate, if the percentage of the placebo treated group showing symptomatic remission is 40 and the NNT is 7, then the percentage of drug treated participants showing symptom remission is 52.5 (100/(7+1)=.125+.40 =.525). Then the effect size is 12.5 percent, or a small to moderate effect size. I think that adding this type of layman-accessible translation will enhance the utility and breadth of appeal of your analysis.
Results - sensitivity analysis
Are there differences between early (first and second) episode patients and those with a more chronic course? I think it reasonable to expect a higher proportion of placebo remissions in early episodes, and perhaps a different (smaller or larger) effect size for the drugs.

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In looking through the titles of the articles included in your review, it seems that most studies are of the more chronic group. If you can segregate the early episode studies form the more chronic ones, I think the field could learn a great deal about whether the drug has different effects at these different stages of illness. In relation to the Rappaport (1978) first episode study, you might consider a comment on the portion of the placebo treated group that appeared to do better without drugs. If there is such a subgroup, this would be important to know.

Results and conclusions - the interaction of drug effects and study design

From what we know of the conventional antipsychotic effect, there is a dopamine blocking action that appears correlated with the effect. The body responds to this blocking by generating additional dopamine receptors. Subsequent withdrawing of antipsychotics can thus increase the likelihood of a subsequent episode of psychosis to be greater than if drugs were never given (Chouinard 1978, Chouinard 1980, Warner 1985). In relation to study design, this effect can operate in a number of ways, potentially introducing bias into study results. If the study is of first episode patients and the control group does not receive antipsychotics, then there is no problem. Warner (1985) calls this design 'initial assignment'. But if, while waiting for participants to be collected, early recruits are given medication that for some of them (subsequently assigned to the control group) is later withdrawn, effect size estimates, particularly those using 'relapse' as the dependent variable, will be biased in favour of the drug treated group. This is due to the increased likelihood of 'supersensitivity' psychosis (Chouinard 1978, Chouinard 1980) associated with drug withdrawal. Warner (1985) calls this design 'drug withdrawal'. These issues become more complex when studying a more chronic population (virtually all of whom have been previously medicated). Certainly a sudden drug withdrawal will insert this bias, but most studies you cite seem to use 'wash-out periods' of varying lengths. The real question here is whether the length of the wash out period is sufficient to conduct a fair test. If it's not, there is a bias favouring the drug treatment group in the design. If there is a way, in your analysis, to control for length of wash-out period, it might produce 'clean' estimates of drug-effect for chronically ill people. It would also help to clarify empirically whether the length of the wash-out period is a significant issue (by whether the effect size changes when length of wash-out is included as a control variable).

Reply

The reviewers would first like to thank Dr Bola for his detailed comment and patience. It has taken us a shamefully long time to address the issues he raised.

Methods - summary statistic

We have taken advice on this comment as regards the use of an additional effect size statistic. The two statisticians consulted suggested that accessibility is best served by the NNT statistic and the effect size adds little. Although it is now well recognised that there are difficulties with the NNT in meta-analysis it is still thought to be of use. The reviewers have tried to reword were necessary and clarify the numbers without decreasing readability.

Results - sensitivity analysis

Dr Bola highlighted that we had not completed the review. We had intended to undertake several additional sensitivity analyses. One of these was to compare, for primary outcomes, if any clear differences were suggested for the effect of chlorpromazine compared with placebo, when a group of people whose illnesses were not chronic were included in the study, as against people with more chronic illnesses. We too expected to see a difference but data were so limited that nothing could be said with confidence. For the outcome of medium term relapse the results of the Rappaport 1978 study (acutely ill people) are different from the synthesised findings of three studies dealing with a more chronic population. This difference was not, however, statistically significant. The other outcomes in this sensitivity analysis do not show any suggestion of a difference. We agree that it would have been important to know with certainty if a portion of the placebo treated group that appeared to do better without drugs. This review generates some hypotheses that could be worth testing. The data are very far from being strong enough to all any clear conclusions to be drawn.

Results and conclusions - the interaction of drug effects and study design

We completely accept Dr Bola's comment about the possible interaction of length of washout and effect of chlorpromazine. There is just not enough data to be able to control for this in the current analyses. Taking this into account, along with the other potential biases that could be operating, often favouring the chlorpromazine group, gives all the more reason to treat the current estimates of the size of the effect of this drug with caution.

Contributors

Comment by John Bola, Los Angeles, CA, USA, March 2000.

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Feedback received, 18 August 2015

Summary

Comment #1: The authors mention in the abstract of this huge review ((55 trials and 5,506 patients) without any reservation that akathisia didn't occur more often in the chlorpromazine group than in the placebo group. The largest trial that contributed data to this outcome even found significantly less akathisia in the active group than in the placebo group, relative risk 0.57, 95% CI 0.37 to 0.88. Since we know that antipsychotics cause akathisia and that placebo cannot cause akathisia, this result speaks volumes about how flawed trials in schizophrenia generally are. What was seen in the placebo group were cold turkey symptoms caused by withdrawal of the antipsychotics the patients had received before randomisation.
Comment #2: I [Professor Gøtzsche] believe this fundamental problem renders the review unreliable
Comment #3 : I [Professor Gøtzsche] refer readers to another review. The most reliable placebo controlled trials are those of first episode schizophrenia where none of the patients have ever received drugs before. There is a Cochrane review that approaches this ideal, but even this review is biased, as the trials are not limited to first episode patients; the review includes studies "with a majority of first and second episode schizophrenia spectrum disorders" (4). The authors of that Cochrane review pointed out that the available evidence doesn't support a conclusion that antipsychotic treatment in an acute early episode of schizophrenia is effective. They felt this was worrying given the widespread use of antipsychotics in the acute treatment of early episode schizophrenia-type psychoses, and also because the use of antipsychotics for millions of people with an early episode appears based on the trials for those with multiple previous episodes (which we know are highly flawed). What does this mean for use of antipsychotics more generally, also for multiple episodes of psychoses? Doesn't it mean that we don't have the evidence to support using antipsychotics at all? In fact, despite the trials being flawed by the cold turkey design, what was seen in recent placebo controlled trials in submissions to the FDA was only a 6 point improvement on the Positive and Negative Syndrome Scale (PANSS) (5,6), far below the minimally relevant clinical effect on this scale, which is about 15 points (7).

Reply

Response #1: Thank you for this comment. The abstract is accurate in that we found, for akathisia, for these trials RR was 0.78 (CI 0.54 to 1.11, 9 RCTs, n=1164). Professor Gøtzsche says that "we know that that antipsychotics cause akathisia and that placebo cannot cause akathisia." Antipsychotics can cause akathisia, but these symptoms are well recognised to also occur in people who have never been on medication. Even a cursory search of the literature highlights study after study illustrating this odd fact [1–3]. It is indeed possible that the akathisia people displayed in these trials was due to preceding medications, but also a whole raft of other factors that are not speculated upon in a balanced argument. Professor Gøtzsche goes on to say that his statement "speaks volumes" about how flawed trials in schizophrenia generally are". Professor Gøtzsche's statement is poorly-supported and - even if it had been supported - generalising his perception of nine trials conducted between 1961 and 1970 to all of trials in schizophrenia is unscientific and not appropriate.
Response #2: The authors of the review make effort to provide a balanced appraisal of the best available evidence and have made efforts within the review to be transparent. Every one of the studies has been rated in detail regarding risk of bias and pre-defined outcomes given particular scrutiny for the Summary of Findings table. Professor Gøtzsche has selected one outcome which he finds fault with, speculates as to its cause, generalises to all of trials relevant to people with schizophrenia, and dismisses the review. We feel this is unwarranted.
Response #3: There is much in this comment that does not relate to this review. Important for this review is the statement "The most reliable placebo controlled trials are those of first episode schizophrenia where none of the patients have ever received drugs before." Professor Gøtzsche does not explain what he means by reliable. It seems likely that he is suggesting the explanatory exploration of the effects of medications - and is right in saying that trials in the group of people who have not had any medication before may help this

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exploration. It does not, however, help exploration of the effects of drugs for the great majority of people who have the illness in real-world circumstances. Professor Gøtzsche goes on to make statements about another review which we also feel are equally unwarranted but are not relevant to this evidence within the Chlorpromazine versus placebo review. Professor Gøtzsche is right in saying that the Chlorpromazine versus placebo review was "huge". He has chosen to comment on one outcome amongst hundreds, has not evidence to support his speculative interpretation of the finding and then used this as a basis for developing the argument across another review and well beyond. His final statements are a rallying call and not relevant to the Chlorpromazine versus placebo review and consistent with his recent statements to the press where he advertises his book attempting to discredit all psychiatry drugs (Daily Mail) to which others have reacted (Royal College of Psychiatrists 2015).

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Contributors

Feedback comment: Peter C Gøtzsche: Director Nordic Cochrane Centre.
Reply: Clive E Adams. Author, Cochrane Schizophrenia Group.

WHAT'S NEW

Date	Event	Description
30 October 2015	Amended	Reply to Feedback received 18 August 2015

HISTORY

Protocol first published: Issue 3, 1996

Review first published: Issue 1, 1998

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Date	Event	Description
7 September 2015	Amended	New Feedback received.
3 December 2013	New citation required but conclusions have not changed	Results of update search added to review, no substantial change to overall conclusions
5 November 2012	New search has been performed	Update search carried out November 2012. Five new trials added to the review
15 May 2012	Amended	Update search of Cochrane Schizophrenia Group's Trial Register (see Search methods for identification of studies), 26 studies added to awaiting classification.
14 March 2012	Amended	Additional table(s) linked to text.
18 January 2012	Amended	Contact details updated.
24 April 2009	Amended	New plain language summary added.
23 April 2008	Amended	Converted to new review format.
30 January 2007	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Clive Adams - protocol development, searching, data extraction, analysis, data interpretation, writing the final report and maintaining the review.

John Rathbone - study selection, data extraction, analysis, writing the report for the update of 2002. Update 2007, study selection, data extraction, data analysis, writing final report.

George Awad - protocol development, data interpretation.

Ben Thornley - completion of earlier versions of this review.

Karla Soares-Weiser - completion of 2012 update.

Nicola Maayan - completion of 2012 update.

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DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- University of Toronto, Canada.
- University of Leeds, UK.

External sources

- NHS Executive Anglia and Oxford R&D Directorate, UK.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We have updated the methods section since the last publication of this review to reflect changes in the Cochrane Schizophrenia Group's methodology.

We have re-ordered some of the outcomes.

INDEX TERMS

Medical Subject Headings (MeSH)

Antipsychotic Agents [adverse effects; *therapeutic use]; Chlorpromazine [adverse effects; *therapeutic use]; Placebo Effect; Randomized Controlled Trials as Topic; Schizophrenia [*drug therapy; prevention & control]; Secondary Prevention

MeSH check words

Humans

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